nature portfolio

Peer Review File

Neuropsychiatric polygenic scores are weak predictors of professional categories

Corresponding Author: Dr Georgios Voloudakis

Version 0:

Decision Letter:

29th October 2022

Dear Dr Voloudakis,

Thank you once again for your manuscript, entitled "Genetic liability for neuropsychiatric traits influences membership to broad profession categories", and for your patience during the peer review process.

Your Article has now been evaluated by 4 referees. You will see from their comments copied below that, although they find your work of potential interest, they have raised quite substantial concerns. In light of these comments, we cannot accept the manuscript for publication, but would be interested in considering a revised version if you are willing and able to fully address reviewer and editorial concerns.

We hope you will find the referees' comments useful as you decide how to proceed. If you wish to submit a substantially revised manuscript, please bear in mind that we will be reluctant to approach the referees again in the absence of major revisions. We are committed to providing a fair and constructive peer-review process. Do not hesitate to contact us if there are specific requests from the reviewers that you believe are technically impossible or unlikely to yield a meaningful outcome.

Editorially, we would like to highlight the following points to guide you in your revisions:

1) The reviewers note that controlling for sex as a biological variable is not enough given the nature of your study, and we ask that you please perform sex-specific analyses as requested by reviewers;
2) Please also include additional analyses with and without EA as a control, as suggested by Reviewer #4;
3) We also ask that you remove all causal language and revise your framing taking into account the comments of our bioethics reviewer;
4) Reviewers believe that your work would become stronger with a few extra analyses, and we ask you to include them. Namely, analyses of indirect/family influences, as well as analyses addressing any potential biases;
5) Finally, please use the latest coding of years of education for the UKBB.

Finally, your revised manuscript must comply fully with our editorial policies and formatting requirements. Failure to do so will result in your manuscript being returned to you, which will delay its consideration. To assist you in this process, I have attached a checklist that lists all of our requirements. If you have any questions about any of our policies or formatting, please don't hesitate to contact me.

If you wish to submit a suitably revised manuscript we would hope to receive it within 4 months. I would be grateful if you could contact us as soon as possible if you foresee difficulties with meeting this target resubmission date.

With your revision, please:

• Include a “Response to the editors and reviewers” document detailing, point-by-point, how you addressed each editor and referee comment. If no action was taken to address a point, you must provide a compelling argument. When formatting this document, please respond to each reviewer comment individually, including the full text of the reviewer comment verbatim followed by your response to the individual point. This response will be used by the editors to evaluate your revision and sent back to the reviewers along with the revised manuscript.

• Highlight all changes made to your manuscript or provide us with a version that tracks changes.

Please use the link below to submit your revised manuscript and related files:

Link Redacted

>strong<Note:>/strong< This URL links to your confidential home page and associated information about manuscripts you may have submitted, or that you are reviewing for us. If you wish to forward this email to co-authors, please delete the link to your homepage.

Thank you for the opportunity to review your work. Please do not hesitate to contact me if you have any questions or would like to discuss the required revisions further.

[redacted]

Reviewer expertise:

Reviewer #1: behavioural genetics

Reviewer #2: neuroscience, complex trait genetics

Reviewer #3: bioethics

Reviewer #4 social science genetics

REVIEWER COMMENTS:

Reviewer #1:
Remarks to the Author:
The study by Voloudakis et al investigates how genetics might influence professional membership by taking advantage of a number of PRS available for different psychiatric conditions and cognitive traits.
The main scope of the paper seems to establish whether predisposition for neuropsychiatric traits, which is mainly intended here as clinically diagnosed conditions, might preferentially lead to certain jobs rather than others.

My main issues for this study are around the motivations of this analysis and data interpretation.

One could argue that data are data and always worth reporting but I am not entirely clear where this kind of work is leading to. The authors justify their research at the beginning of the introduction quoting “increasing interest to understand the genetic bases of complex psycho-social traits”. While it is true the availability of genomic data allows this kind of study is also worth mentioning the controversies around these approaches and especially the utility of the results.

The manuscript ends with this statement “This study aims to reduce the stigma of mental illnesses and provide some evidence that would, hopefully, steer our field away from indiscriminately assigning risk variants to unfavorable outcomes without considering their potentially beneficial effects.”

This take seems to be justified by a previous statement “Despite these limitations, our study suggests that risk variants of neuropsychiatric traits may contribute to critical societal functions and therefore increase the fitness of the overall population; one such example in our study is the association of a high genetic load for serious mental illnesses and the employment category of creative professions.”

My immediate reaction is whether this genetic approach adds significantly more to what we know already from studies such as Burch et al 2006 https://bpspsychub.onlinelibrary.wiley.com/doi/full/10.1348/000712605X60030

Furthermore, I am not entirely sure that the conclusions of the paper and the general narrative of the manuscript are fully justified by the results. As mentioned, the key aim appears to investigate the link between the genetics of neuropsychiatric conditions and professional membership. The authors claim that they found “68 significant associations of neuropsychiatric traits” and that the effect was observed for “most profession categories”.
First, I argue that it is not useful to classify all PRS used as capturing “neuropsychiatric traits”. For example, I do not think that education attainment can be labeled under this category. In fact, as shown in Figure 2 there is a clear distinction between cognitive function and psychopathology.

Accordingly, when re-looking at the data keeping in mind these two basic groups it looks like most of the associations are actually detected for the cognitive function group (i.e. EA and intelligence) while only spurious results are observed for the psychopathology categories.
There seems to be an effect of ADHD, with a reverse trends as observed for EA, and then an effect for the Art and Design category across different PRS.
However, when looking in the CONTROL groups (supp figure 2 and 3), it looks like most of these latter signals for the psychopathology PRS are no longer significant. This is in contrast to the claim made in the main text that “many of the associations remained significant when individuals with mental illness diagnoses were excluded (CONTROLS)”. It looks to

me that the main signal remaining consistently significant is for the EA PRS.

Therefore, while the authors have rightly controlled for different demographic features, it would seem worthwhile to control for other factors, e.g. IQ to test whether the effects of the psychopathology PRS remain significant after controlling for cognitive functions.

Instead, I thought that it was worth noting another pattern that was overlooked. Although not significant, I think it is interesting to look at the difference observed for the military category between the MPV and UK BB cohorts. While there is no signal for this category in the MPV (as expected given the demographic of this cohort, also pointed out by the authors at line 217) there seems to be a large OR for many PRS in the UK Biobank. What would this suggest?

Beyond results interpretation, this observation raises the question of whether the cohorts used are good enough to carry out this type of analyses as these resources which undoubtedly are the current gold standard for genetic studies are affected by many demographic biases, e.g. at the point of recruitment and of participation (see Tyrell et al 2021 https://www.nature.com/articles/s41467-021-21073-y). This problem needs to be addressed in the current study in more details, discussing how it could have affected the results.

Reviewer #2:
Remarks to the Author:
Overall feedback
This is a very interesting and timely study that examines the relationship between genetic architecture of neuropsychiatric traits and profession/jobs in two large population samples. The paper is well-written overall and analyses appear to be appropriate and carefully conducted. Additional strengths include the use of a large size replication cohort (MVP), the careful framing of the results (the authors are careful to not overstate the role of genetics in professional outcomes and also acknowledge a environment that the influence individual differences in professions), and the study design is more nuanced than overly simplistic dichotomies about the relationship between IQ, SES, and mental health that are sometimes found in the literature. Overall, I find the study design and findings to be of medium impact as communicated in the present state of the manuscript, and I thus have some specific suggestions on how to improve its suitability for publication.

Major comments

Some of the most significant findings concern neuropsychiatric PGS predicting Arts & Design professions; the results in Supplementary Figure 6 are very interesting. Please move this figure to the main paper and discuss in more depth.

Environment is addressed but the study design and literature do not really disentangle environment and SES. Please address.

Analyses using years of education as a covariate may result in collider bias. Please address this.

Sex differences are known to influence at least two major factors here: participation bias (see for example Piratsu et al., 2021) and membership in professional categories. It is not sufficient to control for sex as a biological variable as the authors have done here. Sex-specific analyses are needed and please relate to larger literature.

It is not totally clear (to me) in the main analyses what the comparison groups are for each logistic regression; the PGS's for membership of a given profession is being compared to PGS's of whom? Are comparison groups matched in age, sex, and local ancestry? I apologize if this information is stated and I missed it, but it needs to be a bit more clear in the figure legends, etc., and Results section.

Most of the analyses are quite well-powered, but the n's for the military profession are less than 100. Please justify power achieved or remove these. Also, the "Other" category seems to meaninglessly lump together whatever is leftover. I would suggest removing it.

What about familial influences on profession/genetic nurture? Could you address this with the addition of another genotyped dataset with family data and profession info.? I think that additional data is needed to really establish the robustness of the results

The literature cited is incomplete and many claims lack appropriate citations (see for example lines 196 to 210). Please substantiate/elaborate in relation to published literature.

Along similar lines, it will be also important for the reader to know whether the findings align and converge with results from phenotypic-only studies and from behavior genetics (family-based) methods.

Please address value of creative professions in society in the Discussion (line 238).

The Verbal Tilt result is so interesting, especially since language/verbal skills have received far less attention than other complex cognitive traits. Please discuss role of language skills.

Please provide more explicit justification about the use of the Lifestyle Survey. What is the validity and stability of its measures? Are the professions assayed here inclusive of all professions over the lifetime or only current?

