nature portfolio

Peer Review File

Cognitive processing speed and accuracy are intrinsically different in genetic architecture and brain phenotypes

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

Overview: This study uses Genomic SEM to investigate the genetic architecture of cognitive processing speed and accuracy. The authors perform several follow-up analyses that compellingly show that these are two distinguishable constructs and add to the existing literature by pointing to the different biological substrates (e.g., white matter functioning) and external correlates (e.g., psychiatric disorders) that differentiate the two along with elucidation of causal pathways using MR. Overall, the follow-up analyses are very well presented, and the authors should be commended for putting together a strong set of findings. The manuscript is also very well-written and the use of Genomic SEM to extract more reliable signal via the latent factors for CPS and CPA is very sensible and in line with the long-standing tradition in cognitive science to utilize SEM more generally to remove task-specific variance. My primary concerns are around how to structure and report the Genomic SEM analyses to be most informative and whether the currently presented model fits the data or is the most appropriate.

Major points:

This is my largest critique, but I don't know that an EFA is the way to go here given the long-standing theory that is being tested that CPA and CPS are different constructs. Why not start with a CFA that splits accuracy and speed on two factors? EFA is only necessary when there is a lack of existing theory. In this proposed CFA, I would allow residual correlations for any measure from the same task. For example, I would guess that RT speed and accuracy both load on Factor 1 in part because they share some task-specific variance. However, if you allow for the residual correlation between these two measures in a model where RT speed loads on a Speed factor and RT accuracy loads on an Accuracy factor then this circumvents this issue. It might be that this proposed CFA model fits slightly worse than your EFA model, but this provides a cleaner test of the hypothesis at hand and if it still fits the data well that would provide a much more compelling test of the theory than the current model where F1 still includes some accuracy measures. For example, in the discussion the authors interpret the lower genetic correlation between F1 and simple reaction time as indicating meaningful genetic divergence, yet this could also reflect "contamination" of the accuracy measures on this factor:

"Utilizing a GWAS summary 316 with the most significant SNPs from these studies, we found a moderate genetic correlation between reaction time with the composite measurement of CPS (rg = 0.70), signifying a different genetic basis between the CPS and simple reaction time."

Moreover, when the authors report model fit in the method section the CFI of .466 is way below the suggested cut-off of .9 and indicate that this is not a good model to use, which limits interpretability of the follow-up analyses.

I would not report heritability for latent factors from Genomic SEM. You need to be careful about what sample size is used as the heritability estimate is very sensitive to sample size. Summing across all the sample sizes for the cognitive traits is inappropriate given residual genetic variance in the factor model. Backing out the sample size implied by the GWAS is possible, but the author's do not report whether they did this or not. The Z-statistic of the heritability is not contingent on sample size and can be a more straightforward statistic to report as to whether there is significant genetic signal.
"The SNP heritability was estimated as h2 = 0.1838 (0.0069) for CPS and h2 = 0.1876 (0.0074) for CPA using the LDSC method."

Did the author's estimate the QSNP heterogeneity statistic for the factors and remove those SNPs from factor hits?
"Subsequently, a confirmatory factor analysis was employed to estimate SNP effects for the identified CPS and CPA factors (Fig 1b)."

Standardized estimates should be shown in panel A of figure 1 to improve interpretability (e.g., the residual genetic variance estimates could be directly interpreted as the proportion of SNP-based heritability not accounted for by the factors).

The genetic correlation analyses with related phenotypes (cognitive, brain measures) should be performed in the context of the factor model as opposed to using LDSC with the factor summary statistics. The reason is that LDSC will give a deflated estimate of the true genetic correlation because multivariate GWAS summary statistics are estimated with some error as it can include some task-specific variance that does not conform to the factor (which is why the QSNP statistic was developed), while a genetic correlation estimated between F1 and F2 in the context of the model is not biased in this way.

Minor points:

I think this part of the second sentence from the abstract assumes a level of background knowledge in cognitive psychology that may not be appropriate for the general audience at this journal:
"The initial use of these two measures is probably a generalization from empiricism…"

This is an opening sentence in the Introduction is again a little technical and dense for this outlet:
"Behavior that meets the requirements of the specific scene within a reasonable time window is considered a normal cognitive performance, which probably is the empirical perception of the two most common measures, namely response time and accuracy."

This sentence in the abstract is missing a word (or something) after CPS and CPA:
"We found distinct neuroimaging signatures for CPS and CPA that white matter microstructures were predominantly associated with CPS, while cortical volumes were preferably related to CPA."

Given extreme polygenicity for human complex traits in general I don't know that any given SNP (outside of a rare few examples; e.g., APOE) is going to be individually meaningful.
"However, due to limited sample sizes (ranging from n = 1,311 to 32,070), these studies may lack the statistical power to detect meaningful SNPs."

Significant genetic correlations do not by themselves suggest high intercorrelations given GWAS sample sizes that can be quite large and still produce significant estimates for small rg. A mean (or median) and range of point estimates would be more informative here.
"Utilizing linkage disequilibrium score regression (LDSC), the genetic correlation showed 73 significant estimations among all 91 trait pairs (Figure S1), suggesting high intercorrelation with those cognitive phenotypes."

It seems a bit strange that CPA and CPS could be negatively correlated at -.69 but show correlations with EF that are the same direction and magnitude. It would be good if the authors could confirm that the directionality (+/-) on all of these genetic correlation point estimates are correct.

I'm not sure Figure 3a adds much beyond Figure 1b. I understand that 3a is now the SNP-to-gene results, but ultimately they are close recapitulations of one another and there is not much to be gained from Manhattan style plots to begin with (though I do think 1b is worth including as the Miami plot to visualize the divergence in genetic signal across CPS and CPA).

Figure 3d includes acronyms that are not defined in the figure legends or note (e.g., LGN_lnh_LAMP5). The forest plots across the Figure 3b, c, and d are also quite hard to interpret as they don't have a y-axis and are sort of tacked on underneath the bar plots.

It seems like the genetic correlation CPS and CPA and health-related traits is better placed right underneath the brain correlations section so there is consistency in level of analysis. It currently goes genetic correlations -> enrichment -> genetic correlations.

Reviewer #2 (Remarks to the Author):

Li and colleagues used previously published GWAS summary statistics to reveal differential genetic architecture underlying cognitive processing speed and accuracy, which can be replicated by the ABCD cohort. Follow-up functional annotations found two cognitive properties were associated with different neurobiological pathways and neurodevelopmental stages. This is an interesting study. The statistical approaches are sound, results seem robust. However, I still have some major comments. Hopefully, the authors can address these issues.

1. Page 6. The authors employed a battery of 14 cognitive metrics in their study, most of which appear to assess both the speed and accuracy of cognitive task execution. However, fluid intelligence, among these metrics, seems to encompass both processing speed and accuracy. It would be valuable for the authors to clarify why they included fluid Intelligence in their genetic analysis, considering its dual reflection of processing speed and accuracy.
2. In Figure 1, The authors presented genome-wide association results for two cognitive components. They not only described the results obtained at the conventional threshold of 5e-8 but also provided insights into genetic associations at a less stringent threshold of 1e-5. Previous literature extensively suggests that the 5e-8 threshold adequately controls for false positive results. It becomes imperative to address multiple testing issues across phenotypes. For example, it might define independent genetic loci at a threshold of 2.5e-8 (half of 5e-8) and proceed with subsequent functional analyses.
3. Page 7. The methods and results sections did not address the handling of the major histocompatibility complex region on chr6 and the region from chr17:40000000-47000000. Both of these genomic regions contain complex genetic structures, which could potentially lead to false positive results in genetic analysis. Regarding the latter region, despite extensive literature linking it to variations in brain functional structure, its large inversion may introduce spurious associations, particularly in genetic analyses concerning brain structure. Therefore, I suggest excluding these genetically complex regions from subsequent functional annotation (such as gene-level analysis, downstream signaling pathway analysis, and genetic correlation analysis) to mitigate potential confounding effects.
4. Page 8. The authors tested genetic correlations between CPS/CSA and cognitive skills. Since the authors have derived GWAS results for two independent cognitive components, it would be interesting to examine whether there is a genetic correlation between these two components. This analysis could shed light on whether the independent cognitive components manifest distinct genetic underpinnings or if there exists a shared genetic basis underlying both phenotypes.
5. Line 8, Page 8, “not significantly less than 1, corrected $p > 0.05$)”. Is it a typo? Should be corrected $p<0.05$? In addition, the authors might need to indicate the exact p-values for all of the statistic results.
6. Page 9. The authors used publicly available GWAS results for brain gray matter and white matter structures to examine their genetic correlations with two cognitive components. The UKB dataset also offers GWAS results for brain function, where brain functionality is segmented into 25 or 100 independent functional components, each subjected to GWAS analysis. However, the authors did not investigate the genetic relationships between the two cognitive components and brain functionality. It could be insightful for future studies to explore the genetic correction between these cognitive components and brain functionality, potentially uncovering novel insights into the genetic basis of cognitive processes and brain function.
7. Page 9. The author tested genetic correlations between two cognitive components and lots of brain measures. However, I am not sure whether all of the brain measures tested were significantly heritable. I guess it could not make sense to explore genetic correlations with non-heritable brain measures. I am not sure how the authors deal with this issue.

