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

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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 along two fundamental dimensions: cognitive processing speed (CPS) and cognitive processing accuracy (CPA). In this study, we used genomic-wide association studies (GWAS) data from 14 cognitive traits to show the presence of those two factors and revealed the specific neurobiological basis underlying them. 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). Moreover, those two factors showed differential associations with other health-related traits such as screen exposure and sleep status, and a significant causal relationship with psychiatric disorders such as major depressive disorder and schizophrenia. Utilizing an independent cohort from the Adolescent Brain Cognitive Development (ABCD) study, we also uncovered the distinct contributions of those two factors on the cognitive development of young adolescents. These findings reveal two fundamental factors underlying various cognitive abilities, elucidate the distinct brain structural fingerprint and genetic architecture of CPS and CPA, and hint at the complex interrelationship between cognitive ability, lifestyle, and mental health.

Cognitive performance is often assessed by how well an individual completes a task within a given time frame, typically measured using response time and accuracy. The universality of these two measures in evaluating different cognitive abilities reflects that there may be two fundamental dimensions of speed and accuracy underlying most human cognitive activities. Cognitive processing speed (CPS) represents a fundamental cognitive capability that gauges the swiftness of information processing, integration, and execution. It is typically assessed through reaction time or the duration of cognitive tasks[1,2]. In contrast, cognitive processing accuracy (CPA) necessitates individuals to seamlessly coordinate various fundamental cognitive processes such as attention, response inhibition, and working memory, in addition to specific knowledge relevant to the task at hand[3,4]. These functions reflect different aspects of cognitive ability and exhibit significant associations with a wide range of cognitive behaviors and psychiatric disorders[5–7]. As a result, comprehending the neuroimage signature and genetic architecture underlying these two abilities not only provides insights into the foundations

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of various cognitive functions but also sheds light on the neurobiological factors influencing behavior in the context of mental disorders.

Genome-wide association studies (GWAS) can identify single nucleotide polymorphisms (SNPs) contributing to specific phenotypes, revealing potential neurobiological processes associated with these significant SNPs[8]. Several GWAS studies have been conducted to understand the genetic basis of CPS[5–7,9–12]. One such study utilized multiple cognitive tasks to provide a comprehensive assessment of processing speed[7]. However, due to limited sample sizes (ranging from $n = 1311–32,070$), these studies might lack the statistical power to detect significant associations in GWAS analyses. Other studies chose to use the reaction time of a single task (e.g., the 'snap' game) to measure the processing speed[5,6,11,12]. Despite their larger sample sizes (ranging from $n = 282,217–432,297$; details available in Supplementary Data 1), these studies failed to yield consistent results. This inconsistency indicates that using a single cognitive measure to assess CPS may not be adequate. Previous research lacks clear criteria for assessing CPA, and as a result, no studies have directly investigated the genetic basis of this cognitive function.

In this work, we propose an approach using Genomic Structural Equation Modeling (GenomicSEM[13]) based on GWAS data of a range of cognitive measures to obtain reliable and comprehensive descriptor of CPS and CPA. We carry out the genetic correlation and annotation analyses and find the underlying neurobiology, encompassing aspects such as brain structures, and the neurobiological basis of these two cognitive functions. In addition, we find the significant genetic correlation between these two factors and health-related phenotypes, as well as the significant causal relationships between CPS/CPA and psychiatric disorders using Mendelian randomization (MR) analysis[14,15]. Finally, a polygenic scores (PGS) analysis[16] reveals the distinct contributions of those two factors on the cognitive development of young adolescents in the Adolescent Brain Cognitive Development (ABCD) study[17,18].

Results

Genomic structural equation modeling revealed two latent factors corresponding to cognitive processing speed and accuracy

The primary GWAS summary statistics for cognitive measurements utilized in this study were originally presented in a prior study, which compiled a GWAS dataset featuring 2173 traits from 455,422 individuals in the UK Biobank[19]. From this extensive dataset, we specifically identified 14 cognition-related phenotypes from 7 tasks (See detailed information on those phenotypes in Supplementary Data 2). Utilizing linkage disequilibrium score regression (LDSC[20]), the genetic correlation analysis showed 73 significant correlations among all 91 pairs of traits (absolute values of the significant genetic correlations ranged from 0.18 to 0.99, $p < 5.5e^{-4}$, Supplementary Fig. 1, Supplementary Data 3), suggesting high intercorrelation among those cognitive phenotypes.