Please address ascertainment bias of the MVP cohort and how subsequent professions might be impacted by environmental or genetic influences on history of military participation.

The ethics/social dimensions are incorporated somewhat (for example, on lines 204-205 and line 240-243) but need to be elaborated and the authors should cite relevant ELSI literature.

Please address potential mechanisms, including possible neural pathway explanations for the results.

Minor comments

Please parse up the Method section into smaller paragraphs to facilitate readability.

In this context, I would prefer polygenic scores (PGS) rather than PRS; these are not disease phenotypes and risk factors.

Reviewer #3:
Remarks to the Author:
Review of "Genetic liability for neuropsychiatric traits influences membership to broad profession categories" for Nature Reviews Genetics

Firstly, I found this paper rather hard to understand – no doubt that is because I am an ethicist and not a genomic scientist or statistician – but that made is quite hard for me to extrapolate the findings to ethics (or, to understand whether and where 'ethics' is relevant to this article). On the one hand, I think this is just another paper that is trying to work out exactly how useful PRSs are in understanding humans and social life. It's not the first paper of its kind, nor will it be the last. Furthermore, it is certainly not the first paper that links psychiatric illness (or PRS for those) with creativity and as such neither the central premise of the paper, or its findings, is ethically novel or particularly disturbing.

However, I think that whilst individual papers of this kind are not in themselves particularly problematic, the broader quest to explain the human experience through PRSs, does raise important ethical questions. These relate to for instance the desirability of understanding ourselves increasingly in biological and not other terms, issues relating to stigma and discrimination, undesirable uses of this kind of evidence in future, problems of diversity and inclusion, and so forth. Thinking about a journal such as NHB, my feeling is that it is important to explicitly recognize that even if one paper does not raise all these issues, that the overall field does. One way of doing that is by actively inviting social scientists, ethicists and others to write commentaries on the desirability and future challenges of this kind of work. Another is the strategy you have already chosen – specifically invite people to comment on the ethical aspects of the work during peer review. Furthermore, perhaps as editor you can signal in one editorial that there is this broader question about the relevance and desirability of this work that also needs to be interrogated.

W.r.t the particular paper:
One critical component in studies of this kind, I think, is how the data that is used to make the statements, is obtained. For example, this paper speak about how data about the 'oral vs verbal tilt' at school is predictive of professional membership later in life, but it wasn't clear to me a) whether the oral tilt data was derived from genetic evidence (i.e. was this one of the PRSs) or whether this was phenotype data available in the datasets. Perhaps your science reviewers will be able to understand this better, but in work of this kind, what matters a lot is whether the data that is used for these types of studies, was duly collected and explained. More contextualization of the evidence would have helped me to evaluate exactly how much importance to attribute to the findings reported in this paper.

Relatedly, there are obvious shortcomings with the collection of detailed phenotype data in endeavours such as UK Biobank that could confound the results. For instance, what if the people who have high PRS for psychiatric illness are also a bit chaotic and misremember educational performance, and the UK Biobank data collectors rely only on verbal information to capture their data; then that would skew the data that is subsequently used to make statements about PRS and educational performance. Yet those results will be used to build up a body of evidence that – over time – says that people who have high PRS for psychiatric illness may also be more creative. So in an article of this kind, it's very important that there is sufficient information about the kind of data that was used, how it was collected and what the risks or limitations are.

Line 216 on pg 7 of the pdf says that the European countries in which the biobanks that they used data from were based, have 'global social mobility indexes among the top 30 in the world'. Is the aim of this statement to suggest that these findings may have relevance for global populations? That is how I read that sentence and that's obviously very problematic – it doesn't matter whether the countries are diverse; if the data is used is not, then the findings are not representative of diverse people. I'd question the authors on this.

It wasn't clear to me, in the paper, what the authors mean by 'creative professions', how they define those and what they stand in opposition to. This needs to be clarified and commented on in the discussion. E.g. does this only mean people who indicated that they work in the 'arts and design' professions in Figure 1? The authors obviously need to engage with that

idea around ‘creativity’ in their discussion. Surely e.g. architects, teachers and academics are also hugely creative. If the authors’ choice is to use the term ‘creative’ for ‘people self-selecting as working in the arts & design profession’ then they need to explain what they mean by that and why that substitution is justified. Note that the category would include people in the arts & design professions who do non-creative jobs (e.g. management, administration, accounting, financing).

I did find the sentence that ‘risk variants… contribute to critical social functions’ (lines 236-238 on pg 8) to be odd. The authors did not establish that the people included in the ‘arts and design’ category perform a ‘critical social function’ – or explain what they mean by ‘critical’ here. How does the employment of people in the ‘creative professions’ improve the fitness of our population as a whole? That sentence is obviously nonsense – there is no way for the scientists to support that view with evidence (bearing in mind what geneticists normally mean with fitness). The interpretation of the findings needs to be commensurate with the evidence in this paper: here, narrowly, the authors provide evidence of correlation between A (PRS for psych illness) and B (people self-reporting as working in arts&design professions). They haven’t established causality; they do not know whether there may be confounding factors. And so they mustn’t speculate.

I also think it is misleading to suggest that this paper ‘aims to reduce stigma’: it is neither really truthful nor likely to be possible for the authors to aim to have this effect. ‘Not truthful’ in the sense that they themselves seem to want to sensationalise their findings. For instance, instead of saying ‘people who self-self as working in the arts & design professions’ they say ‘creative professions’ and use terms like ‘creativity’. Those two are obviously not the same.

Overall, with some adjustments to the Discussion and some greater explanations of a) what data they used and b) what the limits of that data are in terms of the researcher’s ability to track ‘creativity’, I don’t think this paper is likely to be more ethically controversial than other papers already published in this domain. I do think, though, that if the decision is to publish this article, it’s important for NHB to also provide space (through soliciting commentaries or through editorials) to the bigger questions that this field raises, including questions about the biologisation of the human experience, the potential for stigma, and questions about equity and justice.

Reviewer #4:
Remarks to the Author:
This study conducted an extensive set of analyses examining the association between genetic liability for neuropsychiatric traits and occupational choice in two large samples. The paper is overall interesting and I believe this is an important topic to study. I particularly liked the PCA of the regression coefficients that nicely illustrates the underlying patterns of the associations. However, while the authors discussed the complexity of occupational choice at length in Discussion, I did not find that this was fully considered in their own analyses.

- The authors should make clear what educational attainment is in this context. Is it simply a sociodemographic variable that confounds the association if not accounted for, or is it a neuropsychiatric trait of interest? Currently, it is contradictory that the authors are using educational attainment for both. They do not provide sufficient discussion on this, while their results are substantially relying on educational attainment.

- Also, I believe the authors should carefully think about whether (or why) they should control for educational attainment (years of education). They noted that they controlled for education “due to different requirements of profession categories”. This is actually a reason not to control for education since this implies that education is one of the mediating paths through which genetics contributes to occupational choice. The authors are removing this important source of variation in occupational choice that they should be interested in. If they have to control for education, the reason should be that educational attainment is an indicator of one’s socioeconomic background that may confound how genetic liability for neuropsychiatric traits influences occupational choice. However, just as the authors also used educational attainment as a neuropsychiatric trait, educational attainment is more than just a socioeconomic indicator in that it also reflects a number of important behavioral traits. Currently, the manuscript does not pay much attention to this. Since education can be both a mediator and a confounder of great importance in this context, the authors should report results with or without controlling for education and provide careful interpretations.

- In the variance partitioning analysis, I do not think we can simply state “Other demographic covariates accounted for a much bigger fraction of the variance” without considering a finite sample size of GWAS from which the PRS was derived from. The variance explained by the PRS can be underestimated because its predictive power is lower than it could potentially be. The authors should have used a bias correction method (such as https://www.nature.com/articles/s41562-021-01119-3 or https://www.biorxiv.org/content/10.1101/2021.04.09.439157v4) or at least noted this attenuation bias of the PRS as a limitation for this analysis.

- The most recent GWAS of educational attainment (published in March 2022) showed that the previous coding of years of education in the UKBB does not properly capture different levels of education in a linear index and therefore revised the coding. Since the authors constructed years of education based on this previous coding, they are not sufficiently capturing the variation in education in the UKBB. It is important to use a proper coding here because the authors report and discuss results that critically rely on the quality of education variable, in particular the variance decomposition. The reason that years of education explained a smaller fraction of the variance in the UKBB compared to MVP could simply be this imprecise coding of years of education in the UKBB. Therefore, I would suggest that the authors use the revised coding of years of education for the UKBB. I would also be cautious about interpreting the cross-cohort differences.

- Since each PRS was standardized, the PCA of the PRS coefficients could be driven by a few PRS from disproportionately larger GWAS than the others. I do not think this is an issue that invalidates this analysis, but they should discuss the implications of using the standardized PRS coefficients in this analysis.

- I could only find out the authors partitioned the variance of predicted liability for occupational membership by following the github link in the supplementary text. This is a key detail of this analysis that should be explained in the main text.

- The last paragraph for discussion is too long and should be split.

Version 1:

Decision Letter:

23rd August 2023

Dear Dr Voloudakis,

I am very sorry for an unacceptably long amount of time your paper has spent in review with us.

We have now heard from 3 returning reviewers, whose comments are included at the end of this letter. Based on these comments and our editorial concenrs, we would like to consider your response to these concerns in the form of a revised manuscript before we make a decision on publication.