8. Page 9. The author tested genetic correlations between two cognitive components and regional brain volumes, cortical thicknesses, and surface areas. Cortical thickness and surface area are by-products of brain volume. I guess testing brain measures with overlapping structural characteristics could increase the burden of multiple tests.
9. Page 9. The author only provided the number of brain regions genetically correlated with the two cognitive components without describing the spatial distribution of significantly associated brain regions. The significance of this article lies in mapping two independent cognitive components onto the brain and exploring which brain regions are involved in cognitive processing speed or accuracy. However, the author only mentioned that the brain regions associated with the two cognitive components exhibit distinct patterns. These general descriptions are not helpful in understanding the neural basis of cognition, a detailed spatial distribution of the significantly correlated brain regions would provide deeper insights into the specific brain networks underlying cognitive processing speed and accuracy.
10. Page 10. The authors investigated the biological pathways associated with the cognitive components using predefined gene sets. However, they only reported the significantly enriched biological pathways without listing all the tested pathways along with their corresponding significance p-values in the main text or supplementary materials. It would be beneficial for the authors to provide a comprehensive list of these pathways and their significance p-values. This would enable readers to gain a more in-depth understanding of the molecular processes implicated in these cognitive components.
11. Page 12. The authors appropriately corrected for multiple comparisons in each genetic analysis, which is great. However, many analyses did not specify the exact correction method used; rather, they simply listed significant results as "corrected $p < 0.05$". It would be beneficial for the authors to explicitly state the specific correction methods used in all genetic analyses throughout the manuscript and provide the corresponding p-values to ensure transparency in the study's findings.
12. Page 13. The authors found that, for most of these cognitive traits, the absolute value of the correlation was higher with cognitive processing accuracy (CPA) than cognitive processing speed (CPS), by using a standard t-test formula. I'm not sure why the authors didn't compare the differences in genetic correlation coefficients between CPA and CPS at the group level. The standard t-test formula used in the study seems to calculate differences between two R-values based on their respective standard errors, but this method appears somewhat unreasonable.
13. Page 15. The authors utilized the PRSice-2 method to generate polygenic scores, but this approach heavily relies on threshold selection and genomic clumping thresholds, and it exhibits poor performance in predicting phenotypes. I suggest that the authors consider using threshold-free methods to generate polygenic scores, such as using PRS-CS. This would allow for the validation or replacement of the current study results, resulting in more robust findings.
14. Page 15. The last section of results. It appears that the ABCD cohort includes cognitive function metrics related to cognitive processing accuracy and processing speed. It would be beneficial for the authors to explore associating the polygenic scores with these dimensions of cognitive scores within the ABCD dataset to validate the current findings.

Dear Editor and Reviewers,

We are submitting a revision of our manuscript entitled “Cognitive processing speed and accuracy are intrinsically different in genetic architecture and brain phenotypes” (NCOMMS-24-14796A). We highly appreciate the thoughtful comments and constructive suggestions provided by the reviewers, which greatly helped improve the quality of our manuscript. We appreciate your patience, professionalism, and responsibility.

We revised our manuscript by closely following the comments and suggestions. Three major changes were made in the revision as follows. 1) In response to the reviewer's comments, we optimized the initial CFA model and achieved a better fit. We also estimated QSNP heterogeneity statistics and excluded SNPs with heterogeneity. Additionally, we considered multiple comparison corrections for the two factors, using a threshold of $2.5e^{-8}$ for subsequent enrichment analyses. We updated all relevant results, and the new findings were similar to the previous ones, with the overall conclusions remaining nearly unchanged. 2) We updated the method for estimating genetic correlations. We now estimated the genetic correlation between the two factors and other phenotypes within the updated CFA model. While the significance levels of some results have changed, the overall conclusions remained consistent. 3) We used the reviewer-recommended PRS-CS to reanalyze the PGS and updated the entire PGS analysis results. Given the substantial update of results, we have thoroughly revised the article based on the updated results. We have also carefully addressed all other concerns, regarding rephrasing, typos, clarification, and improving the visualizations of findings recommended by the reviewers in the revised manuscript.

In the response letter below, we reproduced all comments in blue and provided one-to-one responses. We also highlighted the changes in the revised manuscript with annotations (R1Q1, R2Q1, etc. See “Related Manuscript” for the article containing the annotations) corresponding to the following labels. We hope that the revised manuscript meets your journal’s standards, and again, we sincerely thank you for your help in improving our work.

Best Regards,

Dan Wu on behalf of the authors

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

Overview: This study uses Genomic SEM to investigate the genetic architecture of cognitive processing speed and accuracy. The authors perform several follow-up analyses that compellingly show that these are two distinguishable constructs and add to the existing literature by pointing to the different biological substrates (e.g., white matter functioning) and external correlates (e.g., psychiatric disorders) that differentiate the two along with elucidation of causal pathways using MR. Overall, the follow-up analyses are very well presented, and the authors should be commended for putting together a strong set of findings. The manuscript is also very well-written and the use of Genomic SEM to extract more reliable signal via the latent factors for CPS and CPA is very sensible and in line with the long-standing tradition in cognitive science to utilize SEM more generally to remove task-specific variance. My primary concerns are around how to structure and report the Genomic SEM analyses to be most informative and whether the currently presented model fits the data or is the most appropriate.

Major points:

R1Q1. This is my largest critique, but I don't know that an EFA is the way to go here given the long-standing theory that is being tested that CPA and CPS are different constructs. Why not start with a CFA that splits accuracy and speed on two factors? EFA is only necessary when there is a lack of existing theory. In this proposed CFA, I would allow residual correlations for any measure from the same task. For example, I would guess that RT speed and accuracy both load on Factor 1 in part because they share some task-specific variance. However, if you allow for the residual correlation between these two measures in a model where RT speed loads on a Speed factor and RT accuracy loads on an Accuracy factor then this circumvents this issue. It might be that this proposed CFA model fits slightly worse than your EFA model, but this provides a cleaner test of the hypothesis at hand and if it still fits the data well that would provide a much more

compelling test of the theory than the current model where F1 still includes some accuracy measures. For example, in the discussion the authors interpret the lower genetic correlation between F1 and simple reaction time as indicating meaningful genetic divergence, yet this could also reflect "contamination" of the accuracy measures on this factor:

"Utilizing a GWAS summary 316 with the most significant SNPs from these studies, we found a moderate genetic correlation between reaction time with the composite measurement of CPS (r_g = 0.70), signifying a different genetic basis between the CPS and simple reaction time."

Moreover, when the authors report model fit in the method section the CFI of .466 is way below the suggested cut-off of .9 and indicate that this is not a good model to use, which limits interpretability of the follow-up analyses.

Response: Thank you for your insightful feedback. While we fully understand your concerns from a classic cognitive science view, please allow us to explain our rationale for the current study design. Although some cognitive measures were labeled as "accuracy" or "reaction time" by name, they may actually reflect cognitive ability from another domain. For instance, in this task RT_acc was defined as "Mean time to correctly identify matches", and thus it essentially measures cognitive processing speed. Therefore, we first used Exploratory Factor Analysis (EFA) to determine how tasks load on the two abilities and then calculated cognitive processing speed and accuracy based on these loadings. This data-driven approach may reduce biases stemming from subjective assumptions.

We further fitted and compared two models. As the reviewer predicted, the data-driven model showed a better fit, while the hypothesis-based model performed worse (AIC = 1197 V.S. 4098, CFI = 0.999 V.S. 0.997, SRMR = 0.07 V.S. 0.12; Fig S5). Moreover, the correlation between F1 and F2 was lower using the data-driven model than that using the hypothesis-based model, indicating less dependence between the two extracted factors with EFA.

