REVIEWS FROM NATURE GENETICS

Reviewer #1:  
Remarks to the Author:  
  
This manuscript utilizes a common factor model of the p-factor fit to 11 psychiatric disorders followed by a series GWAS-by-subtraction models for each of the 11 disorders to partial out transdiagnostic and disorder-specific signal. GWAS-by-subtraction results reveal SNPs associated with disorder-specific signal and biological annotation of these SNPs showed pathways implicated in the nervous system and developmental signal. The Introduction is well-written and the study team is well-equipped to perform these analyses, including Dr. Malanchini’s introduction and validation of the GWAS-by-subtraction method in a prior Nature Genetics publication. I also thought the genetic correlation results comparing patterns with and without correcting for p were well-presented and revealed interesting findings. My primary criticism is that the common factor model of p does not provide the most useful test of disorder-specific effects. Although the author’s highlight that the specification of a common factor model could be considered a limitation, since this is the central framework for the whole submission, I view this as a more central issue. Aside from this problem, the significance and novelty of this manuscript is not the same as the original GWAS-by-subtraction paper (which had both empirical application and introduction of a methodological approach + analytic pipeline) and would be more appropriate in a slightly less high-impact outlet.  
  
My specific concerns about the common factor specification of the p-factor are:  
  
1. The authors cite the Grotzinger et al. (2022) study as evidence for the p-factor. However, the conclusion reached in that article was that the p-factor was more statistical artifact than useful construct. This conclusion was also made for a hierarchical specification of p that provided reasonable fit to the data, whereas the study authors here utilize a common factor for p that did not provide good fit to the data (CFI=.823; SRMR=.119). Phenotypic models of the p-factor also tend to specify hierarchical or bifactor structures as common factor models often do not sufficiently account for the observed covariance structure across disorders or symptoms.  
  
2. The case made for p below is not appropriate given that a factor model of g has been shown to fit the data well at both the phenotypic and genomic level, whereas the opposite can be said for p (especially when specified as a common factor).  
  
“Another limitation is that p is a statistical construct for which there is no consensus on what it is or how to measure it, which leaves non-p even further adrift from reality. However, similar accusations could be levelled at g, the general factor that emerges from diverse cognitive traits, but g is one of the most stable and predictive variables in the behavioural sciences 38.”  
  
3. A central focus of the manuscript is around identifying disorder-specific effects. However, the common factor specification is not well-suited for this research question. This is evident in Figure 2 where the author’s show that several disorders still have strong genetic correlations with one another, which directly shows that the common factor does not do a good job of accounting for patterns of psychiatric genetic overlap (it also stood out to me that many of these strong correlations for the non-p outcomes are among the disorders that were found to load on separate factors in the Grotzinger et al. study.). The case could be made that this is just removing the broadest level of genetic overlap, but that in and of itself does not tell the reader much about disorder-specificity given the residual genetic correlations displayed in the right-panel of Figure 2.  
  
4. As far as I can tell, the GWAS summary statistics for the p-factor were not pruned for QSNP. This means that the GWAS-by-subtraction was also set-up to remove some disorder specific effects. This raises a further issue that even when pruning at some threshold for Q, that there will still be plenty of SNPs that are not significant for this heterogeneity metric that still deviate from the pattern of observed univariate GWAS betas. That is, the multivariate GWAS is estimated with error. To get around this issue for a GWAS-by-subtraction, I think you would want to specify the “subtracting” (preceding) variables in the Cholesky within the model itself, as opposed to carrying forward the imperfect multivariate GWAS summary statistics as the authors have done here. That could look like either a common factor specified in the model that subtracts out the effect or a series of extended Cholesky models that includes all the other disorders as predictors of one disorder at a time.  
  
  
My more specific comments are:  
  
The Grotzinger et al. study utilized 23andMe summary statistics whereas the current study does not. Changing the text to the “most recent publicly available summary statistics” seems appropriate (I’m not suggesting the author’s get access to the 23andMe data as I think it’s beneficial to have a public data reference point).  
  
“We constructed a genomic p factor using the most recent summary statistics from GWAS of 11 major psychiatric disorders (Grotzinger et al., 2022 10 ; see Supplementary Table 1).”  
  