I am attaching a marked up word file with our preliminary edits and requests.

In addition to the comments provided by reviewers and our suggestions in the attached manuscript file, we ask that you:

1. Following examples of FAQs on Human Genomics Studies (https://www.thehastingscenter.org/genomic-findings-on-social-and-behavioral-outcomes-faqs/) include a list of FAQs to minimize the risk of misinterpretation as part of your SI.

2. Since your approved UKB application summary for project 18177 does not cover social phenotypes, we ask that you seek additional approval from UKB for this specific study of social and psychiatric phenotypes. Please share both MVP and UKB approvals with us.

3. Discuss limitations and contextualize effect sizes transparently from the very start, i.e. Abstract and Introduction.

In sum, we invite you to revise your manuscript taking into account all reviewer and editor comments. We are committed to providing a fair and constructive peer-review process. Do not hesitate to contact us if there are specific requests from the reviewers that you believe are technically impossible or unlikely to yield a meaningful outcome.

We hope to receive your revised manuscript within two months. I would be grateful if you could contact us as soon as possible if you foresee difficulties with meeting this target resubmission date.

With your revision, please:

• Include a “Response to the editors and reviewers” document detailing, point-by-point, how you addressed each editor and referee comment. If no action was taken to address a point, you must provide a compelling argument. When formatting this document, please respond to each reviewer comment individually, including the full text of the reviewer comment verbatim followed by your response to the individual point. This response will be used by the editors to evaluate your revision and sent back to the reviewers along with the revised manuscript.

• Highlight all changes made to your manuscript or provide us with a version that tracks changes.

Please use the link below to submit your revised manuscript and related files:

Link Redacted

>strong<Note:>/strong< This URL links to your confidential home page and associated information about manuscripts you may have submitted, or that you are reviewing for us. If you wish to forward this email to co-authors, please delete the link to your homepage.

We look forward to seeing the revised manuscript and thank you for the opportunity to review your work. Please do not hesitate to contact me if you have any questions or would like to discuss these revisions further.

[redacted]

REVIEWER COMMENTS:

Reviewer #1:
Remarks to the Author:
I thank the authors for having addressed the comments raised by myself and the other reviewers. I think that the manuscript has greatly improved.

However, I am still concerned that the results have been affected by too many biases and limitations intrinsic to the cohorts used. I do not think there is much that can be done about this and I note that biases are acknowledged in the discussion.

I am still unconvinced by the motivations underlying this study which risks to be badly misinterpreted. The final paragraph provides some justifications and applications of the results (i.e.in PGS-assisted preimplantation embryo selection and drug development). I do not think the results presented here contribute to such applications and I suggest rewriting this final paragraph which still hyper-sensationalize the results.

I agree with the suggestion of reviewer #3 that, in case of publication, this paper needs to be paired with expert commentaries and/or editorials to avoid misleading interpretations.

Reviewer #3:
Remarks to the Author:
The authors have very carefully revised the paper and addressed all of my previous comments. The end result is excellent and I look forward to seeing this interesting paper published.

Reviewer #5:
Remarks to the Author:
The authors adequately addressed my previous concerns. I only have minor comments about the mediation section (Interplay with observed educational attainment and socioeconomic status proxies).

I noticed that the authors wrote “causal mediation model” here. However, there is nothing causal in their analysis and what they did is really a conventional (statistical) mediation analysis. Identifying causal mediation effects requires a series of assumptions (sequential ignorability) that are difficult to satisfy with observational data. In order to avoid confusing readers, I would drop the word “causal” here (in the table notes, too).

It is great that the authors discussed potential collider bias. However, I think the collider bias scenario is more likely and relevant for SES proxies than EA. The example of physicians is nice, but for most of the professions, EA is more likely to act as a mediator than a collider. On the other hand, SES proxies are likely to be a collider, especially income (PGS → occupation → income ← PGS). Some statistically significant associations that were found here but not found in the primary analysis (or those with stronger associations) could just be an outcome of introducing collider bias. I would suggest that the authors discuss the collider bias at the end of this section, covering both EA and SES.

Version 2:

Decision Letter:

Our ref: NATHUMBEHAV-22071782B

31st July 2024

Dear Dr. Voloudakis,

Thank you for submitting your revised manuscript "Neuropsychiatric polygenic scores are weak predictors of professional categories" (NATHUMBEHAV-22071782B).

We will be happy in principle to publish it in Nature Human Behaviour, pending minor revisions to satisfy the referees' final requests and to comply with our editorial and formatting guidelines.

We are now performing detailed checks on your paper and will send you a checklist detailing our editorial and formatting requirements within two weeks. Please do not upload the final materials and make any revisions until you receive this additional information from us.

Please do not hesitate to contact me if you have any questions.

[redacted]

Version 3:

Decision Letter:

Dear Dr Voloudakis,

We are pleased to inform you that your Article "Neuropsychiatric polygenic scores are weak predictors of professional categories", has now been accepted for publication in Nature Human Behaviour.

Please note that >i<Nature Human Behaviour>/i< is a Transformative Journal (TJ). Authors may publish their research with us through the traditional subscription access route or make their paper immediately open access through payment of an article-processing charge (APC). Authors will not be required to make a final decision about access to their article until it has been accepted. >a href="https://www.springernature.com/gp/open-research/transformative-journals"< Find out more about Transformative Journals>/a<

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If you have posted a preprint on any preprint server, please ensure that the preprint details are updated with a publication reference, including the DOI and a URL to the published version of the article on the journal website.

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[redacted]

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Dear Dr. Radzvilavicius and reviewers,

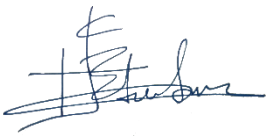
Thank you for the opportunity to submit a revised manuscript for your consideration for publication in *Nature Human Behaviour* and for your efforts in conducting a well-rounded review that takes also into account the ethical challenges of this line of work. Integrating the editorial recommendations and addressing the reviewers' concerns has resulted in a much-improved manuscript that provides a deeper exploration of the potential genetic basis of membership to profession categories while addressing ethical, legal and social implications of this work.

We hope that our revisions and additions adequately address the concerns of the reviewers. Our responses to their individual comments follow.

Thank you for your consideration.

Sincerely,

Panagiotis Roussos, M.D., Ph.D.
Director of the Center for Disease Neurogenomics
Professor of Psychiatry & Genetics and Genomic Sciences
Icahn School of Medicine at Mount Sinai Friedman Brain Institute
Icahn Genomics Institute
VA/MIRECC Research Physician
James J. Peters VA Medical Center



Georgios Voloudakis, M.D., Ph.D.
Assistant Professor of Psychiatry & Genetics and Genomic Sciences
Director, Translational Bioinformatics and Precision Therapeutics Group, Center for Disease Neurogenomics
Icahn School of Medicine at Mount Sinai

Reviewer #1 (Behavioural Genetics):
Remarks to the Author:
The study by Voloudakis et al investigates how genetics might influence professional membership by taking advantage of a number of PRS available for different psychiatric conditions and cognitive traits.
The main scope of the paper seems to establish whether predisposition for neuropsychiatric traits, which is mainly intended here as clinically diagnosed conditions, might preferentially lead to certain jobs rather than others.

We thank the reviewer for carefully reviewing our manuscript and providing constructive criticism. As stated by the reviewer, the underlying hypothesis was that increased genetic likelihood for certain neuropsychiatric traits may be associated with membership to specific broad profession categories.

R1.1: My main issues for this study are around the motivations of this analysis and data interpretation.
One could argue that data are data and always worth reporting but I am not entirely clear where this kind of work is leading to. The authors justify their research at the beginning of the introduction quoting “increasing interest to understand the genetic bases of complex psycho-social traits”. While it is true the availability of genomic data allows this kind of study is also worth mentioning the controversies around these approaches and especially the utility of the results.
The manuscript ends with this statement “This study aims to reduce the stigma of mental illnesses and provide some evidence that would, hopefully, steer our field away from indiscriminately assigning risk variants to unfavorable outcomes without considering their potentially beneficial effects.”
This take seems to be justified by a previous statement “Despite these limitations, our study suggests that risk variants of neuropsychiatric traits may contribute to critical societal functions and therefore increase the fitness of the overall population; one such example in our study is the association of a high genetic load for serious mental illnesses and the employment category of creative professions.”

We thank the reviewer for their constructive feedback. We have revised the discussion to include a brief summary of the response below which clarifies our original motivations (lines **365-385**) and we have also changed the wording accordingly in the abstract, introduction and discussion sections. In addition, we have greatly expanded the context and discussion on ethical, legal and social implications of our work (additionally in response to **R2.15** and **R3.1**). Finally, in the revised manuscript, we demonstrate how

e.g. the mediation analysis for ADHD PGS corroborates the need for additional educational policy changes

Overall, it would be helpful to see this study in the broader context of the genetically based risk stratification, drug development and drug repurposing applications. Firstly, it has been reported that private testing companies are already marketing polygenic risk score analyses on embryos for preimplantation embryo selection and it appears that at least one child has been born after such a procedure (PMID: 34916614). Given the lax regulatory framework of such applications (PMID: 33462079) in many countries (e.g. USA) the risk of inappropriately using PRS scores for screening is high. Thus, it is important to characterize pleiotropic effects of genetic liability for neuropsychiatric disorders such as positive associations of schizophrenia and ASD PRS with “Arts & Design” and a propensity for “Computers & Math” respectively. In addition, over the past several years, our team and other groups have been developing methods to leverage genetic and molecular profiling data to identify associated genes, prioritize gene targets (e.g. PMIDs: 32492425, 36064543) and existing medications (e.g. PMIDs: 28805813, 31444360) for the treatment of heritable disorders. However, in these methods, we use summary statistics from GWA studies and assume that all the associated variants should be treated equally even though future studies may reveal that within genetically correlated traits such as membership in “Arts & Design” and schizophrenia (based on preliminary data for another study we are preparing), some variation associated with “creativity” should (ideally) be preferentially preserved. Similarly with e.g. ASD and membership to “Computers & Math” profession, there may be some variants that help carry out this form of work. Thus, with this study, we are planting the seeds towards a more cautious use of GWAS summary statistics of complex neuropsychiatric traits. Tools such as mtCOJO can then be used to regress out the genetic effects of e.g., a creativity GWAS from schizophrenia GWAS for downstream analyses and applications.