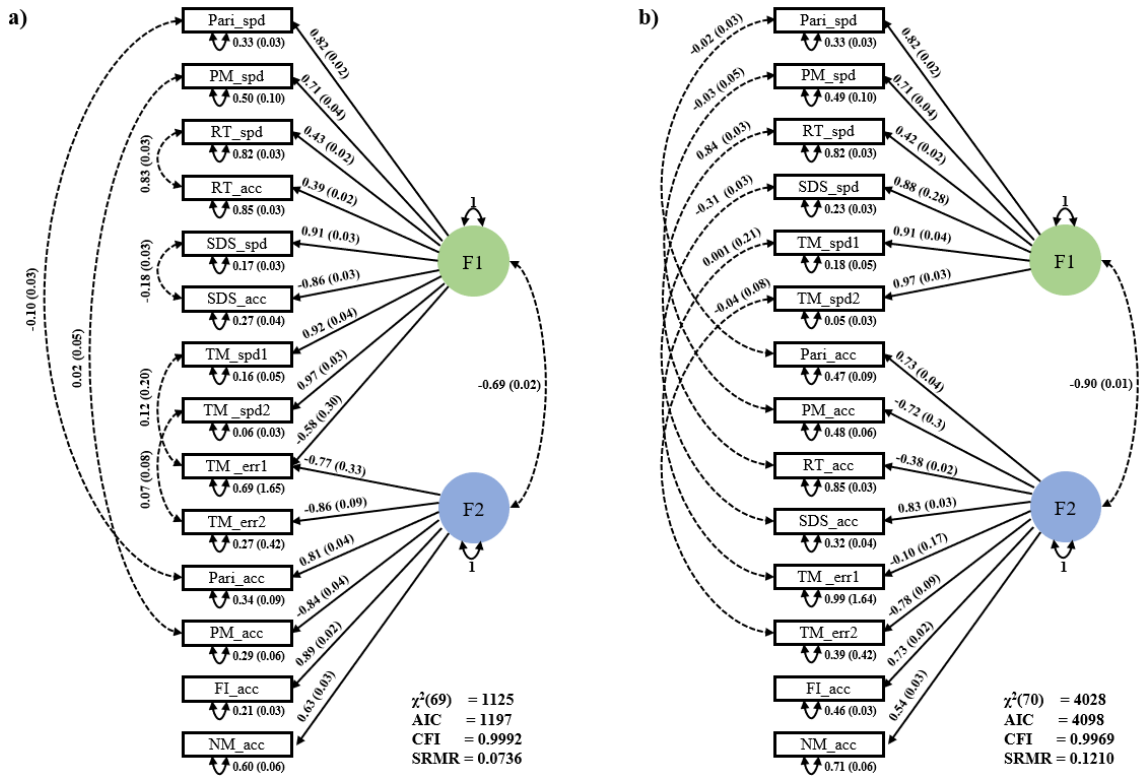


Figure S4. Comparison of two confirmatory factor models: a) Model based on loadings from exploratory factor analysis, b) Model based on a priori assumptions with loadings on accuracy and reaction time of cognitive tasks.

Therefore, we further conducted genetic correlation analyses between the factors obtained from the two models and the cognitive components reported in previous literature (Table S7). Notably, the genetic correlation between the Factor 1 obtained using a data-driven framework and previously reported reaction time [1] is 0.55 (se = 0.02), whereas the correlation between Factor 1 obtained using a hypothesis-driven approach and reaction time is 0.50 (0.02). This result indicated that the component obtained through the data-driven method shows a comparable (if not stronger) association with reaction time compared to the hypothesis-driven result, and also pointed out that the difference between Factor 1 and reaction time is unlikely due to the contamination of accuracy measures.

Additionally, we greatly appreciated the reviewer's suggestion. We incorporated residual correlations between tasks in the model, which improved the final model fit, achieving a CFI of 0.999 (Fig S4).

Based on these results, we would like to retain the data-driven framework for analysis in our study. Nevertheless, we found the comments to be very helpful, and we have added a

comparison of the two models in the methods section and explained our reasons for using the data-driven model.

Methods section: “We further compared the data-driven EFA results with another CFA model purely based on hypothesis, where the F1 factor only included items measuring reaction time, and the F2 factor included items measuring accuracy. This model showed a lower goodness-of-fit compared to the data-driven results (Fig S4), which might be because although some cognitive measures were labeled as “accuracy” or “speed” by name, they may reflect cognitive ability from another domain. For instance, “RT_acc” which was defined as “mean time to correctly identify matches”, inherently reflects cognitive processing speed. Therefore, we chose to use the data-driven framework for the following analysis in our study. We also conducted genetic correlation analyses between the factors obtained from the two models and the cognitive components reported in previous literature (Table S7) and found that the genetic correlations were similar between the two models.”

Table S7. The genetic correlation between the two factors and related phenotypes in previous studies [1-6].

Paired Traits	**data-driven framework**		**hypothesis-driven framework**	
	genetic correlation	**se**	**genetic correlation**	**se**
F1 and reaction time [1]	0.55	0.02	0.50	0.02
F1 and common executive function [2]	-0.85	0.02	-0.87	0.02
F1 and noncognitive skills [3]	0.25	0.03	0.27	0.03
F1 and noncognitive factor [4]	0.32	0.03	0.33	0.03
F1 and cognitive factor [4]	-0.66	0.02	-0.68	0.02
F1 and general cognitive performance [5]	-0.64	0.04	-0.66	0.04
F1 and educational attainment [5]	-0.26	0.02	-0.26	0.02
F1 and cognitive performance [6]	-0.64	0.02	-0.65	0.02
F1 and cognitive skills [3]	-0.63	0.02	-0.65	0.02
F2 and reaction time	-0.20	0.03	-0.41	0.03
F2 and common executive function	0.86	0.02	0.94	0.02
F2 and non-cognitive skills	0.01	0.02	-0.05	0.03
F2 and non-cognitive factor	-0.04	0.03	-0.12	0.03
F2 and cognitive factor	0.98	0.02	0.95	0.02
F2 and general cognitive performance	0.98	0.05	0.93	0.05
F2 and educational attainment	0.68	0.02	0.61	0.02
F2 and cognitive performance	0.98	0.02	0.93	0.02
F2 and cognitive skills	0.98	0.03	0.94	0.02

Reference

[1] Davies, G. et al. Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. Nat. Commun. 9, 1–16 (2018).
[2] Hatoum, A. S. et al. Genome-wide Association Study Shows That Executive Functioning Is Influenced by GABAergic Processes and Is a Neurocognitive Genetic Correlate of Psychiatric Disorders. Biol. Psychiatry 93, 59–70 (2023).
[3] Demange, P. A. et al. Investigating the genetic architecture of noncognitive skills using GWAS-by-subtraction. Nat. Genet. 53, 35–44 (2021).
[4] Lam, M. et al. Collective genomic segments with differential pleiotropic patterns between cognitive dimensions and psychopathology. Nat. Commun. 13, (2022).
[5] Lee, J. J. et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nat. Genet. 50, 1112–1121 (2018).
[6] Savage, J. E. et al. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. Nat. Genet. 50, 912–919 (2018).

R1Q2. I would not report heritability for latent factors from Genomic SEM. You need to be careful about what sample size is used as the heritability estimate is very sensitive to sample size. Summing across all the sample sizes for the cognitive traits is inappropriate given residual genetic variance in the factor model. Backing out the sample size implied by the GWAS is possible, but the author's do not report whether they did this or not. The Z-statistic of the heritability is not contingent on sample size and can be a more straightforward statistic to report as to whether there is significant genetic signal.
"The SNP heritability was estimated as h2 = 0.1838 (0.0069) for CPS and h2 = 0.1876 (0.0074) for CPA using the LDSC method."

Response: Thank you for these suggestions. We have removed the heritability estimates from this section and replaced them with z-scores.

Results section: "The SNP heritability was estimated as z = 25.9 for CPS and z = 25.5 for CPA using the LDSC method."

R1Q3. Did the author's estimate the QSNP heterogeneity statistic for the factors and remove those SNPs from factor hits?
"Subsequently, a confirmatory factor analysis was employed to estimate SNP effects for the identified CPS and CPA factors (Fig 1b)."

Response: No, we didn't estimate the QSNP in the original manuscript. According to the reviewer's suggestion, we now re-estimated the model and calculated the QSNP heterogeneity statistics. SNPs with significant QSNP value ($p < 5e^{-8}$) were excluded from the results for both factors. All relevant results have been updated in the manuscript. Methods section: "We estimated the QSNP heterogeneity statistic for the two factors and removed the SNPs showed a significant effect ($p < 5e^{-8}$), resulting in 3750 SNPs removed in the first factor and 404 SNPs removed in the second factor."

R1Q4. Standardized estimates should be shown in panel A of figure 1 to improve interpretability (e.g., the residual genetic variance estimates could be directly interpreted as the proportion of SNP-based heritability not accounted for by the factors).

Response: We have revised the Figure 1, replacing the previous results with standardized estimates.