It is worth highlighting in this excerpt that the disorders with unique hits are in line with expectation as they have the largest residual variance components in the model:  
  
“After applying a standard clumping algorithm (outside a 250-kb window, or within a 250-kb 108 window if LD r2 <0.1), we identified genome-wide significant lead SNPs independent of p for 109 schizophrenia (SCZ, 114 hits), bipolar disorder (BIP, 19 hits), attention-deficit /hyperactivity 110 disorder (ADHD, 11 hits), anorexia nervosa (AN, 6 hits) and alcohol use (ALCH, 2 hits).”  
  
The following two lines in the Results seem redundant:  
  
“These newly detected SNP associations are presented in Supplementary Tables 4-8.”  
-and-  
“Novel SNP associations uncovered for the other four ‘non-p’ GWASs are presented in the Supplementary Notes and Supplementary Tables 5-8.”  
  
The scaling of the axis labels and size of the parameter estimates on the path diagram in Figure 1 are barely legible and I think many of these numbers could be enlarged for readability without taking up too much additional space.  
  
These panels of Figure 1 would be easier to compare if they were merged and the bars for SNP-based heritability before and after accounting for genetic p were displayed adjacent to one another.  
  
“Figures 1F and 1G, and Supplementary Table 38 show the SNP-based h2 estimates for the 11 disorders (on the liability scale) and for the residual variance in each psychiatric disorder after accounting for the genetic effects associated with p (on the observed scale).”  
  
It would be helpful if the authors could provide some intuition as to under what circumstances this outcome of increased SNP h2 after a GWAS-by-subtraction is to be expected.  
  
“Slight increases in SNP h2 were observed for ASD, OCD, AN, and TS.”  
  
Figure 2 could be a single heatmap with genetic correlations after controlling for p displayed above the diagonal.  
  
The authors write: “The most dramatic pattern of change emerged for the psychotic disorders of MDD, BIP and SCZ...”. MDD is not a psychotic disorder.  
  
Figure 3 does not include any measures of precision.  
  
This section of the Discussion over-interprets results given the very small SNP-based heritability for MDD when controlling for p.  
  
“Other genetic correlations presented a more dramatic pattern of change. The genetic correlations between SCZ and MDD and between MDD and BIP switched from strongly positive to strongly negative after considering transdiagnostic effects. This negative correlation implies that, once transdiagnostic effects are accounted for, a genetic liability for one disorder conveys a lower genetic liability for the other disorder, this has the potential to inform diagnostic categorization and has far-reaching implications for future studies aimed at understanding biological causes and treatments for these disorders.”  
  
My understanding of HiTop is that it reflects applying SEM to the disorders to extract higher-order latent dimensions that “explain” patterns of co-morbidity. This read to me as a suggestion for how phenotypes are measured in psychiatric GWAS, but given that the analytic framework (Genomic SEM) employed could specify such a factor model using available GWAS I’m not sure this recommendation quite follows.  
  
“The origin of psychiatric nosology is historical rather than empirical; progress depends on more empirically derived dimensional approaches such as HiTop and Rdoc”  
  
When the author’s write the following in the Method section about novelty criteria it’s not clear if they compared the specific rsID to the original GWAS or a broader LD region. The latter is appropriate as some reshuffling of SNP effects, relative to the ordering in the original GWAS, is expected when performing the GWAS-by-subtraction.  
  
“Independent significant SNPs were considered novel under the following criteria: 1) they were not present in the original disorder GWAS...”  
  
  
  
Reviewer #2:  
Remarks to the Author:  
  
The authors use genomic SEM to model shared genetic effects (i.e. p-factor) across 11 psychiatric disorders, and then partition the effects of each disorder into what is shared with the p-factor and what is unique. They then examine changes in patterns of SNP effects, genes, h2snp and genetic correlations after controlling for the p-factor. While I find this study interesting, I have some major concerns with the methodology that should be addressed.  
  
General methodological concerns:  
  
I have concerns about the two-step approach you have employed to identify disorder genetic effects independent of the p-factor – i.e. first estimating the p-factor and its SNP effects, and then second in an entirely separate model using GWAS-by-subtraction. Each step of the analysis is estimated with error; using a two-step approach when much more elegant single-step approaches are available will certainly increase error and uncertainty in your results. For example, your aim could be achieved with:  
  
- An independent pathways model – regressing all of the 11 disorders directly onto the SNP (rather than regressing the p-factor onto the SNP) would estimate the the SNP effect on the residual of the disorder after removing common variation – exactly the aim of your analysis in a single step.  
  