R1.2: My immediate reaction is whether this genetic approach adds significantly more to what we know already from studies such as Burch et al 2006
https://bpspsychub.onlinelibrary.wiley.com/doi/full/10.1348/000712605X60030

We agree with the reviewer that many of the results we find with the genetic liability methods employed in our study are supported by more traditional studies (such as the one provided as an example); however, our study is of a larger scale, has a greater scope and has a discovery and replication cohort in its design. Please look at our previous response on why we think it is important to approach this subject from a genetics perspective, this is particularly important as PGS-based scoring applies to non-affected individuals as well. The most closely related study to ours was performed in 2015 (PMID: 26053403) and only explored the association of creative professions with schizophrenia

and bipolar disorder. Finally, using again the “Arts & Design” as an example, there is concordance for some findings (e.g. positive association of membership to creative professions with schizophrenia or bipolar disorder) but not others (e.g. positive association of membership to creative professions with depression) when compared to prior large-scale epidemiological studies (PMID: 21653945).

R1.3: Furthermore, I am not entirely sure that the conclusions of the paper and the general narrative of the manuscript are fully justified by the results. As mentioned, the key aim appears to investigate the link between the genetics of neuropsychiatric conditions and professional membership. The authors claim that they found “68 significant associations of neuropsychiatric traits” and that the effect was observed for “most profession categories”.
First, I argue that it is not useful to classify all PRS used as capturing “neuropsychiatric traits”. For example, I do not think that education attainment can be labeled under this category. In fact, as shown in Figure 2 there is a clear distinction between cognitive function and psychopathology.
Accordingly, when re-looking at the data keeping in mind these two basic groups it looks like most of the associations are actually detected for the cognitive function group (i.e. EA and intelligence) while only spurious results are observed for the psychopathology categories.

We thank the reviewer for providing constructive feedback. In response to the reviewer’s concern, we have updated the manuscript as follows:

In the revised manuscript:

1. We have followed the reviewer’s recommendation (and **R4.1**) and have excluded traits that reflect overall cognitive and educational performance to focus on the main theme of our paper which is the effect of neuropsychiatric trait PGS on profession category membership. Thus, we are retaining for PGS: a) neuropsychiatric disorders, b) personality domains corresponding to the five factor model and c) cognitive domains which, based on our recent study (PMID: 36624241), capture differential performance and can be associated with psychopathology (verbal and oral tilt at school). Furthermore, by excluding the aforementioned traits we avoid ethical pitfalls that have previously been documented about cognitive performance and education attainment genetic studies (summarized in lines **350-361**).
2. We removed two profession categories in response to **R2.7**.

After these changes, the total number of neuropsychiatric PGS - profession categories pairs is now 374 and there are 43 significant associations.

Since, the revised approach doesn't utilize intelligence and educational attainment PGS, we are reintroducing them as observed covariates (self-reported or measured):

1. We re-introduce intelligence (as a proxy of cognitive performance) as an observed measure in a post-hoc UKBB-specific analysis (in response to **R1.6**) and we find that its effects are independent from neuropsychiatric PGS (**Supplementary Figures 10-11**).
2. Our main analysis is not adjusted for years of education (in response to **R2.3** and **R4.2**) and we provide an exploration of how observed educational attainment may be mediating for example the association of ADHD PGS with some of the professions (**Fig. 6**, **Supplementary Figure 12**, **Table 1**).

We changed the wording from "Our results suggest that aggregated genetic liability for a diverse set of neuropsychiatric traits is associated with membership to most profession categories" to highlighting that our results show that most profession categories are associated with aggregated genetic liability for at least one neuropsychiatric trait. Looking at **Fig. 1**, this statement is now true since: a) there only 2 profession categories without associations "Healthcare support" and "Office and Admin support" and b) we have limited the analysis to exclude purely cognitive function traits as above.

It is unclear why the associations with traits of the psychopathology category are considered "spurious". We provide results from two independent cohorts with moderate correlation (Pearson's *r* ranges from 0.352 in CONTROLS and 0.55 in ALL; **Supplementary Figure 5**) and many of these associations are significant in both cohorts (**Supplementary Figures 3** and **4**) and survive multiple testing correction with the most stringent test (Bonferroni). Finally, our findings also replicate previously reported associations in a similar type of PGS-profession association (schizophrenia and bipolar disorder with "creative professions"; PMID: 26053403).

R1.4. There seems to be an effect of ADHD, with a reverse trends as observed for EA, and then an effect for the Art and Design category across different PRS.

After applying the revisions as proposed above the new summary of the revised results is as follows: "Arts & Design" displayed the most PGS associations. ADHD PGS was associated with more than two thirds of the professions, strongly mediated via observed educational attainment.".

R1.5. However, when looking in the CONTROL groups (supp figure 2 and 3), it looks like most of these latter signals for the psychopathology PRS are no longer significant. This is in contrast to the claim made in the main text that "many of the associations remained significant when individuals with mental illness diagnoses were excluded

(CONTROLS)". It looks to me that the main signal remaining consistently significant is for the EA PRS.

It does indeed look like there are a lot of significant pairs being lost when comparing ALL and CONTROLS within cohorts (now **Supplementary Figure 3 and 4**). However, it is important to note that in CONTROLS we have a considerable reduction in power for two reasons: a) the sample size drops by 44% and b) since we are removing individuals who have mental health disorders, we are also removing disproportionally more individuals with high PGS for those mental disorders (PMID: 31416338 and PMID: 36103194). Thus, these two analyses (ALL cohort vs. CONTROL group) should not be interpreted based on how many significant hits each one has but rather on how concordant the results are: the PGS-profession association log(OR) for ALL and CONTROLS are very strongly correlated (Pearson's r = 0.92; new **Supplementary Figure 1)**.

Despite the above limitations, in response to the reviewer's concern, we now also provide the number of significant results that are retained (22 out of 43; 51%) in lieu of using the expression "many of the associations". We have also included a brief version of this response in the revised manuscript for clarity.

R1.6. Therefore, while the authors have rightly controlled for different demographic features, it would seem worthwhile to control for other factors, e.g. IQ to test whether the effects of the psychopathology PRS remain significant after controlling for cognitive functions.

We thank the reviewer for this great suggestion, we have added a new section with this post hoc analysis in UKBB (we don't have intelligence information in MVP to do this study). In fact, we see that measured (not genetic liability) intelligence explains a good portion of the variance (**Supplementary Figure 11**). We cannot really discuss how many associations "remain significant" since unfortunately we only have fluid intelligence data for about 40% of the UKBB cohort. However, we find that the PGS-profession association log(OR) are largely unaffected when adjusting for fluid intelligence (**Supplementary Figure 10**) suggesting that the neuropsychiatric trait PGS has an independent effect.

R1.7. Instead, I thought that it was worth noting another pattern that was overlooked. Although not significant, I think it is interesting to look at the difference observed for the military category between the MPV and UK BB cohorts. While there is no signal for this category in the MPV (as expected given the demographic of this cohort, also pointed out by the authors at line 217) there seems to be a large OR for many PRS in the UK Biobank. What would this suggest?

In response to another reviewer's comment (**R2.7**), the military category has been removed from the analysis due to sample size constraints (which resulted in large OR with large confidence intervals).

R1.8. Beyond results interpretation, this observation raises the question of whether the cohorts used are good enough to carry out this type of analyses as these resources which undoubtedly are the current gold standard for genetic studies are affected by many demographic biases, e.g. at the point of recruitment and of participation (see Tyrell et al 2021 https://www.nature.com/articles/s41467-021-21073-y). This problem needs to be addressed in the current study in more details, discussing how it could have affected the results.

We thank the reviewer for bringing this up, we have added this important point as a limitation of our study in the discussion. Unfortunately, we don't feel confident to comment on how this could have affected the results in this context without engaging in speculation.

Reviewer #2 (Neuroscience, Complex Trait Genetics):
Remarks to the Author:
Overall feedback
This is a very interesting and timely study that examines the relationship between genetic architecture of neuropsychiatric traits and profession/jobs in two large population samples. The paper is well-written overall and analyses appear to be appropriate and carefully conducted. Additional strengths include the use of a large size replication cohort (MVP), the careful framing of the results (the authors are careful to not overstate the role of genetics in professional outcomes and also acknowledge a environment that the influence individual differences in professions), and the study design is more nuanced than overly simplistic dichotomies about the relationship between IQ, SES, and mental health that are sometimes found in the literature. Overall, I find the study design and findings to be of medium impact as communicated in the present state of the manuscript, and I thus have some specific suggestions on how to improve its suitability for publication.