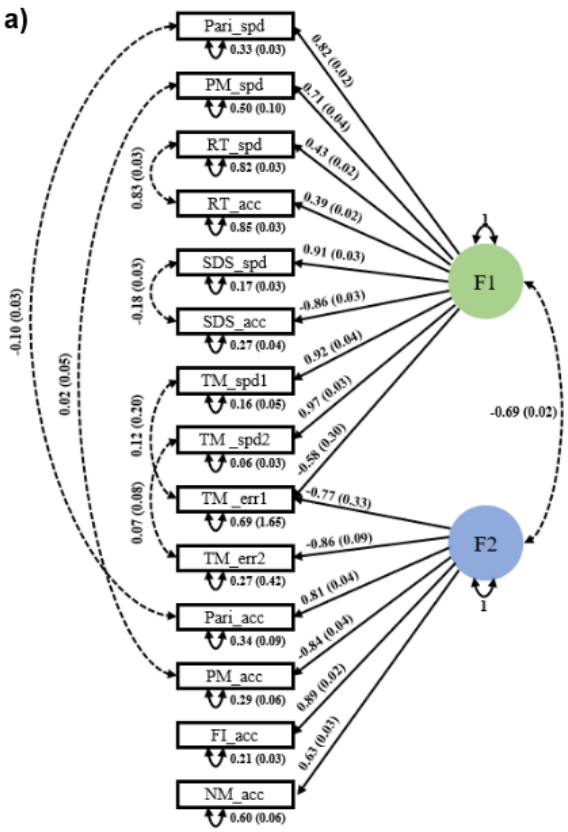


Figure 1a) The results of a confirmatory factor analysis with two latent factors across 14 cognitive traits.

R1Q5. The genetic correlation analyses with related phenotypes (cognitive, brain measures) should be performed in the context of the factor model as opposed to using LDSC with the factor summary statistics. The reason is that LDSC will give a deflated estimate of the true genetic correlation because multivariate GWAS summary statistics are estimated with some error as it can include some task-specific variance that does not conform to the factor (which is why the QSNP statistic was developed), while a genetic correlation estimated between F1 and F2 in the context of the model is not biased in this way.

Response: Thank you for pointing out these issues, which made us realize that directly calculating LDSC in the study may introduce estimation bias. Therefore, following the suggestions, we re-estimated the genetic correlations between the two factors and other phenotypes within the model context, reported the standardized results, and updated the entire manuscript accordingly. See updated Figure 2-3 and Supplementary Table 7-10.

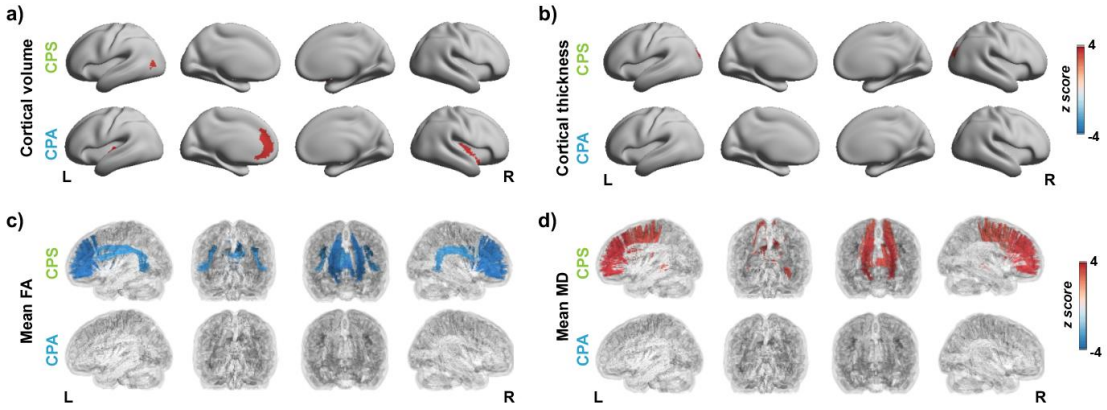


Figure 2. Genetic correlation between the two cognitive factors and brain structural phenotypes. a) The cortical volumes in the Destrieux-a2009s parcellation (148 regions), and b) the cortical thickness that was significantly correlated with CPS/CPA in the Destrieux-a2009s parcellation. c) and d) show the mean FA and MD in the ICBM-DTI white matter atlas (48 tracts) that were significantly correlated with CPS/CPA. The color indicates the standard z score of the genetic correlation (estimation/standard error), non-significant results are gray in the figure. CPS = cognitive processing speed, CPA = cognitive processing accuracy.

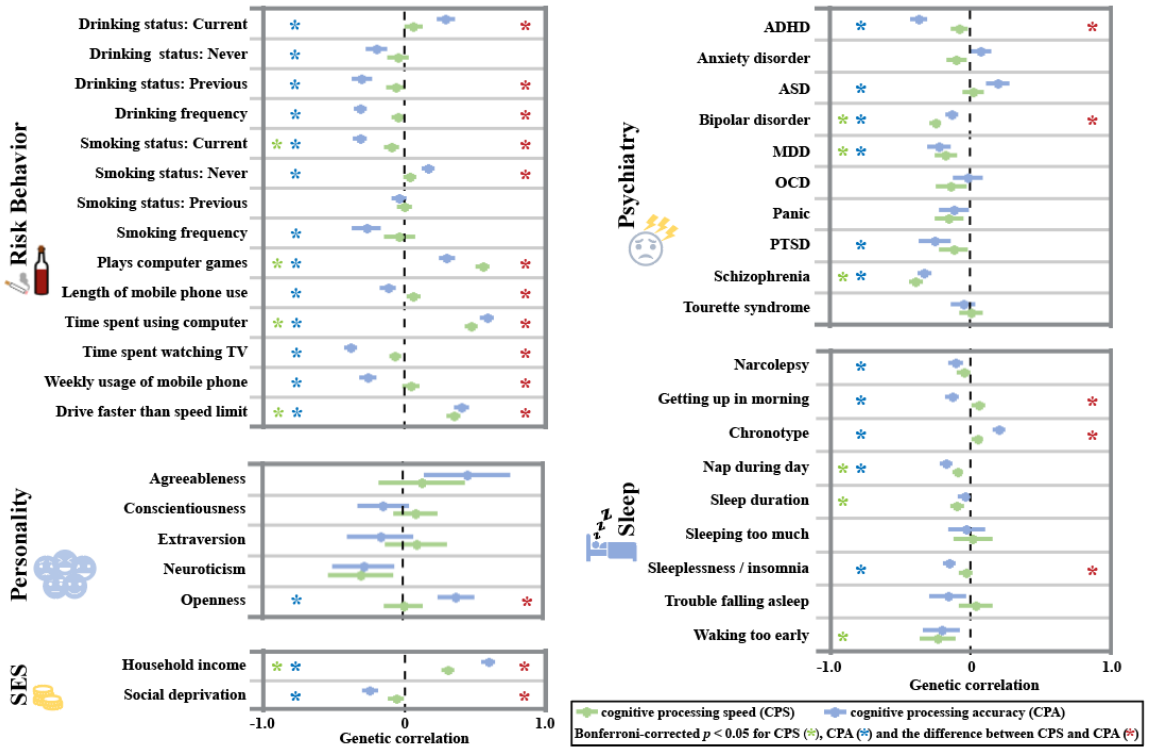


Figure 3. Genetic correlations between the two factors and 40 mental health-related traits. The traits were classed into five categories including risk behaviors (e.g. smoking, drinking, screen exposure, and driving), personality, socioeconomic status (SES), psychiatric disorders, and sleep-related phenotypes. The forest plot indicates the estimated value (dot) and standard error (line) of the genetic correlations between other traits and the cognitive processing speed (CPS, green) or accuracy (CPA, blue). The green or blue sign (*) indicates a significant genetic correlation compared to zero, while the red sign indicates a significant difference in the genetic correlations between the two factors.

Minor points:

R1Q6. I think this part of the second sentence from the abstract assumes a level of background knowledge in cognitive psychology that may not be appropriate for the general audience at this journal:

"The initial use of these two measures is probably a generalization from empiricism…"

Response: We have revised the sentence in the abstract for better clarity and accessibility. "Since the birth of cognitive science, researchers have used reaction time and accuracy to measure cognitive ability. Although recognition of these two measures is often based on empirical observations, the underlying consensus is that most cognitive behaviors may be understood along two fundamental dimensions: cognitive processing

speed (CPS) and cognitive processing accuracy (CPA)."

R1Q7. This is an opening sentence in the Introduction is again a little technical and dense for this outlet:
"Behavior that meets the requirements of the specific scene within a reasonable time window is considered a normal cognitive performance, which probably is the empirical perception of the two most common measures, namely response time and accuracy."
Response: To enhance readability and accessibility, we have revised the opening sentence in the Introduction.
"Cognitive performance is often assessed by how well a person completes a task within a given time frame, typically measured using response time and accuracy."

R1Q8. This sentence in the abstract is missing a word (or something) after CPS and CPA:
"We found distinct neuroimaging signatures for CPS and CPA that white matter microstructures were predominantly associated with CPS, while cortical volumes were preferably related to CPA."
Response: Thank you for pointing out the missing word in the abstract. We have revised the sentence for clarity: "We identified that CPS and CPA had distinct brain phenotypes (e.g. white matter microstructure), neurobiological bases (e.g. postsynaptic membrane), and developmental periods (i.e. late infancy)."