- Another approach would be to estimate the p-factor within the GWAS-by-subtraction framework itself. Note the GWAS-by-subtraction model is not limited to two input traits – you could construct the p-factor (excluding disorder X), and then in the same model partition disorder X into what is shared with the p-factor and what is unique.  
  
Another concern I have with your approach is that I don’t think it is statistically appropriate to include the same disorder in the construction of the p-factor when you are partitioning that disorder into shared and unique effects. While using one of the more elegant single-step models would bypass this issue, at a minimum I would like to see sensitivity analyses where the GWAS-by-subtraction model is run with a p-factor that excludes the focal disorder.  
  
It is not stated in the methods or the supplementary which estimator was used in Genomic SEM. This needs to be reported, as it is relevant for the interpretation of your results. If the default DWLS estimator was used, then this may not have been an appropriate choice in the context of the current study. I quote the original Genomic SEM paper (Grotzinger et al. 2018):  
  
“WLS estimation more heavily prioritizes reducing misfit in those cells in the S matrix that are estimated with greater precision. This has the desirable property of potentially decreasing sampling variance of the genomic SEM parameter estimates, which may boost power for SNP discovery and increase polygenic prediction. However, because the precision of cells in the Smatrix is contingent on the sample sizes for the contributing univariate GWASs, WLS may produce a solution that is dominated by the patterns of association involving the most well-powered GWASs, and contain substantial local misfit in cells of S that are informed by lower-powered GWASs. In other words, WLS relative to maximum likelihood may more heavily prioritize minimizing sampling variance of the parameter estimates in the so-called variance bias tradeoff48. We expect that this will only occur when the model is overidentified (that is, d.f. > 0), such that exact fit cannot be obtained, and that divergence in WLS and maximum likelihood estimates will be most pronounced when there is lower sample overlap and the contributing univariate GWASs differ substantially in power. Maximum likelihood estimation may be preferred when the goal is to most evenly weight the contribution of the univariate sample statistics.”  
  
The key aim of this paper is not to identify novel SNPs for the p-factor, but rather to isolate the p-factor in order to separate out disorder residual genetic effects. It would therefore seem much more important that the p-factor is unbiased and evenly weighted from each of the disorders (i.e. maximum likelihood estimation), rather than maximising power. Furthermore, the context where the most pronounced differences between DWLS and ML estimation would be expected, describes exactly the context of the current study.  
  
IF you did use the DWLS estimator in the current study, this may explain why, for example, zero non-p MDD hits were found and you observed substantial reduction in genetic variance. In other words, is it the case that substantially more MDD variance is accounted for by the p-factor than other disorders? Or is it the case that the p-factor solution was dominated by / biased toward MDD given it is one of the most powered GWAS available?  
  
This is extremely important for the interpretation of the results. I would like to see a thorough set of sensitivity analyses / comparisons between the estimators to be sure.  
  
Throughout the manuscript, the term disorder-specific effects or specific component is used often. This is not correct, as the residual factors represent genetic effects of the disorder independent of P. Case in point – ANX and MDD retained an rg of 0.68 – and hence these residual traits clearly do not present disorder-specific effects.  
  
  
  
Reviewer #3:  
Remarks to the Author:  
  
Comments  
  
In this manuscript, the authors derived a p factor using a common factor model in genomicSEM using the latest GWAS on 11 psychiatric disorders, then performed GWAS-by-subtraction to derive the genetics of each disorder after regressing out the p factor (they call it the non-p or specific genetics of each disorder). They then went on to identify significant loci for each of the non-p GWAS, and assessed how the genetic correlations among psychiatric disorders or between psychiatric disorders and other complex traits are different when the p factor is removed from the genetics of each disorder. This is a fairly straightforward paper. I don't have a lot of concerns over the technicalities - the steps of analyses are fairly standard and well-performed. My only concerns are with the authors' hypothesis and their interpretation of the results.  
  
The authors remained mostly descriptive when it comes to explaining their new results, and did not demonstrate how these results could be used to delve deeper into the nature of p factor or the relationships between p and non-p genetics. This issue is pervasive throughout the paper.  
  
For example, the authors note, rightly, that it is very interesting that there are significant shifts (sometimes from positive to negative) genetic correlations among psychiatric disorders after correcting for p factor. What does this mean for each pair of disorder, and how does this relate to the nature of the p factor? These questions are not explored nor answered in analyses.  
  