We thank the reviewer for commending the strengths of this study and for providing constructive criticism which has resulted in an improved manuscript. We have incorporated all feasible analyses as proposed.

Major comments

R2.1. Some of the most significant findings concern neuropsychiatric PGS predicting Arts & Design professions; the results in Supplementary Figure 6 are very interesting. Please move this figure to the main paper and discuss in more depth.

In response to the reviewer's comment, we have moved this figure to the main text (now **Fig. 3**).

R2.2. Environment is addressed but the study design and literature do not really disentangle environment and SES. Please address.

In response to the reviewer's suggestion, we have added a series of secondary analyses where we explore the interplay of PGS-profession associations by performing adjustments for income brackets and location-based SES (**Supplementary Figures 15 - 17)**. As we are also noting in the discussion, these are not childhood SES proxies and as such are dependent on the outcome (profession categories) with significant differences among profession categories (**Supplementary Figure 13** and **14**). Thus, we are cautioning the readers to carefully interpret these analyses since as the reviewer highlights in **R2.3** they are susceptible to bias.

R2.3. Analyses using years of education as a covariate may result in collider bias. Please address this.

We thank the reviewer for bringing this important issue to our attention. In response, we added a theoretical example in the revised manuscript (lines **226-233**) where collider bias can be observed. However, we are not aware of any method that can conclusively prove the existence and quantify collider bias beyond simulation studies (PMID: 12859030 and PMID: 19689488). On the other hand, we were able to identify evidence for mediation (as also hypothesized in **R4.2**) of ADHD PGS effect on profession membership by years of education which accounts, on average, for ~55% of the total effect which we have included in the main manuscript. Finally, in response to this concern and **R4.2,** the main analyses now don't use years of education as a covariate and the readers are cautioned about bias in the secondary analyses where it does.

R2.4. Sex differences are known to influence at least two major factors here: participation bias (see for example Piratsu et al., 2021) and membership in professional categories. It is not sufficient to control for sex as a biological variable as the authors have done here. Sex-specific analyses are needed and please relate to larger literature.

In response to the reviewer's concern, we have included: a) the citation about sex-specific participation bias and b) a secondary sex-specific analysis (**Supplementary Figures 7-9**) in UKBB (in MVP females comprise a very small portion of the cohort). Indeed, we observe sex-specific effects despite moderate correlation in our PGS-profession log(OR) estimates. Overall, we find more significant associations in males when compared to females for which we were unable to find a support for a satisfying explanation (based on data beyond speculation) after ruling out systematic differences in power and effect size estimate distributions. It is important to note that we didn't find significant opposite effects so it is more a matter of presence/magnitude of the effect rather than the direction that is sex-specific. We also provide an example of potential sex specific effects that is supported by the literature and our data: "Arts & Design" - depression. The full results of the sex-specific analyses are provided for those who want to take a deeper dive; however, we believe that detangling these differences is beyond the scope of this study and is extremely challenging given that there is unequal distribution among profession categories despite the female and male population in UKBB being of equal proportions.

R2.5. It is not totally clear (to me) in the main analyses what the comparison groups are for each logistic regression; the PGS's for membership of a given profession is being compared to PGS's of whom?

We understand how this may have been confusing. We have revised the manuscript to make it clearer and we have added the main logistic regression formula in the legend of **Fig. 1**: $profession_i \sim PGS_j + age + age^2 + sex +$ ancestral PC1 to PC20 + genotyping batch (needed only for UKBB), for each of the 374 PGS_j -$profession_i$ pairs. So for each profession (membership = 1; non-membership = 0), the PGS of a trait (continuous variable with a normal distribution scaled to mean=0 and SD=1) is a predictor. The methods section has this information in more detail.

R2.6. Are comparison groups matched in age, sex, and local ancestry? I apologize if this information is stated and I missed it, but it needs to be a bit more clear in the figure legends, etc., and Results section.

As with the above comment, we have revised the manuscript for clarity. We are not performing matching but adjustment for age, sex and local ancestry. Based on the logistic regression formula (now also provided in the legend of **Fig. 1**), we use the following:

1. Age: covariates are age and age^2 (to additionally capture nonlinear relationships).
2. Sex: we use it as covariate and perform sex-specific analysis (as per **R2.4** above).
3. Local ancestry: local ancestry is accounted for by using as covariates 20 ancestry-specific population PCs. Of note, this is past the elbow at the scree plot with the PCA eigenvalues. The new default for the widely used PLINK2 tool is 10 PCs. So by using 20 PCs we feel confident that we are adequately controlling for local ancestry and we are more stringent than most studies controlling for ancestral PCs.

R2.7. Most of the analyses are quite well-powered, but the n's for the military profession are less than 100. Please justify power achieved or remove these. Also, the "Other" category seems to meaninglessly lump together whatever is leftover. I would suggest removing it.

We thank the reviewer for catching this limitation. As per reviewer's recommendation, we have removed the categories for the military profession and "Other" in the revised manuscript.

R2.8. What about familial influences on profession/genetic nurture? Could you address this with the addition of another genotyped dataset with family data and profession

info.? I think that additional data is needed to really establish the robustness of the results

This is an interesting point and it would be great if we could explore it. However, we don't have access to another genotyped dataset that would be well powered for a family study such as the one proposed.

R2.9. The literature cited is incomplete and many claims lack appropriate citations (see for example lines 196 to 210). Please substantiate/elaborate in relation to published literature.

We thank the reviewer for this suggestion. For the first main point in this section, referring to the "complex and dynamic interplay between genetic and environmental factors shaping the psycho-social identity of an individual", we cited two papers that leverage twin-based cohorts. The first (PMID: 26796983) examines the genetic heritability of several measures of creativity, and is described in more detail below. The second (PMID: 11138754) dissects additive genetic and nonshared environmental structures underlying personality traits measured by the Multidimensional Personality Questionnaire. For the second main point of this section, referring to professions "requir[ing] a variable combination of skills… and attitudes (a subset of which is captured by defined personality structures)", we cited two relevant papers from the industrial-organization and personality fields of psychology. These studies examine the relationship between FFM personality dimensions and overall job performance (PMID: 24016206; PMID: 21142341).

R2.10. Along similar lines, it will be also important for the reader to know whether the findings align and converge with results from phenotypic-only studies and from behavior genetics (family-based) methods.

We used the profession with most associations ("Arts & Design") to compare our findings with the literature. We compare our results with a phenotypic-only family based study (PMID: 21653945) which also found the association of creative professions with schizophrenia and bipolar disorder but not depression. A twin study from 2016 (PMID: 26796983) also demonstrated FFM openness and extraversion to be significant predictors of perceived creativity scores (measured by peer and self-report), and openness was also predictive of scores on a test of figural creativity and video-based observer ratings of participant creativity while performing verbal tasks. Leveraging this family-based design, the study additionally showed that a substantial proportion of genetic variance in video-based observer ratings and tested figural creativity scores could be accounted for by genetic variance in openness. This work also demonstrated the strong component of environmental factors in driving differences in the creativity-related metrics

examined. Such findings align with the positive association between FFM openness PGS and the “Arts & Design” category in our study, although FFM extraversion PGS was not significantly associated with this profession category in either of our cohorts.

R2.11. Please address value of creative professions in society in the Discussion (line 238).

We couldn’t find conclusive evidence in the literature supporting our previous claim. In response, we have revised that section of the discussion and deferred from making similar statements.

R2.12. The Verbal Tilt result is so interesting, especially since language/verbal skills have received far less attention than other complex cognitive traits. Please discuss role of language skills.

We agree with the reviewer that this is a very interesting topic. Our work on these cognitive dimensions was recently published (PMID: 36624241) and a lot of context is provided there. The verbal tilt (increased language performance compared to math), especially, is positively associated with “Arts & Design” which is covered in the cited manuscript. The negative association with “Computers & Math” and “Business & Finance” is a new finding but also expected since these are math heavy professions. Since there is limited space and there are 43 significant associations, we opted to focus more on associations with neuropsychiatric disorders as the main theme of this paper.

R2.13. Please provide more explicit justification about the use of the Lifestyle Survey. What is the validity and stability of its measures? Are the professions assayed here inclusive of all professions over the lifetime or only current?

This is a survey where among other questions, participants self-report their professional membership. We are not aware of any study that has benchmarked the validity and stability of its measures in regards to reported professional membership. However, when comparing self-report data (questionnaires) in MVP with observations recorded in the electronic health records, the self-reported data are reliable to a reasonable degree with mismatch rates as follows (PMID: 33117892): height 0.7%, weight 3.9%, date of birth 1.82%, gender 0.05%/2.07% for male/female respectively, and race ranging from 0.44% for Asian to 3.4% for White.

“Are the professions assayed here inclusive of all professions over the lifetime or only current?”. This really depends on how the participant chooses to answer the following question in the questionnaire: “Please mark the category that best describes your

principal occupation. If you are retired, please mark the category that best describes what you considered to be your principal occupation." (**Supplementary Table 29**)

R2.14. Please address ascertainment bias of the MVP cohort and how subsequent professions might be impacted by environmental or genetic influences on history of military participation.

In response to this comment, we have added ascertainment bias of the MVP cohort as an inherent limitation of our study in the revised manuscript.