R1Q9. Given extreme polygenicity for human complex traits in general I don't know that any given SNP (outside of a rare few examples; e.g., APOE) is going to be individually meaningful.
"However, due to limited sample sizes (ranging from n = 1,311 to 32,070), these studies may lack the statistical power to detect meaningful SNPs."
Response: Thank you for your comment. We understand that referring to "meaningful SNPs" may not be appropriate given the extreme polygenicity of human complex traits. To address this, we have revised the sentence to better reflect the challenges in GWAS analysis:

"However, due to limited sample sizes (ranging from n = 1,311 to 32,070), these studies might lack the statistical power to detect significant associations in GWAS analyses."

R1Q10. Significant genetic correlations do not by themselves suggest high intercorrelations given GWAS sample sizes that can be quite large and still produce significant estimates for small r_g. A mean (or median) and range of point estimates would be more informative here.

"Utilizing linkage disequilibrium score regression (LDSC), the genetic correlation showed 73 significant estimations among all 91 trait pairs (Figure S1), suggesting high intercorrelation with those cognitive phenotypes."

Response: We have revised the results to include the range of genetic correlation values and added detailed information on all estimates in the supplementary materials:

"Utilizing linkage disequilibrium score regression (LDSC), the genetic correlation analysis showed 73 significant estimations among all 91 trait pairs (The absolute value of the significant genetic correlation ranged from 0.18 to 0.99, $p < 5.5e^{-4}$, Figure S1, Table S3), suggesting high intercorrelation with those cognitive phenotypes."

R1Q11. It seems a bit strange that CPA and CPS could be negatively correlated at -.69 but show correlations with EF that are the same direction and magnitude. It would be good if the authors could confirm that the directionality (+/-) on all of these genetic correlation point estimates are correct.

Response: Thank you for pointing it out. Upon re-examination, we discovered a typographical error. We have corrected the context in the results section.

"Common EF exhibited a comparable genetic correlation with both CPA (r_g = 0.86, se = 0.02) and CPS (r_g = -0.85, se = 0.02)".

R1Q12. I'm not sure Figure 3a adds much beyond Figure 1b. I understand that 3a is now the SNP-to-gene results, but ultimately they are close recapitulations of one another and there is not much to be gained from Manhattan style plots to begin with (though I do think 1b is worth including as the Miami plot to visualize the divergence in genetic signal across CPS and CPA).

Response: According to your suggestion, we have removed Figure 3a.

R1Q13. Figure 3d includes acronyms that are not defined in the figure legends or note (e.g., LGN_lnh_LAMP5). The forest plots across the Figure 3b, c, and d are also quite hard to interpret as they don't have a y-axis and are sort of tacked on underneath the bar plots.

Response: We have added the full names of the terms in the main figure legends, and provided the full list of the cell types in the Supplementary Table 17.

Regarding Figures 3b, c, and d, we agree that the forest plots were not sufficiently clear and did not provide much useful information, so this part was removed from the plot. Meantime, because we adjusted the order of the results, this figure is now Figure 5.

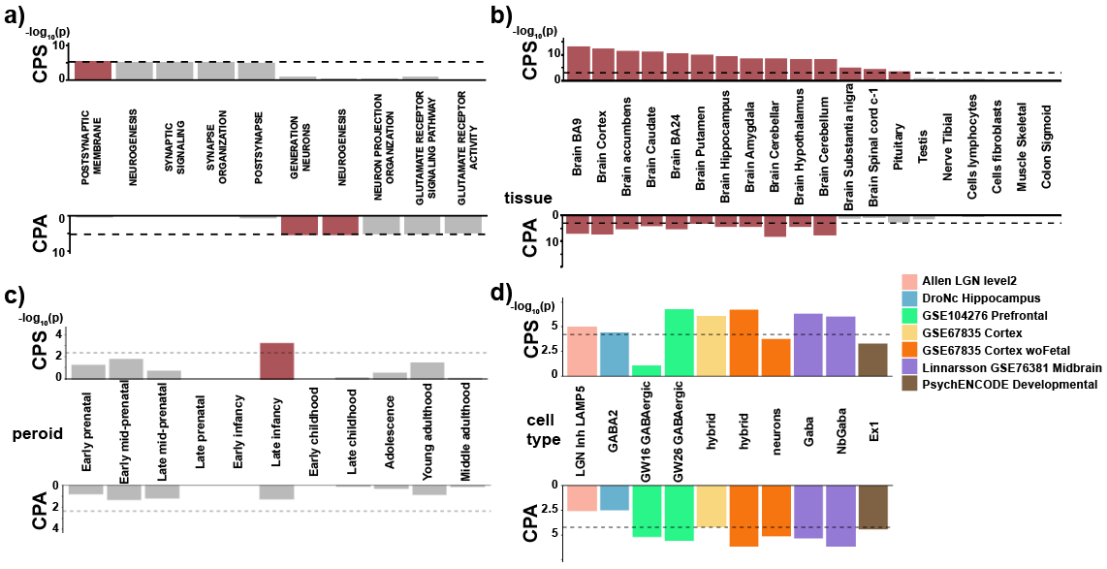


Figure 5. Results of the annotation analysis for cognitive processing speed and accuracy. a) The top 5 results of the MAGMA gene-set analysis for the two factors separately (full results were shown in Table S15-16). b) The top 20 results of GTEx tissue-specific enrichment analysis (full results were shown in Table S17). c) BrainSpan general development stage enrichment analysis. Significant results are shown in brown. d) Results of the cell-type-specific annotation analysis and different colors indicate different datasets. The dashed line in all the panels indicates the significance threshold after the Bonferroni correction. CPS = cognitive processing speed; CPA = cognitive processing accuracy; LGN inh LAMP5 = inhibitory lysosome-associated membrane protein 5 in the lateral geniculate nucleus; GABA = Gamma-aminobutyric acid; Ex = excitatory.

R1Q14. It seems like the genetic correlation CPS and CPA and health-related traits is better placed right underneath the brain correlations section so there is consistency in level of analysis. It currently goes genetic correlations -> enrichment -> genetic correlations.

Response: Thank you for the suggestion. We agree that placing the genetic correlations between CPS and CPA and health-related traits right underneath the brain correlations section would provide better consistency in the level of analysis. To address this, we have reorganized the manuscript structure. Now the paper was arranged as Genomic SEM result (Fig. 1 and Table S4-6)→ Genetic correlation between CPS/CPA and other cognitive phenotypes (Table S7) → Genetic correlation between CPS/CPA and neuroimaging phenotypes (Fig. 2 and Table S8-9) → Genetic correlation between CPS/CPA and health-related phenotypes (Fig. 3 and Table S10) → Mendelian randomization between CPS/CPA and psychiatric disorders (Fig. 4 and Table S11-12) → Annotation analysis (Fig. 5 and Table S13-19) → Polygenic score analysis (Fig. 6 and Table S20).

Reviewer #2 (Remarks to the Author):

Li and colleagues used previously published GWAS summary statistics to reveal differential genetic architecture underlying cognitive processing speed and accuracy, which can be replicated by the ABCD cohort. Follow-up functional annotations found two cognitive properties were associated with different neurobiological pathways and neurodevelopmental stages. This is an interesting study. The statistical approaches are sound, results seem robust. However, I still have some major comments. Hopefully, the authors can address these issues.

R2Q1. Page 6. The authors employed a battery of 14 cognitive metrics in their study, most of which appear to assess both the speed and accuracy of cognitive task execution. However, fluid intelligence, among these metrics, seems to encompass both processing speed and accuracy. It would be valuable for the authors to clarify why they included fluid Intelligence in their genetic analysis, considering its dual reflection of processing speed and accuracy.

Response: Thank you for your comment. As the reviewer correctly noted, fluid intelligence should encompass both cognitive processing speed (CPS) and accuracy (CPA).

However, in this study, we used the fluid intelligence score from the UK Biobank, which was calculated based on the unweighted sum from 13 other tasks. From the measurement perspective, these tasks only assessed the accuracy [e.g. numeric addition test and identifying the largest number. https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100027.]. We included fluid intelligence in our analysis because it represents an important aspect of cognitive ability. Using a data-driven approach, we aimed to determine its loadings on the underlying factors. Our analysis revealed that the fluid intelligence score appeared to load more heavily on cognitive processing accuracy rather than speed, possibly due to the way it was measured in Biobank. Therefore, we included fluid intelligence under the loadings for cognitive processing accuracy in the following CFA model.

We have included these descriptions in the Methods Section, "The fluid intelligence score we used was derived from the UK Biobank, where it was calculated based on the unweighted sum from 13 other tasks (https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100027)".

We also added the interpretation of the fluid intelligence result in the Results Section, "It is worth noting that the fluid intelligence may contain both speed and accuracy components. Our analysis revealed that the fluid intelligence score loaded more heavily on CPA rather than CPS, possibly due to the way it was measured in UK Biobank, i.e., the 13 fluid intelligence tasks mainly assessed the accuracy".