Similarly, genetic correlations with other complex traits are sometimes very different before and after controlling for the p factor. These can be used as clues for understanding the nature of p factor, and how the genetic sharing of psychiatric disorders with these other complex traits may overlap with genetics captured by the p factor. Again I do not see adequate discussion as an important and natural extension of their analysism, or any attempts at delving deeper into this question.  
  
In fact, the authors do not attempt to explain what the p factor is, or why it should exist. Though the authors wrote in discussions that it is a limitation that "p is a statistical construct for which there is no consensus on what it is or how to measure it", their paper does not make much advance in helping us understand what p is. The authors continue to write that "we embrace the possibility that p, like g, is not one thing - it is precisely what diverse traits have in common", which seems obvious given that it is, by definition, the common factor derived from the genetic covariance matrix by genomicSEM. What I am hoping for in a Nature Genetics paper on p factor and non-p genetics of each psychiatric disorder, is the use of genetics tools to assess and characterise p factors, such that we get closer to knowing  
  
1) whether it is an entity and what is is biologically. For example, p factor could be the early developmental issues with neurons that cause issues across all psychaitric and behavioural phenotypes later in life, or p factor is the signaling challenges common to all psychiatric disorders, etc. These are testable hypotheses using enrichment analyses that are not beyond the scope of the paper.  
  
2) its genetic relationship with each psychiatric disorder. For example, what is BIP without the p factor? Is it truly the "specific BIP" genetics that the authors write about? What does genetic sharing between psychiatric disorders mean after controlling for p factors? These are questions the authors should be answering.  
  
Finally, the authors write in the discussion that the data that went into the GWAS of each disorder needs to more closely correspond to the genetic architecutre of psychopathology, and "case-control GWAS based on traditional diagnoses perfused with transdiagnostic effects". This seems like an afterthought, when it should have been central to the whole endeavour. Given the authors know that the input GWAS from different disorders are heterogeneous in terms of collection strategy, diagnostic accuracy, inclusion and exclusion criteria, and level of comorbidity with other disorders, how seriously should we take the results from this study? The authors have not corrected for any of the limitations listed in their discussion, even when there are methods to correct for volunteer bias and quantify likely biases in genetic correlations due to assortative mating. Perhaps the authors feel it is out of the scope of this paper to do so, but in my view without these considerations it is very difficult to know how much of the results in this paper (though very interesting, I agree!) I should take to heart.

REVIEWS FROM BIOLOGICAL PSYCHIATRY

**Reviewer 1:** Comments to authors:  
  
Review of BPS-D-25-00046:  
  
Researchers interested in the classification and causes of psychopathology have recently focused on transdiagnostic approaches, in particular hierarchical dimensional models such as the Hierarchical Taxonomy of Psychopathology (HiTOP) framework. These approaches have been used not only at the phenotypic level, but also in a genetic context, as in the current study. Such research has been fueled by novel statistical approaches, specifically the development of programs such as Genomic-SEM, that can test alternative dimensional models of psychopathology at the genomic level and conduct multivariate GWAS of the resulting dimensions. The current study uses this approach in an attempt to characterize the genetic architecture of (e.g., # of significant SNPs and genes, SNP heritabilities) and genetic correlations among 11 psychiatric disorders after controlling for a general psychopathology factor (i.e., "p"). For this, the authors use summary statistics from large-scale GWAS of case-control studies of these psychiatric disorders conducted (mostly) through the Psychiatric Genetics Consortium (PGC). The goal of identifying important aspects of the genetics of specific forms of psychopathology after accounting for (multiple) higher-order psychopathology dimensions is both interesting and worthwhile.  
  