R2.15. The ethics/social dimensions are incorporated somewhat (for example, on lines 204-205 and line 240-243) but need to be elaborated and the authors should cite relevant ELSI literature.

In response to this comment (in addition to **R1.1** and **R3.1)**, we have greatly expanded our coverage of ELSI considerations and literature in the revised manuscript.

R2.16. Please address potential mechanisms, including possible neural pathway explanations for the results.

This study attempts to provide a large-scale overview of the profession category landscape across many neuropsychiatric traits. It is beyond the scope of this study to attempt an explanation of the results with neural pathways. However, we have recently demonstrated (and we are including a reference in the revised manuscript) that e.g. ADHD PGS is negatively associated with both nonverbal and verbal reasoning test performance (PMID: 36702997) which provides some support for ADHD PGS being linked with neurocognitive phenotypes even in the absence of diagnosis.

Minor comments

R2.17. Please parse up the Method section into smaller paragraphs to facilitate readability.

In response to the reviewer's comment, we have updated the Methods section accordingly.

R2.18. In this context, I would prefer polygenic scores (PGS) rather than PRS; these are not disease phenotypes and risk factors.

As per reviewer’s valid recommendation, we have changed PRS to PGS in the manuscript. In addition, we have accordingly changed genetic liability to genetic likelihood.

Reviewer #3 (Bioethics):
Remarks to the Author:
Review of “Genetic liability for neuropsychiatric traits influences membership to broad profession categories” for Nature Reviews Genetics

Firstly, I found this paper rather hard to understand – no doubt that is because I am an ethicist and not a genomic scientist or statistician – but that made is quite hard for me to extrapolate the findings to ethics (or, to understand whether and where ‘ethics’ is relevant to this article). On the one hand, I think this is just another paper that is trying to work out exactly how useful PRSs are in understanding humans and social life. It’s not the first paper of its kind, nor will it be the last. Furthermore, it is certainly not the first paper that links psychiatric illness (or PRS for those) with creativity and as such neither the central premise of the paper, or its findings, is ethically novel or particularly disturbing.

We would like to thank the reviewer for providing feedback on the ethics consideration of our manuscript and the editor for engaging an ethicist in the review process. Firstly, we would like to note that our study has a much larger scale and scope than whatever has been previously done; it both covers all broad profession categories except military (in response to valid concerns raised by **R2.7**) and a wide range of neuropsychiatric traits. It may seem that we focus a lot on the “Arts & Design” profession category, but this is the profession category with a) most PGS associations and b) most existing studies that need to be addressed. Secondly, in the revised manuscript, we explore sex specific effects, and the interplay with observed fluid intelligence, educational attainment and SES proxies.

R3.1. However, I think that whilst individual papers of this kind are not in themselves particularly problematic, the broader quest to explain the human experience through PRSs, does raise important ethical questions. These relate to for instance the desirability of understanding ourselves increasingly in biological and not other terms, issues relating to stigma and discrimination, undesirable uses of this kind of evidence in future, problems of diversity and inclusion, and so forth. Thinking about a journal such as NHB, my feeling is that it is important to explicitly recognize that even if one paper does not raise all these issues, that the overall field does. One way of doing that is by actively inviting social scientists, ethicists and others to write commentaries on the desirability and future challenges of this kind of work. Another is the strategy you have already chosen – specifically invite people to comment on the ethical aspects of the work during peer review. Furthermore,
perhaps as editor you can signal in one editorial that there is this broader question about the relevance and desirability of this work that also needs to be interrogated.

In response to this comment, **R1.1** and **R2.15**, we have greatly increased our coverage of ELSI (ethical, legal and social implications) considerations and literature in the revised manuscript. Notably, we have expanded on the motivation behind this work and why we think that our study is critical in revealing the high level of pleiotropy governing neuropsychiatric risk variants but also quantifying the level of variation that they explain in complex traits such as profession category membership. There is a cyclicity in revisiting the human experience from biological vs. non-biological terms; even though both approaches are concurrently advancing it often seems that the spotlight is shining brighter on one of them. This is especially true for psychiatry which is currently (most likely) undergoing its third wave of biological psychiatry (PMID: 24046754). Science and technology often outrun the law and policy, and as technology enables new methods, addressing, the ethical considerations that arise become more pressing. We can either be reactive, or as the reviewer suggests, be proactive in discussing how these new technologies are employed. Our biological approach has merit since visiting neuropsychiatric disorders from a genetic perspective is valid; psychiatric disorders are heritable and e.g. schizophrenia's heritability (which is one of the highest) is estimated to be 79% in a recent large-scale twin study (PMID: 28987712). Thus, there is a biological component that cannot be ignored. For example, in our study we are now providing evidence for a potential issue: our data support the notion that individuals with high ADHD PGS (even without an ADHD diagnosis) are more likely to have shorter education which in turn mediates less access to high income professions (**Table 1;** not "rescued" by fluid intelligence) and as per prior literature increased chances for mid-to-late life somatic health conditions (particularly in cardiometabolic domain; PMID: 35399118). Studies such as ours suggest that it would be worth exploring changes in educational policy regarding accommodations, instruction and evaluation approaches, in a way that hopefully educational systems won't systematically penalize individuals with high ADHD PGS.

R3.2. W.r.t the particular paper:
One critical component in studies of this kind, I think, is how the data that is used to make the statements, is obtained. For example, this paper speak about how data about the 'oral vs verbal tilt' at school is predictive of professional membership later in life, but it wasn't clear to me a) whether the oral tilt data was derived from genetic evidence (i.e. was this one of the PRSs) or whether this was phenotype data available in the datasets. Perhaps your science reviewers will be able to understand this better, but in work of this kind, what matters a lot is whether the data that is used for these types of studies, was duly collected and explained. More contextualization of the evidence would have helped me to evaluate exactly how much importance to attribute to the findings reported in this paper.

We have revised the manuscript to make this more clear. In all cases, we are referring to genetic likelihood for these traits (PGS); the only phenotype data that we use are the following: a) age, b) sex, c) years of education, d) income, e) location-based SES proxies and f) fluid intelligence. We have also simplified the revised manuscript to not include PGS for neurocognitive traits (in response to **R1.3** and **R4.1**) that correspond to overall cognitive performance and educational attainment. Regarding the "oral vs. verbal tilt" at school, we are using genetic evidence (PGS) derived from our recent genome-wide association study performed in large population-based Danish cohorts (PMID: 36624241).

R3.3. Relatedly, there are obvious shortcomings with the collection of detailed phenotype data in endeavours such as UK Biobank that could confound the results. For instance, what if the people who have high PRS for psychiatric illness are also a bit chaotic and misremember educational performance, and the UK Biobank data collectors rely only on verbal information to capture their data; then that would skew the data that is subsequently used to make statements about PRS and educational performance. Yet those results will be used to build up a body of evidence that – over time – says that people who have high PRS for psychiatric illness may also be more creative. So in an article of this kind, it's very important that there is sufficient information about the kind of data that was used, how it was collected and what the risks or limitations are.

In the revised manuscript, we are listing participation bias (MVP and UKBB) and ascertainment bias (MVP) as inherent limitations of the study. We are not aware of any reason for which people systematically in the absence of a neuropsychiatric disorder (and we mitigate that by having a CONTROLS group with individuals that have no diagnoses of neuropsychiatric disorders) would misreport demographic information e.g. what educational qualifications they have completed or whether they finished high school or how many years of college they did. Regarding the quality of the data, there have been studies that have examined the reliability and validity of e.g self-report data (PMID: 33117892 for MVP) and cognitive tests (PMID: 32310977 for UKBB). The UKBB and MVP are well-resourced established biobanks with core teams that put a lot of effort in designing studies, collecting data and at times adjudicating them. No design is perfect but at least best practices are followed to the extent possible. In addition, these biobanks have extensively published their methods, questionnaires, tests, etc., and we are just secondary users of these data. Thus, beyond providing citations that readers can follow for more information, it would be outside the scope of this study to address whether self-reported data are of a concern beyond known limitations.

The reviewer employed the association of creative professions with psychiatric illness as an example but this is a good opportunity to state that in the revised manuscript we

expanded the comparison of our findings with existing literature (also in response to **R2.10)**. Especially the link between e.g. schizophrenia and bipolar disorder with creative professions is well established at this point with support from both epidemiological data and other genetic studies. We are highlighting it as a result not only because it is interesting but because a) the “Arts & Design" category is the profession with the highest number of significant PGS-professional associations and b) we can demonstrate that our approach replicates findings that have been epidemiologically identified.

R3.4. Line 216 on pg 7 of the pdf says that the European countries in which the biobanks that they used data from were based, have ‘global social mobility indexes among the top 30 in the world’. Is the aim of this statement to suggest that these findings may have relevance for global populations? That is how I read that sentence and that’s obviously very problematic – it doesn’t matter whether the countries are diverse; if the data is used is not, then the findings are not representative of diverse people. I’d question the authors on this.

The above information is given to highlight how the external validity of the study should be interpreted. Firstly, this study has reached conclusions only based on individuals of European ancestry in two countries (US and UK); this is due to the inability to apply our approach to other ancestries since there are no well-powered GWAS studies to be leveraged for PGS generation. Secondly, there needs to be a certain level of social mobility for this study to make sense (the higher the better); if there was no social mobility then all the offspring of farmers would become farmers and people’s professional membership wouldn’t be affected by e.g. years of education. Thus, the aim of the statement was to set reasonable expectations of the external validity of our findings; we would expect to replicate our results in e.g. Austria but it is unknown if similar findings would apply to Nigeria (predominantly African ancestry) or Moldova (European ancestry but much lower social mobility than the cohorts we studied).