R2Q2. In Figure 1, The authors presented genome-wide association results for two cognitive components. They not only described the results obtained at the conventional threshold of 5e-8 but also provided insights into genetic associations at a less stringent threshold of 1e-5. Previous literature extensively suggests that the 5e-8 threshold adequately controls for false positive results. It becomes imperative to address multiple testing issues across phenotypes. For example, it might define independent genetic loci at a threshold of 2.5e-8 (half of 5e-8) and proceed with subsequent functional analyses.

Response: Thank you for the suggestion. We have adopted a more stringent threshold of 2.5e-8 for defining independent genetic loci (see Fig. 1b below) and updated the subsequent functional analyses. We also modified the Figure 1 with a new threshold.

Moreover, we conducted subsequent enrichment analysis under this threshold, updated Figure 5 and Supplementary Table 13-19. Most of the results were similar to the previous one.

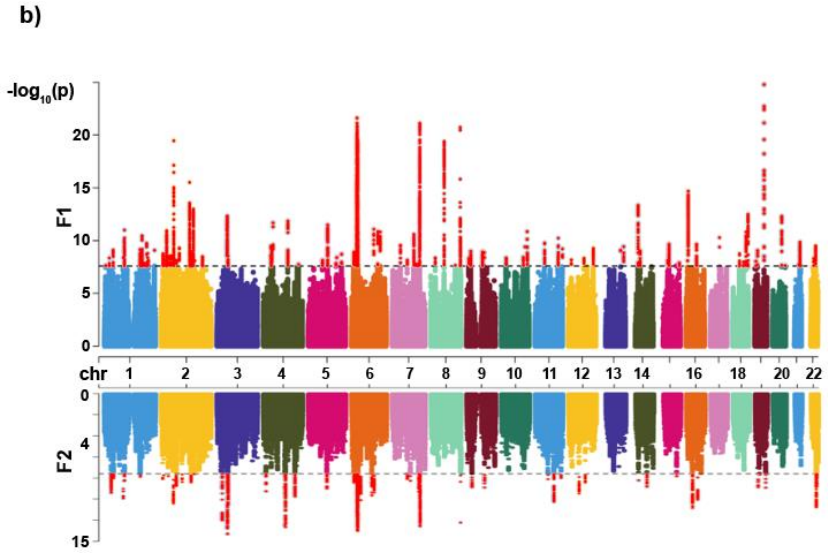


Figure 1b). Manhattan plot of the two factors. Red dots denote the significant results with $p< 2.5e^{-8}$.

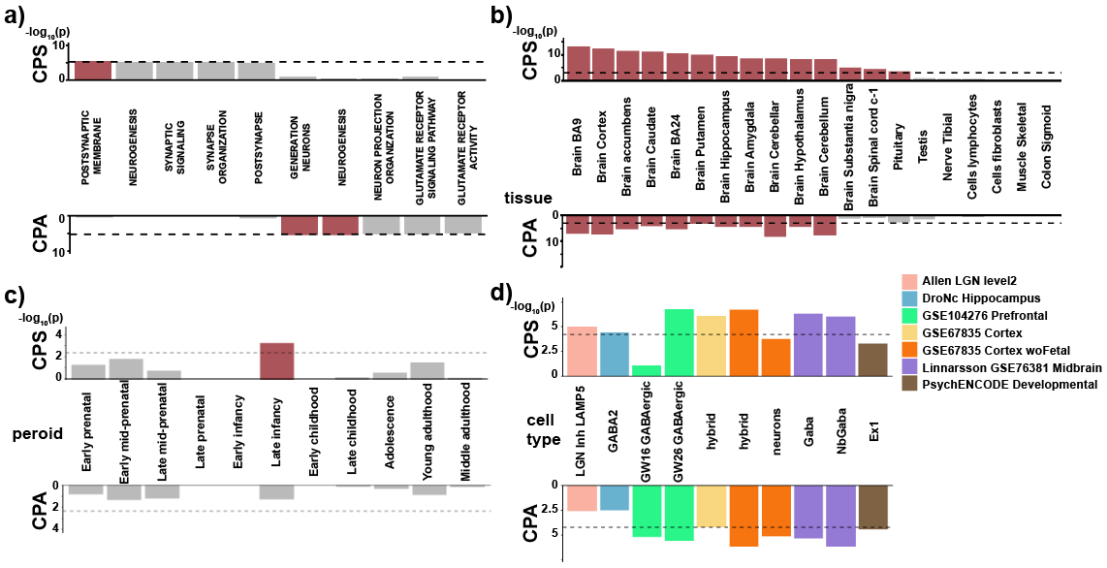


Figure 5. Results of the annotation analysis for cognitive processing speed and accuracy. a) The top 5 results of the MAGMA gene-set analysis for the two factors separately (full results were shown in Table S15-16). b) The top 20 results of GTEx tissue-specific enrichment analysis (full results were shown in Table S17). c) BrainSpan general development stage enrichment analysis. Significant results are shown in brown. d) Results of the cell-type-specific annotation analysis and different colors indicate different datasets. The dashed line

in all the panels indicates the significance threshold after the Bonferroni correction. CPS = cognitive processing speed; CPA = cognitive processing accuracy; LGN inh LAMP5 = inhibitory lysosome-associated membrane protein 5 in the lateral geniculate nucleus; GABA = Gamma-aminobutyric acid; Ex = excitatory.

R2Q3. Page 7. The methods and results sections did not address the handling of the major histocompatibility complex region on chr6 and the region from chr17:40000000-47000000. Both of these genomic regions contain complex genetic structures, which could potentially lead to false positive results in genetic analysis. Regarding the latter region, despite extensive literature linking it to variations in brain functional structure, its large inversion may introduce spurious associations, particularly in genetic analyses concerning brain structure. Therefore, I suggest excluding these genetically complex regions from subsequent functional annotation (such as gene-level analysis, downstream signaling pathway analysis, and genetic correlation analysis) to mitigate potential confounding effects.

Response: Thank you for pointing this out. We previously excluded SNPs from the MHC region in our analyses, but we realized that this was not clearly stated in the manuscript. We have now added this information to the methods section to clarify our approach.

"Specifically, we retained all HapMap3 SNPs with allele frequency > 0.01, information scores > 0.9, and those outside the major histocompatibility complex (MHC) regions. This step ensured that our analyses were not confounded by the complex genetic structures in these regions".

R2Q4. Page 8. The authors tested genetic correlations between CPS/CSA and cognitive skills. Since the authors have derived GWAS results for two independent cognitive components, it would be interesting to examine whether there is a genetic correlation between these two components. This analysis could shed light on whether the independent cognitive components manifest distinct genetic underpinnings or if there exists a shared genetic basis underlying both phenotypes.

Response: Thank you for your suggestion. We have examined the genetic correlation between the two components in the initial manuscript.

"Moreover, CPS and CPA showed a moderate correlation (r_g = -0.69, se = 0.02). It is essential to highlight that CPS is measured in response time, and shorter response time

means higher cognitive processing speed, thus the two factors showed a positive genetic correlation in terms of cognitive skills".

R2Q5. Line 8, Page 8, "not significantly less than 1, corrected $p > 0.05$)". Is it a typo? Should be corrected $p<0.05$? In addition, the authors might need to indicate the exact p-values for all of the statistic results.

Response: The CPA measure did not significantly differ from general cognitive ability (corrected $p > 0.05$). We realize the previous expression was not straightforward, so have rephrased this sentence as follows.

"Strong correlations were observed between CPA and general cognitive phenotypes (r_g = 0.981 – 0.983), possibly because the previously reported general cognitive abilities are common factors extracted from the accuracy of various cognitive tasks."

We also added the exact p-values for all statistical results in the Supplementary Tables.

R2Q6. Page 9. The authors used publicly available GWAS results for brain gray matter and white matter structures to examine their genetic correlations with two cognitive components. The UKB dataset also offers GWAS results for brain function, where brain functionality is segmented into 25 or 100 independent functional components, each subjected to GWAS analysis. However, the authors did not investigate the genetic relationships between the two cognitive components and brain functionality. It could be insightful for future studies to explore the genetic correction between these cognitive components and brain functionality, potentially uncovering novel insights into the genetic basis of cognitive processes and brain function.

Response: Thank you for your suggestion. We agree that resting functional MRI in UKB provides another important perspective on brain phenotypes. We have added a section in the discussion highlighting the potential for future studies to explore the genetic correlations between CPS/CSA and brain functionality using the UKB dataset's GWAS results for brain function.

"In the current study, our primary focus was on structural aspects (gray matter and white matter) rather than functional components. Nevertheless, we appreciate the importance of extending this analysis to include brain functionality measures in future studies".