Initially, exploratory factor analysis was performed to determine the number of latent factors from these traits. The analysis revealed that a two-factor model (58%) could explain more variation compared to a model with a common factor (49%). Models with factors beyond two failed to converge. The two factors were robustly loaded [abs(loading) > 0.4] on traits reflecting cognitive processing speed (CPS) and cognitive processing accuracy (CPA), respectively (Fig. 1a and Supplementary Data 4). It is clear that speed-related tasks were all loaded to the first factor while most of the accuracy-related tasks were clustered to the second factor. It is worth noting that fluid intelligence might 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.

Subsequently, a confirmatory factor analysis was employed to estimate SNP effects for the identified CPS and CPA factors (Fig. 1b). The SNP heritability was estimated as $z = 26.64$ for CPS and $z = 25.35$ for CPA using the LDSC method. We identified 118 and 55 leading SNPs for CPS and CPA, respectively, with p-values $< 2.5e^{-8}$, window size <250 kb, and $r^2 < 0.1$ (Supplementary Data 4–5). For the leading SNPs of CPS, 101 loci have been reported for certain traits such as cognitive ability

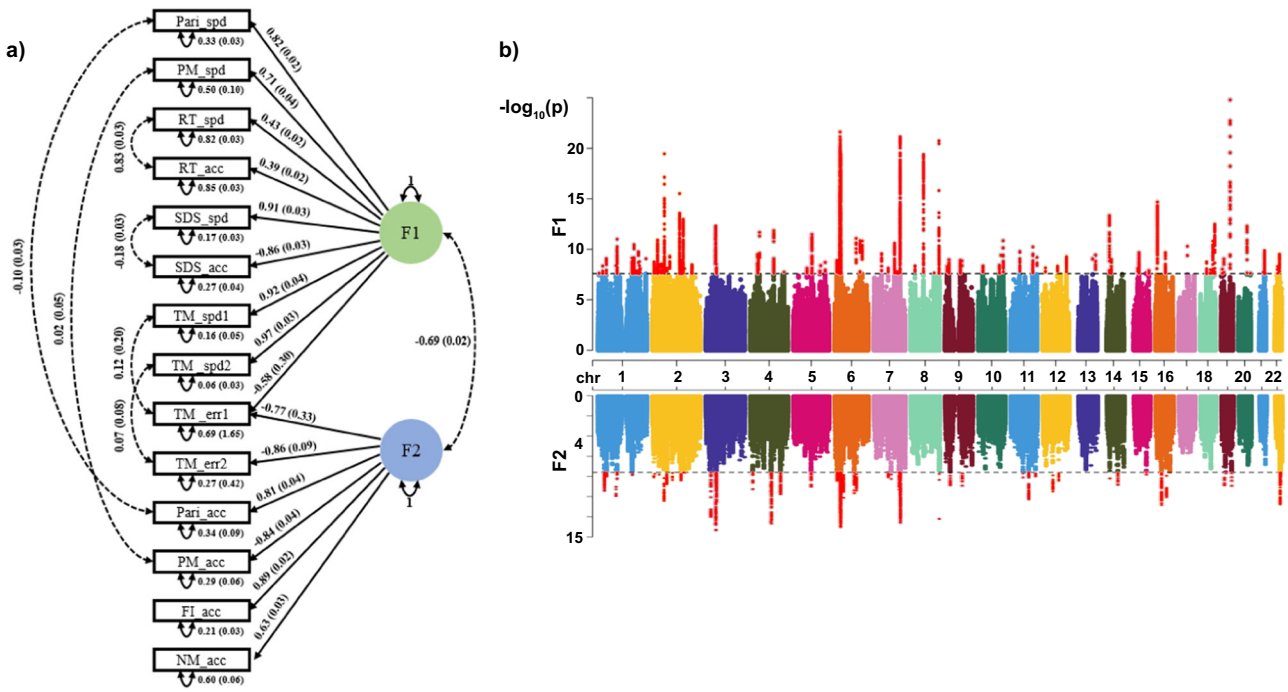

Fig. 1 | Genomic structural equation modeling revealed two factors corresponding to cognitive processing speed and accuracy. a The results of a confirmatory factor analysis with two latent factors from 14 cognitive traits. Arrows indicate the factor loading and the standard error was in the brackets. **b** Manhattan plot of the two factors, the color of the dot suggests the significance value of 2.5 e^{-8} (red, Bonferroni correction for two phenotypes).