R3.5. It wasn’t clear to me, in the paper, what the authors mean by ‘creative professions’, how they define those and what they stand in opposition to. This needs to be clarified and commented on in the discussion. E.g. does this only mean people who indicated that they work in the ‘arts and design’ professions in Figure 1? The authors obviously need to engage with that idea around ‘creativity’ in their discussion. Surely e.g. architects, teachers and academics are also hugely creative. If the authors’ choice is to use the term ‘creative’ for ‘people self-selecting as working in the arts & design profession’ then they need to explain what they mean by that and why that substitution is justified. Note that the category would include people in the arts & design professions who do non-creative jobs (e.g. management, administration, accounting, financing).

The definition that we use is based on reported job/employment/occupation and the profession category for the creative professions is “Arts & Design”. In detail:

- In the MVP, profession self-report is obtained by participants answering this question: “Please mark the category that best describes your principal occupation. If you are retired, please mark the category that best describes what you considered to be your principal occupation.” (look at **Supplementary Table 29** for available answers).
- In the UKBB, profession is obtained at the baseline Verbal Interview (look at **Supplementary Table 34** for available categories and how we mapped them to the ones in MVP).

By referring to “creativity” and “creative profession”, we have been using the same terminology employed by prior studies on the same topic (both epidemiological and genetic) that are cited in our manuscript. We agree with the reviewer that we shouldn’t conflate creativity with membership to the “Arts & Design” professional category and we have revised the manuscript accordingly. We still use the term “creative professions” when we are citing a study that is referring to a particular profession group as such.

R3.6. I did find the sentence that ‘risk variants… contribute to critical social functions’ (lines 236-238 on pg 8) to be odd. The authors did not establish that the people included in the ‘arts and design’ category perform a ‘critical social function’ – or explain what they mean by ‘critical’ here. How does the employment of people in the ‘creative professions’ improve the fitness of our population as a whole? That sentence is obviously nonsense – there is no way for the scientists to support that view with evidence (bearing in mind what geneticists normally mean with fitness). The interpretation of the findings needs to be commensurate with the evidence in this paper: here, narrowly, the authors provide evidence of correlation between A (PRS for psych illness) and B (people self-reporting as working in arts&design professions). They haven’t established causality; they do not know whether there may be confounding factors. And so they mustn’t speculate.

We thank the reviewer for raising this valid point. We couldn’t find literature support for our prior statement and we have revised the manuscript to refrain from speculation.

R3.7. I also think it is misleading to suggest that this paper ‘aims to reduce stigma’: it is neither really truthful nor likely to be possible for the authors to aim to have this effect. ‘Not truthful’ in the sense that they themselves seem to want to sensationalise their findings. For instance, instead of saying ‘people who self-self as working in the arts & design professions’ they say ‘creative professions’ and use terms like ‘creativity’. Those two are obviously not the same.

We have devoted a portion of the revised discussion to elaborate on how we think that our study aims to reduce stigma (also in response to **R1.1**). Regarding the use of the term "creative professions", its use is common practice in the field by both epidemiologic (e.g. PMID: 21653945) and genetic (e.g. PMID: 26053403) studies. However, we agree with the reviewer that this may come off as sensationalization so we have corrected it accordingly. Specifically, in the revised manuscript, we have refrained from using the terms "creative professions" and "creativity" except when citing papers that refer to it as such.

R3.8. Overall, with some adjustments to the Discussion and some greater explanations of a) what data they used and b) what the limits of that data are in terms of the researcher's ability to track 'creativity', I don't think this paper is likely to be more ethically controversial than other papers already published in this domain. I do think, though, that if the decision is to publish this article, it's important for NHB to also provide space (through soliciting commentaries or through editorials) to the bigger questions that this field raises, including questions about the biologisation of the human experience, the potential for stigma, and questions about equity and justice.

We thank the reviewer for providing feedback that increased our awareness of suboptimal language use in the manuscript and helped us enrich our discussion section.

Reviewer #4 (Social Science Genetics):

Remarks to the Author:
This study conducted an extensive set of analyses examining the association between genetic liability for neuropsychiatric traits and occupational choice in two large samples. The paper is overall interesting and I believe this is an important topic to study. I particularly liked the PCA of the regression coefficients that nicely illustrates the underlying patterns of the associations. However, while the authors discussed the complexity of occupational choice at length in Discussion, I did not find that this was fully considered in their own analyses.

We thank the reviewer for their constructive comments that assisted us in improving our manuscript.

R4.1. - The authors should make clear what educational attainment is in this context. Is it simply a sociodemographic variable that confounds the association if not accounted for, or is it a neuropsychiatric trait of interest? Currently, it is contradictory that the authors are using educational attainment for both. They do not provide sufficient discussion on this, while their results are substantially relying on educational attainment.

As the reviewer points out, in the original submission we were using both:

1) polygenic scores (PGS) for neuropsychiatric trait "Educational attainment" captured the genetic liability for educational attainment. The association of this PGS score with broad employment categories was then tested
2) self-reported level of education (sociodemographic variable) was used as a covariate in the association analysis of PGS for various neuropsychiatric traits with membership to broad employment categories.

To address the reviewer's concern (as well as **R1.3** and **R4.1**) and broad ethical considerations, we have removed the PGS based on the traits: "Educational attainment", "Overall school performance" and "Intelligence" from our analyses. Thus, we are retaining PGS for: a) neuropsychiatric disorders, b) personality domains corresponding to the five factor model and c) cognitive domains which, based on our recent study (PMID: 36624241), capture differential performance and can be associated with psychopathology (verbal and oral tilt at school). Furthermore, by excluding the aforementioned traits we avoid ethical pitfalls that have previously been documented about cognitive performance and education attainment genetic studies (summarized in lines **350-363**).

We still use self-reported levels of education as a covariate in a secondary association analysis and, as per suggestion below, we present both the unadjusted and adjusted association results in the revised manuscript.

R4.2. Also, I believe the authors should carefully think about whether (or why) they should control for educational attainment (years of education). They noted that they controlled for education "due to different requirements of profession categories". This is actually a reason not to control for education since this implies that education is one of the mediating paths through which genetics contributes to occupational choice. The authors are removing this important source of variation in occupational choice that they should be interested in. If they have to control for education, the reason should be that educational attainment is an indicator of one's socioeconomic background that may confound how genetic liability for neuropsychiatric traits influences occupational choice. However, just as the authors also used educational attainment as a neuropsychiatric trait, educational attainment is more than just a socioeconomic indicator in that it also reflects a number of important behavioral traits. Currently, the manuscript does not pay much attention to this. Since education can be both a mediator and a confounder of great importance in this context, the authors should report results with or without controlling for education and provide careful interpretations.

We thank the reviewer for his insightful comment. Our main motivation for adjusting for education was to:

1. better harmonize the association effect sizes from MVP and UKBB to improve our meta-analytic approach across cohorts. We hypothesized that different educational requirements for certain professional categories in UK vs. USA (e.g. physicians, lawyers etc.) would decrease the comparability of our results. However, it is important to note that after trying all PGS-profession association models (described in this study), the correlation is best when using the base model (Pearson's r = 0.55); for comparison, in the base model + EA, Pearson's r = 0.39.
2. estimate direct and not total effect of PGS on profession in an attempt to capture individual preference vs. inability to meet requirements.

Based also on the reviewer's suggestion, we thought that this would be a great opportunity to demonstrate and quantify the mediation by years of education. While looking at how adjusting for observed years of education affects the variance explained across PGS-profession pairs (**Supplementary Figure 12**), the associations based on ADHD PGS (**Fig. 6**) were the most promising. Indeed, we found that years of education mediated most of the significant (in **Fig. 1**) ADHD PGS-profession associations in at least one cohort.

To address the reviewer's concern (and **R2.3**), we now provide both adjusted and unadjusted results.

R4.3. In the variance partitioning analysis, I do not think we can simply state “Other demographic covariates accounted for a much bigger fraction of the variance” without considering a finite sample size of GWAS from which the PRS was derived from. The variance explained by the PRS can be underestimated because its predictive power is lower than it could potentially be. The authors should have used a bias correction method (such as https://www.nature.com/articles/s41562-021-01119-3 or https://www.biorxiv.org/content/10.1101/2021.04.09.439157v4) or at least noted this attenuation bias of the PRS as a limitation for this analysis.

We thank the reviewer for pointing out this limitation in our study. As we recently documented (https://doi.org/10.1101/2022.04.28.22274437), the level of phenotypic misclassification also affects the predictive power of derived PRS. Given the complexity of addressing this issue, we have revised the manuscript to note attenuation bias of the PGS as a limitation for this analysis.

R4.4. The most recent GWAS of educational attainment (published in March 2022) showed that the previous coding of years of education in the UKBB does not properly capture different levels of education in a linear index and therefore revised the coding. Since the authors constructed years of education based on this previous coding, they are not sufficiently capturing the variation in education in the UKBB. It is important to use a proper coding here because the authors report and discuss results that critically rely on the quality of education variable, in particular the variance decomposition. The reason that years of education explained a smaller fraction of the variance in the UKBB compared to MVP could simply be this imprecise coding of years of education in the UKBB. Therefore, I would suggest that the authors use the revised coding of years of education for the UKBB. I would also be cautious about interpreting the cross-cohort differences.