R2Q7. Page 9. The author tested genetic correlations between two cognitive components and lots of brain measures. However, I am not sure whether all of the brain measures tested were significantly heritable. I guess it could not make sense to explore genetic correlations with non-heritable brain measures. I am not sure how the authors deal with this issue.

Response: Thanks for the comments. In this study, we used heritability estimates from previous GWAS studies and ensured that only those brain measures with significant heritability were included in our analysis. We have updated the methods section of the manuscript to explicitly state that only significantly heritable brain measures were included in the genetic correlation analysis.

"For the brain structure phenotypes, we used the cortical brain volume, cortical thickness, the mean FA, and MD value in the white matter tracts, only phenotypes with significant heritability were included in our analysis. A looser criterion was used to include all potential brain phenotypes, and all 408 brain phenotypes survived this threshold (FDR-corrected $p < 0.05$)."

R2Q8. Page 9. The author tested genetic correlations between two cognitive components and regional brain volumes, cortical thicknesses, and surface areas. Cortical thickness and surface area are bi-products of brain volume. I guess testing brain measures with overlapping structural characteristics could increase the burden of multiple tests.

Response: Thank you for the suggestion. We have removed the surface area related phenotypes in the article.

R2Q9. Page 9. The author only provided the number of brain regions genetically correlated with the two cognitive components without describing the spatial distribution of significantly associated brain regions. The significance of this article lies in mapping two independent cognitive components onto the brain and exploring which brain regions are involved in cognitive processing speed or accuracy. However, the author only mentioned that the brain regions associated with the two cognitive components exhibit distinct patterns. These general descriptions are not helpful in understanding the neural

basis of cognition, a detailed spatial distribution of the significantly correlated brain regions would provide deeper insights into the specific brain networks underlying cognitive processing speed and accuracy.

Response: Thank you for the comment. First of all, the spatial maps in Fig. 2 illustrate the spatial distributions of the significantly genetically correlated brain phenotypes. We have added a more detailed description of the spatial distribution of the significant results:

"Generally, CPA exhibited significant correlations with the brain volumes of anterior cingulate and insula areas (r_g = 0.14 to 0.21, FDR corrected $p < 0.05$; Fig 2a, Table S8), and CPS showed more limited correlations with the brain volumes, primarily in the left lateral ventricle (Fig S2), left anterior occipital, and right medial orbital areas (r_g = 0.11 to 0.27, FDR corrected $p < 0.05$; Fig 2a, Table S8). Only CPS had selected correlations with mean cortical thickness of bilateral superior transversal areas (r_g = 0.12 and 0.13, FDR corrected $p < 0.05$; Fig 2b, Table S8)."

"In contrast, CPS demonstrated strong correlations with the FA in 11 tracts (r_g = -0.15 to -0.11, FDR corrected p < 0.05; Fig 2c, Table S8), and the MD in 8 tracts (r_g = 0.10 to 0.14, FDR corrected p < 0.05; Fig 2f). Those tracts mainly included the bilateral anterior corona radiata, superior longitudinal fasciculus, superior frontal-occipital fasciculus, and corpus callosum. None of the white matter tracts were significantly correlated with CPA".

We also added a discussion about the potential function of the regions to help the reader better understand the association between the brain regions and the CPA/CPS:

"These fibers mainly included superior longitudinal fasciculus, superior frontal-occipital fasciculus, corona radiata, and corpus callosum. The dorsal association fiber such as the superior frontal-occipital fasciculus connects the occipital and frontal lobes, serving as an important bridge between visual processing and executive functions, and thus could be an important basis for the cognitive processing speed in vision-based tasks. The corpus callosum is the largest interhemispheric commissure and an important pathway for information processing between the hemispheres. Previous studies have also revealed associations between the myelination of the corpus callosum and processing speed in healthy adults. As for brain volume, CPS-related regions were located in the anterior and

dorsal occipital cortex, which may reflect that CPS is more dependent on basic sensory abilities. In contrast, the CPA-related regions were located in the insula and the anterior cingulate gyrus. The insula has been linked to various cognitive functions, such as executive functions, and the anterior cingulate gyrus is involved in error monitoring, both of which are crucial for accurately completing tasks."

R2Q10. Page 10. The authors investigated the biological pathways associated with the cognitive components using predefined gene sets. However, they only reported the significantly enriched biological pathways without listing all the tested pathways along with their corresponding significance p-values in the main text or supplementary materials. It would be beneficial for the authors to provide a comprehensive list of these pathways and their significance p-values. This would enable readers to gain a more in-depth understanding of the molecular processes implicated in these cognitive components.

Response: Thank you for the comment. We have added a comprehensive list of these pathways and their significance p-values in the supplementary tables. See Supplementary Table 15-16.

R2Q11. Page 12. The authors appropriately corrected for multiple comparisons in each genetic analysis, which is great. However, many analyses did not specify the exact correction method used; rather, they simply listed significant results as "corrected $p < 0.05$". It would be beneficial for the authors to explicitly state the specific correction methods used in all genetic analyses throughout the manuscript and provide the corresponding p-values to ensure transparency in the study's findings.

Response: We added detailed methods for the correction in the results and methods sections such as Bonferroni-corrected p, and we have provided the exact p-values in all analyses. See updated Results, Methods, and Supplementary Tables 8-20.

R2Q12. Page 13. The authors found that, for most of these cognitive traits, the absolute value of the correlation was higher with cognitive processing accuracy (CPA) than cognitive processing speed (CPS), by using a standard t-test formula. I'm not sure why

the authors didn't compare the differences in genetic correlation coefficients between CPA and CPS at the group level. The standard t-test formula used in the study seems to calculate differences between two R-values based on their respective standard errors, but this method appears somewhat unreasonable.

Response: We appreciate your concern regarding the method used to compare the differences in genetic correlation coefficients between CPA and CPS. Generally, R-values obtained from correlations may not follow a normal distribution, and therefore, transformations such as Fisher-Z are often applied before conducting statistical tests. Using direct genetic correlation estimates from LDSC might also have issues as you mentioned.

To address this, we have updated our estimation method for genetic correlations. We estimated genetic correlations between the latent factors and other phenotypes within the context of the updated CFA model (also see R1Q5), to obtain the standardized estimates and corresponding standard errors. This method should improve the accuracy of the estimates, and the point estimates can be approximated as normally distributed. We then used these standardized estimates and standard errors to compare the differences in genetic correlations.

"The comparison of correlation coefficients between the two factors with other traits was computed using the standard z-test formula:

$$z = \frac{b_1 - b_2}{\sqrt{se_1^2 + se_2^2}}$$

Where *b* is the estimate of the genetic correlation, *se* is the standard error of the estimate."

For the reviewer's suggestion of performing a comparison at the group level, it would involve conducting a t-test on the genetic correlation estimates of a group of phenotypes with the two factors, rather than focusing on the differences between the two factors for an individual phenotype. This approach would not address the differences at the individual phenotype level, which is why we did not pursue it.

All related results have been updated in the manuscript. See updated Figure 3 and Supplementary Tables 9, 10, 17, 18.