In the face of this interesting topic and the study's strengths, there are some significant drawbacks that unfortunately seriously limit its potential contributions to the relevant literature. Two of these stand out as most important and are related. First, the authors control for the p-factor, despite it being strongly called into question phenotypically for statistical reasons in a number of recent studies, as well as at the genomic level based on model fit and other statistical problems in at least two recent studies using almost the identical 11 disorders, one of which the authors cite [Grotzinger AD et al. (2022). Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic and molecular genetic levels of analysis. Nat Genet. 54:548-559; and Waldman ID et al. (2020). Testing Structural Models of Psychopathology at the Genomic Level. World Psychiatry, 19, 350-359]. Problems with fitting a single genetic p factor to the 11 disorders can readily be seen in their factor loadings, as some of the disorders are clearly much more genetically correlated than others, echoing these studies' findings of multiple correlated genetic factors, rather than a single p-factor. The authors also could have assessed this by performing Q-SNP analyses of heterogeneity as outlined and demonstrated in the Grotzinger et al paper. Unfortunately, this modeling choice (relying on a single p-factor) affects all of the subsequent findings in the study. This leads to the second problem, namely the very large change in genetic correlations among many of the 11 disorders, such that some of these correlations shift from being strongly positive to strongly negative after controlling for p. As I read through the results, I couldn't help but wonder whether these very large shifts would have occurred if the authors had controlled for a set of correlated factors as in the above-mentioned 2 papers, or whether those very large positive correlations would simply have been substantially decreased (but not changed sign). It also raises the central question as to whether these positive-to-negative genetic correlations have any real substantive meaning or are merely statistical artifacts of partialling. There are a lot of statistical issues in making inferences from partial versus zero-order correlations, and this is much more complicated than is typically appreciated by researchers. Two helpful papers the authors may wish to consult on this topic are: Wysocki et al (2022). Statistical control requires causal justification. Practices in Psychological Science, 5, 1-19; Lynam et al (2006). The Perils of Partialling. Assessment, 13, 328-341.  
  
Second, maybe I missed it, but although the authors discuss using MAGMA to conduct pathway and functional analyses, these results and their importance to the topic of the study never seemed to be discussed anywhere. Third, in describing the procedure for testing differences in genetic correlations before and after partialling out p the authors state they used a two-sample z test, but these are being compared in the same sample. Fourth, was it not possible to estimate SNP effects on p and all of the 11 specific disorders simultaneously in the multivariate GWAS? Fifth, many of the genetic correlations with external traits (e.g., sensitivity to environmental stress) before and after partialling out p seem to be capturing negative emotionality and the high loadings of associated disorders on p. Sixth, the utility of disorder-specific PRSs mentioned in the Discussion totally hinges on the structural model of psychopathology used in the genetic-SEM being correct; if there are multiple psychopathology factors instead of p, as others have found, then it seems those PRSs also would be problematic.  
  
In sum, I think the authors would be better off using multiple psychopathology factors instead of p in a revision, as I believe their results would then be more accurate and valid.

**Reviewer 2:** Comments to authors:  
  
In this work, Kesler et al. seek to study the diagnosis-specific genetic loading of 11 specific diagnoses after correcting for shared genetic signal across traits (called the p-factor here). To achieve this, they first define the p-factor through a genomic SEM, fitting 1 common factor on the summary statistics of 11 GWAS; then they identify residual genetic signal for each diagnosis by adjusting for p. These "non-p" summary statistics are then used to interrogate the heritability, the genetic correlations among the diagnoses, genetic correlations with external traits, and gene and tissue level enrichment with each diagnosis.  
  
This is a clever and timely approach that aligns well with the current goal of identifying diagnoses-specific genetic signal across gwas.  
  
I have a few major concerns, however:  
- As the authors acknowledge in their discussion, the p-factor is "adrift from reality". Since the p-factor consists of the shared signal between the traits included in genomic SEM, precisely which traits are included matters, and affects the genetic non-p signal left. The results may look entirely different if not 11 but 14 traits were included, or only 5. Given this, it becomes difficult to interpret the non-p signal that is the topic of this paper and all downstream analyses. The authors could evaluate the stability of p and downstream results by: bootstrapping including various numbers and subsets of traits stratified by their heritability, sample size, and degree of polygenicity.  
  
- The authors do not acknowledge or compare their results to the existing literature on identifying diagnoses-specific effects (e.g., ccgwas PMID: 33686288), or specific diagnoses comparison between, say schizophrenia and bipolar disorder (PMID: 29906448), or between mood disorders (PMID: 31926635,<https://doi.org/10.1192/bjp.2024.125>). This is especially relevant given that the authors highlight a negative correlation between MDD and BD after accounting for p, which seems at odds with what has been reported in the literature before (as well as the clinical trajectories of the majority of patients with BD starting with depressive symptoms).  
  
And a few more minor concerns:  
- Figure 1 show h2 of the 11 traits before and after correcting for p, and the authors conclude that the results are similar. However, one is displayed on the liability scale whereas the other on the observed scale. Please use observed for both (assuming non-p signal cannot be converted to liability scale)  
- Figure 2 is interesting but is missing standard error, please add. Also, there are some odd features that are not discussed in detail: e.g., the genetic correlation often flips sign, which can indicate low power. For most traits, the genetic correlation with MDD drops to negative. Why do the authors think this is the case?  
- As a sort of validation the authors present a second algorithm by using the GWAS-by-substraction approach, but it is not fully clear to me how this differentiate form their initial approach.  
- Please include the number of tests when describing Bonferroni correction.  
- sloppiness: some results are repeated, e.g., p 7 paragraph ln33, and paragraph starting line ln44 include the same result; & comments in the margin are still present.  
- I was not able to locate references for the traits included in genetic correlation analyses of Fig 3 and 4.