We thank the reviewer for bringing this to our attention. We have rerun the analyses with the revised coding of educational attainment. We are also refraining from drawing conclusions based on variance explained by education when comparing the two different cohorts.

R4.5. Since each PRS was standardized, the PCA of the PRS coefficients could be driven by a few PRS from disproportionately larger GWAS than the others. I do not think this is an issue that invalidates this analysis, but they should discuss the implications of using the standardized PRS coefficients in this analysis.
We agree that when GWAS of two different traits have considerably different sample sizes and power, the study with larger power has a larger influence on the PCA. This is expected and ensures that the PCA is driven by the signal in the GWAS, rather than

equally weighting all studies. In general, we agree that scaling of features can affect PCA loadings. However, we perform a two step approach here: we have scaled the PRS in the original logistic regression analysis, and then perform PCA on the matrix of log ORs. In this case, scaling the PRS does not introduce artifacts in the PCA. We thank the reviewer for their constructive feedback. We have added a note “Of note, PGS loading magnitude also depends on source GWAS power and that should be taken into account when comparing loading magnitude between traits” in the figure to address this comment.

R4.6. I could only find out the authors partitioned the variance of predicted liability for occupational membership by following the github link in the supplementary text. This is a key detail of this analysis that should be explained in the main text.

We thank the reviewer for pointing out this important issue. We have added a section in the Methods termed “Estimation of variance explained” that outlines our approach. Since the original submission, the method has been implemented in the `calcVarPart()` function of the variancePartition R package which is available on Bioconductor.

R4.7. The last paragraph for discussion is too long and should be split.

We thank the reviewer for bringing this to our attention. While incorporating necessary points for this revision, the discussion section has expanded and is now split in 4 paragraphs.

Dear Drs. Radzvilavicius, Kousta, and reviewers,

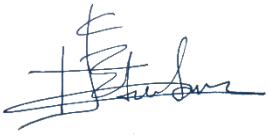
Thank you for the opportunity to submit a revised manuscript for your consideration for publication in Nature Human Behaviour and for your efforts in conducting a well-rounded review that takes also into account the ethical challenges of this line of work. Integrating the editorial recommendations and addressing the reviewers' concerns has resulted in a much-improved manuscript that provides a deeper exploration of the potential genetic basis of membership to profession categories while addressing ethical, legal and social implications of this work.

We hope that our revisions and additions adequately address the concerns of the reviewers. Our responses to their individual comments follow.

Thank you for your consideration.

Sincerely,

Panagiotis Roussos, M.D., Ph.D.
Endowed Professor of Translational Psychiatry
Professor of Psychiatry & Genetics and Genomic Sciences
Director, Center for Disease Neurogenomics
Icahn School of Medicine at Mount Sinai
Investigator, VA/MIRECC
Director, Center for Precision Medicine and Translational Therapeutics
James J. Peters VA Medical Center



Georgios Voloudakis, M.D., Ph.D.
Associate Professor of Psychiatry, Genetics and Genomic Sciences & Artificial Intelligence and Human Health
Director, Translational Bioinformatics and Precision Therapeutics Group, Center for Disease Neurogenomics
Icahn School of Medicine at Mount Sinai
Investigator, VA/MIRECC
Associate Director, Center for Precision Medicine and Translational Therapeutics
James J. Peters VA Medical Center

Editorial requests

I am attaching a marked up word file with our preliminary edits and requests.

Thank you for a lot of constructive feedback. All points have been integrated and addressed except for:

- **Suggestion in Ln 258**: Bonferroni-adjusted two-tailed p value < 0.05 is a requirement for consideration (filtering approach), the full list of p values can be found in Table 1.

In addition to the comments provided by reviewers and our suggestions in the attached manuscript file, we ask that you:

1. Following examples of FAQs on Human Genomics Studies (https://www.thehastingscenter.org/genomic-findings-on-social-and-behavioral-outcomes-faqs/) include a list of FAQs to minimize the risk of misinterpretation as part of your SI.

Thank you, a FAQs document is provided in the revised submission at the end of the Supplementary Information. Please note that we requested and received permission from Dr. Daniel Benjamin to quote some sections of their FAQ for SGAC papers and in particular from Okbay et al. (2022), “Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals” published in *Nature Genetics* (see uploaded communication). We assumed that it is possible to reproduce sections with permission and attribution by Dr. Benjamin since both journals are part of the Nature Portfolio. If this is an issue please let us know. A copy of the approval communication with Dr. Benjamin is also attached as a pdf file.

2. Since your approved UKB application summary for project 18177 does not cover social phenotypes, we ask that you seek additional approval from UKB for this specific study of social and psychiatric phenotypes. Please share both MVP and UKB approvals with us.

Thank you, we have taken the appropriate steps to comply with the editorial request:

- For MVP please find the manuscript approval by the MVP publications team
- For UKBB, we had the scope extension request approved on 2023-11-30 and are attaching the manuscript approval.

3. Discuss limitations and contextualize effect sizes transparently from the very start, i.e. Abstract and Introduction.

Addressed in the revised abstract and introduction.

In sum, we invite you to revise your manuscript taking into account all reviewer and editor comments. We are committed to providing a fair and constructive peer-review

process. Do not hesitate to contact us if there are specific requests from the reviewers that you believe are technically impossible or unlikely to yield a meaningful outcome.

We hope to receive your revised manuscript within two months. I would be grateful if you could contact us as soon as possible if you foresee difficulties with meeting this target resubmission date.

Thank you for your patience, for providing constructive feedback, and for being available to address our questions towards improving this manuscript.

With your revision, please:

• Include a “Response to the editors and reviewers” document detailing, point-by-point, how you addressed each editor and referee comment. If no action was taken to address a point, you must provide a compelling argument. When formatting this document, please respond to each reviewer comment individually, including the full text of the reviewer comment verbatim followed by your response to the individual point. This response will be used by the editors to evaluate your revision and sent back to the reviewers along with the revised manuscript.

Please find enclosed. In addition, there have been some unanticipated changes resulting from feedback from the UKBB Scientific Team and our final check of our analyses:

1. While making one last pass of our results we realized that we had an allele flipping issue with the anorexia nervosa summary statistics in the PGS analyses of one of our cohorts, we have made all necessary changes and have updated all relevant tables and figures. Overall, these corrections show a very minimal improvement of our results.

2. We received the following feedback from the Scientific Team of the UK Biobank “The health related/ public health impact should be discussed in the discussion, but we also require it in the abstract as most of our participants are unable to access manuscripts, and this ensures it is clear to all who look at the paper how it fulfils our criteria of health related and in the public interest.” Thus, we have complied with the request and made the necessary changes in the abstract to address requirements from both the UKBB and the editorial team. Please note that the current abstract exceeds the 150 word limit (currently 195 words), but we think that all the included information is either important or required.

• Highlight all changes made to your manuscript or provide us with a version that tracks changes.

All changes in the main manuscript are highlighted in red.

Reviewer #1:
Remarks to the Author:

I thank the authors for having addressed the comments raised by myself and the other reviewers. I think that the manuscript has greatly improved.

Thank you for your constructive feedback.

However, I am still concerned that the results have been affected by too many biases and limitations intrinsic to the cohorts used. I do not think there is much that can be done about this and I note that biases are acknowledged in the discussion.

Thank you for your understanding.

I am still unconvinced by the motivations underlying this study which risks to be badly misinterpreted. The final paragraph provides some justifications and applications of the results (i.e.in PGS-assisted preimplantation embryo selection and drug development). I do not think the results presented here contribute to such applications and I suggest rewriting this final paragraph which still hyper-sensationalize the results.

The relevant sections with perceived hyper-sensationalization have been removed as per the reviewer's concern and editorial recommendation.

I agree with the suggestion of reviewer #3 that, in case of publication, this paper needs to be paired with expert commentaries and/or editorials to avoid misleading interpretations.

This is an excellent idea if the journal can accommodate this.

Reviewer #3:
Remarks to the Author:
The authors have very carefully revised the paper and addressed all of my previous comments. The end result is excellent and I look forward to seeing this interesting paper published.

We thank the reviewer for their positive feedback.

Reviewer #5:
Remarks to the Author:
The authors adequately addressed my previous concerns. I only have minor comments about the mediation section (Interplay with observed educational attainment and socioeconomic status proxies).

I noticed that the authors wrote "causal mediation model" here. However, there is nothing causal in their analysis and what they did is really a conventional (statistical) mediation analysis. Identifying causal mediation effects requires a series of assumptions (sequential ignorability) that are difficult to satisfy with observational data.

In order to avoid confusing readers, I would drop the word “causal” here (in the table notes, too).

Thank you for raising this important point, we have incorporated the proposed changes.

It is great that the authors discussed potential collider bias. However, I think the collider bias scenario is more likely and relevant for SES proxies than EA. The example of physicians is nice, but for most of the professions, EA is more likely to act as a mediator than a collider. On the other hand, SES proxies are likely to be a collider, especially income (PGS → occupation → income ← PGS). Some statistically significant associations that were found here but not found in the primary analysis (or those with stronger associations) could just be an outcome of introducing collider bias. I would suggest that the authors discuss the collider bias at the end of this section, covering both EA and SES.

Thank you for raising this important point, we have incorporated the proposed changes. We have added the provided collider bias example in the SES proxy analysis results section and additionally refer to it in the discussion.