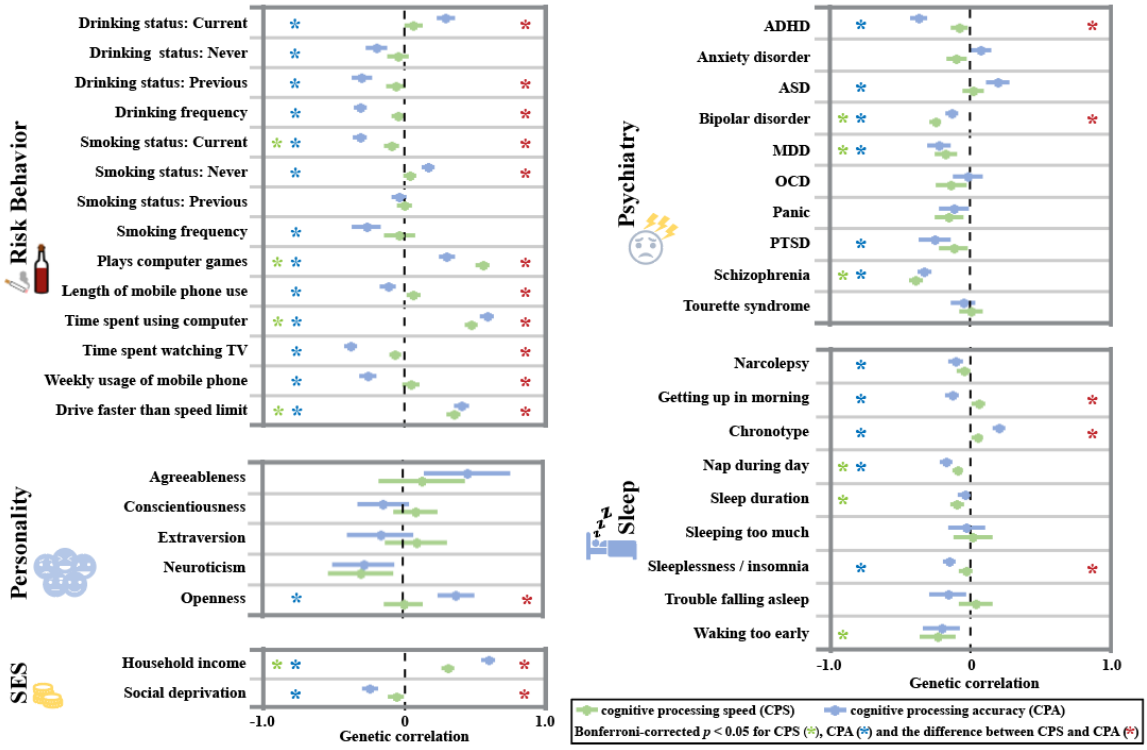


Figure 3. Genetic correlations between the two factors and 40 mental health-related traits. The traits were classed into five categories including risk behaviors (e.g. smoking, drinking, screen exposure, and driving), personality, socioeconomic status (SES), psychiatric disorders, and sleep-related phenotypes. The forest plot indicates the estimated value (dot) and standard error (line) of the genetic correlations between other traits and the cognitive processing speed (CPS, green) or accuracy (CPA, blue). The green or blue signs (*) indicate a significant genetic correlation compared to zero (Bonferroni-corrected $p < 0.05$), while the red signs indicate a significant difference in the genetic correlations between the two factors (Bonferroni-corrected $p < 0.05$).

R2Q13. Page 15. The authors utilized the PRSice-2 method to generate polygenic scores, but this approach heavily relies on threshold selection and genomic clumping thresholds, and it exhibits poor performance in predicting phenotypes. I suggest that the authors consider using threshold-free methods to generate polygenic scores, such as using PRS-CS. This would allow for the validation or replacement of the current study results, resulting in more robust findings.

Response: Thank you for your valuable feedback. We have now replaced the previous analysis with PRScs and updated the results and methods accordingly. Similar to the previous results, we found that the polygenic scores of the two factors could significantly predict the cognitive abilities of adolescents from ABCD. Based on the new scores, we

added analyses to explore the specific effects of CPS/CPA on cognitive scores in ABCD. We found that CPS better explains cognitive tasks related to fluid intelligence, while CPA better explains tasks related to crystallized intelligence. We have updated the methods and results accordingly.

Methods section: "PRScs (https://github.com/getian107/PRScs) [1] was used for the PGS analysis. The European data from the 1000 Genomes Project Phase 3 were used as the LD reference, with all other parameters set to default. After obtaining the PGS for CPS/CPA, we conducted a regression analysis of the PGS scores and the cognitive scores of adolescents. Before the analysis, we randomly excluded one sibling from each pair, preterm children (gestational age < 37 weeks), as well as individuals with incomplete data. We used a linear mixed-effects model, with age, sex, and PGS scores as fixed effects, and the data collection sites as random effects to predict each cognitive score. Given the high correlation between CPS and CPA, we included both PGS scores simultaneously in the regression analysis to obtain the specific effects of CPS/CPA. To address multiple tests, Bonferroni-corrections were applied."

Results section: "Here, we investigated whether the two cognitive factors can elucidate individual variations in cognitive abilities in children and early adolescents, using polygenic score (PGS) analyses on 8-10-year-old adolescents from the ABCD study. PGS scores for both factors demonstrated a significant correlation with all 7 cognitive abilities and 2 composite scores (Bonferroni-corrected $p < 0.05$, Table S20). Considering the high correlation between CPA and CPS, we further included the PGS scores of the two factors in the same regression model to explore their specific effects on children's cognitive scores. The results showed that the PGS score of CPS was significantly associated with flanker, list sorting working memory, dimensional change card sort, pattern comparison processing speed, and the picture sequence memory task. In contrast, the PGS score of CPA was significantly associated with picture vocabulary, list sorting working memory, picture sequence memory, and oral reading recognition (Fig 6, Table S20). Moreover, this analysis revealed distinct effects in which the PGS for CPS was significantly associated with the fluid intelligence composite ($b = -0.114$, $se = 0.017$, $p < 10\text{-}10$) but not the crystallized intelligence composite ($b = -0.016$, $se = 0.017$, $p > 0.3$). Conversely, the PGS for CPA was strongly associated with the crystallized intelligence composite (b

= 0.229, se = 0.017, p < 10-39) and a weaker association with the fluid intelligence composite (b = 0.081, se = 0.017, p < 10-5, Fig 6, Table S20). These findings demonstrated the separation of the two gene scores in relation to fluid and crystallized intelligence tasks, and highlighting their substantial contributions to the development of diverse cognitive abilities in children".

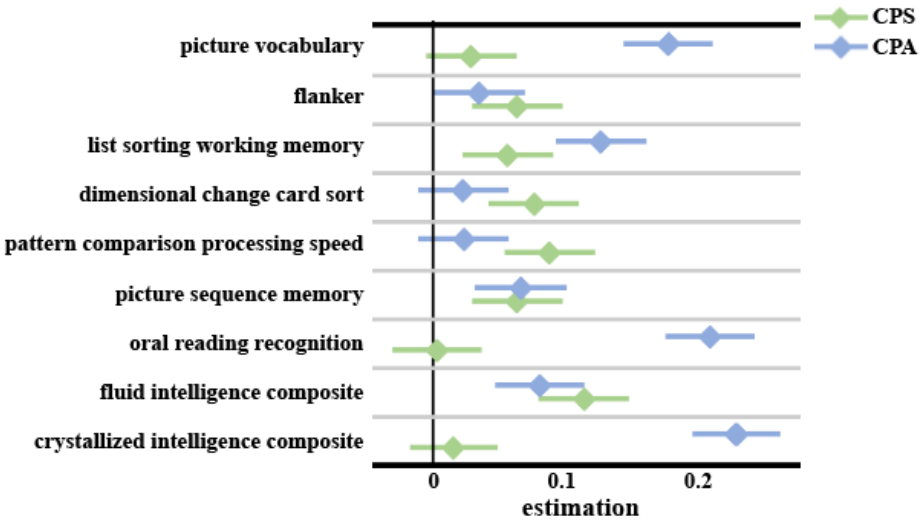


Figure 6. Polygenic score analysis of the two factors on the multiple cognitive abilities in young adolescents. The forest plots showed the estimation of the effects of PGS scores on all 7 cognitive abilities and 2 composite scores cognitive scores in the ABCD datasets.

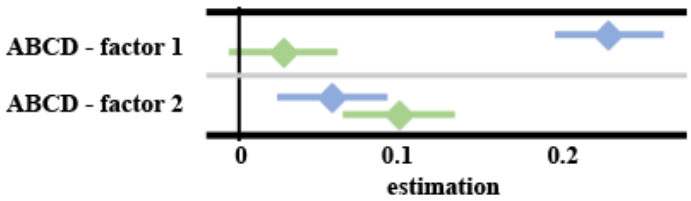
Reference

[1] Ge, T., Chen, C. Y., Ni, Y., Feng, Y. C. A. & Smoller, J. W. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat. Commun. 10, 1–10 (2019).

R2Q14. Page 15. The last section of results. It appears that the ABCD cohort includes cognitive function metrics related to cognitive processing accuracy and processing speed. It would be beneficial for the authors to explore associating the polygenic scores with these dimensions of cognitive scores within the ABCD dataset to validate the current findings.

Response: Thank you for your suggestions. We performed factor analysis on the ABCD cognitive scores and acquired two factors for the PGS analysis. However, these tasks are different from those used in GenomicSEM analysis. Also, the ABCD study doesn't include reaction time data, which may result in less consistent components. We found that these

two components represent a separation of crystallized intelligence and fluid intelligence, similar to the ABCD composite score 1 (fluid intelligence composite) and 2 (crystallized intelligence composite). We then performed a regression analysis using these two components and found that the PGS for CPS was significantly associated with the second factor (fluid factor) of ABCD cognitive scores but not the first factor (crystallized factor). Conversely, the PGS for CPA was strongly associated with the first factor of ABCD cognitive scores and weakly associated with the second factor, though both effects were significant. Because the factor analysis used for ABCD was very different from UKBiobank and also the resultant components were similar to the composite scores already provided by ABCD (the fluid and crystallized intelligence score, see Fig. 6), we did not include these results in the current paper to avoid confusion.



The forest plots showed the estimation of the effects of PGS scores on the two factors derived from 7 ABCD NIH cognitive scores. These results are similar to the ABCD fluid and crystallized intelligence composite scores.

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

The authors were responsive to my comments and the manuscript is much improved.

Reviewer #2 (Remarks to the Author):

The authors have addressed my concerns. I think it's a very interesting study. I am glad to see it will be published in Nature Communications.