**Reviewer 3:** Comments to authors:  
In this work, Keser et al. has presented an interesting analysis that attempts to study the genetic component of major psychiatric disorders beyond the component (referred to as "p factor") that is shared across the disorders. The authors have used genomic structural equation modeling (genomic SEM) to isolate the disorder-specific effects from the transdiagnostic effects for 11 major psychiatric disorders. The authors then run GWASs for the 11 disorders, capturing the potential disease-specific genetic effects. The resulting GWAS summary statistics were then used to perform standard set of GWAS secondary analyses. The work has yielded some interesting findings related to how the disease-specific and transdiagnostic components of 11 psychiatric disorders relate to each other and to a range other disease phenotypes.  
  
Overall, I find this work interesting and in line with the current thinking of the genetics of psychiatric disorders in the field. However, I have few comments and criticisms, which I'll briefly describe below.  
  
1. One of my concerns regarding the presentation of the results is that the authors have almost exclusively focussed on the genetic correlation analysis, leaving the rest of the results in the supplementary for the readers to dig through. It would have been informative if the authors have discussed briefly on the genome-wide significant loci found for the individual disorders after accounting for the p factor, how they differ from the loci associated with the p factor, if any insights from the novel loci etc.  
2. Regarding the genomic SEM, could the authors comment on how the sample overlap between the different disorder GWAS summary statistics impact the results. This is important as interpretation of some of the results depends on the assumption that sample overlap has minimal impact on the genetic correlation results. For example, on page 7, lines 33-43, the authors discuss how the genetic correlations of ADHD with MDD and PTSD changed after correcting for p factor. While the genetic correlation between ADHD and MDD dropped significantly after correction (0.52 to -0.08), the genetic correlation between ADHD and PTSD didn't (0.72 to 0.50). The authors interpret this results as "the ostensible genetic relationship between ADHD and MDD is completely mediated by p." How confident are the authors with this interpretation? The ADHD GWAS is primarily driven by the iPSYCH sample. The MDD GWAS also involved a large chunk of iPSYCH sample. However, PTSD GWAS has no contribution from iPSYCH. The substantial drop in the genetic correlation between ADHD and MDD might be due to the sample overlap? Could the authors replicate this finding using MDD GWAS that exclude iPSYCH sample? Perhaps, by using MDD GWAS based on UK Biobank sample only?  
3. One major concern is the lack of replication. I wonder how reproducible are the genetic correlation findings that the authors report in the manuscript. Ideally, one should use two independent sets of GWAS summary statistics for each of the disorder and perform the discovery analysis in the first set and replication analysis in the second, which, I understand, is not easily possible. Alternatively, could the authors try some sensitivity analysis by using leave-one-disorder-out kind of analysis? For example, to test the genetic correlation of depression with anxiety, could the authors run the genomic SEM to remove transdiagnostic effect from MDD using all disorders except anxiety. Likewise, run the genomic SEM to remove transdiagnostic effect from anxiety using all disorders except MDD. Then, test the genetic correlation between MDD and anxiety? Likewise, for all pairs of traits. Will the results from such an analysis would align with the results from the original analysis?  
4. Removing the transdiagnostic effects from each of the disorders leaves behind substantial residual genetic signals, which the authors interpret as genetic signals specific to the individual disorders and not shared with the others. However, it's not clear if such residual signals are related to the biology of the disorders or something else. It could be some sort of bias (e.g. ascertainment bias related to a specific cohort like UK Biobank) that is specific to a GWAS run and so left behind when adjusting for p factor. Is there a way to do some sort of exploratory analysis to look into this? Did the authors look into the genetic correlations with the phenotypes that capture participation bias such as the ones reported by Mignogna et al. 2023 (<https://www.nature.com/articles/s41562-023-01632-7>).  
5. I find the usage of the phrasing "isolating transdiagnostic genetic signal" bit confusing. The aim of authors' work is to remove the transdiagnostic genetic signal and studying the disorder-specific effects. Could the authors use "removing" instead of "isolating" when referring transdiagnostic genetic signal?