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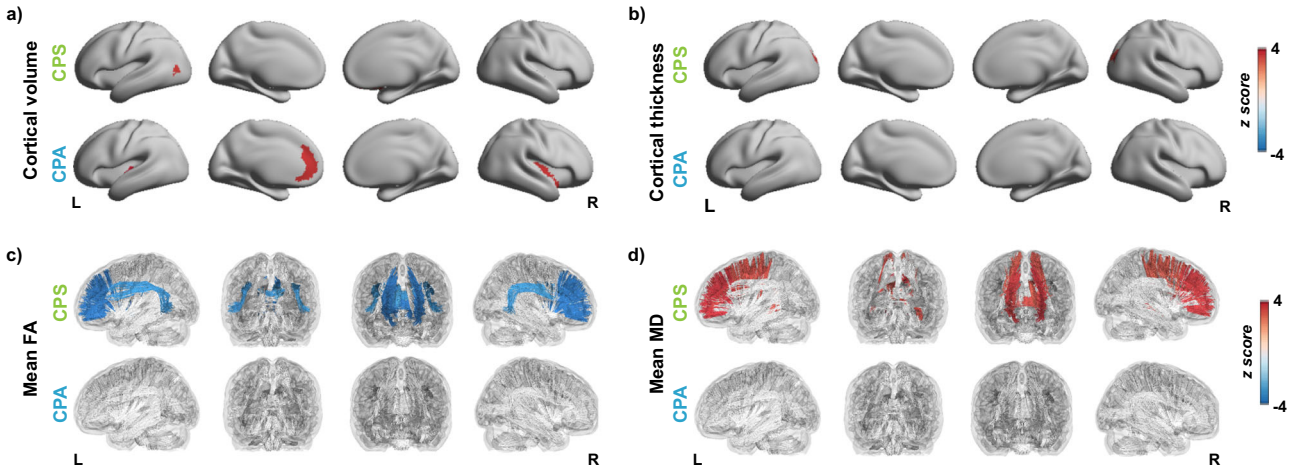

Fig. 2 | Genetic correlations between the two cognitive factors and brain structural phenotypes. a, **b** show the cortical volumes and cortical thickness that were significantly correlated with CPS/CPA in the Destrieux-a2009s parcellation[74] (148 regions). **c**, **d** show the mean FA and MD in the ICBM-DTI white matter atlas[75] (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 tracts were grayed in the figure. CPS cognitive processing speed, CPA cognitive processing accuracy.

(30 loci), intelligence (24), reaction time (20), and cognitive speed (2). Seventeen were novel based on the reference of the GWAS Catalog (Supplementary Data 5). Three of the Seventeen loci showed significant association ($p < 5e^{-8}$) with at least one original trait. For the leading SNPs of CPA, 54 loci were reported for traits like cognitive ability (42 loci) and intelligence (39). Only one SNP (rs111959380) was new in the current analysis (Supplementary Data 6).

Genetic correlation between CPS/CPA and related cognitive measures in previous studies

Given the operational definition used here, the results of the above two factors may be associated with existing cognitive measures, such as common executive function (cEF[11]), general intelligence (g factor[10,21,22]), educational attainment[23], cognitive and noncognitive skills[24], and two principal components underlying multiple cognitive performance[25]. We compare the factors deciphered from the present analysis and those in the prior studies using genetic correlation. Strong correlations were observed between CPA and general intelligence[10,21,22] ($r_g = 0.981–0.983$), while moderate correlations were found between CPS and reaction time[5] ($r_g = 0.55$, $se = 0.02$). cEF[11] exhibited a comparable genetic correlation with both CPA ($r_g = 0.86$, $se = 0.02$) and CPS ($r_g = -0.85$, $se = 0.02$), indicating it measures a mixture of speed and accuracy. Additionally, educational attainment[23] displayed a moderate correlation with CPA ($r_g = 0.68$, $se = 0.02$) and a weak correlation with CPS ($r_g = -0.26$, $se = 0.019$). Noncognitive phenotypes[24,25] showed weak correlations with both CPS and CPA ($r_g = -0.04$ to 0.32; see Supplementary Data 7 for complete results of this analysis). Moreover, CPS and CPA showed a moderate correlation ($r_g = -0.69$, $se = 0.02$). It is essential to highlight that CPS was measured in response time, and shorter response time meant higher cognitive processing speed, thus the two factors showed positive genetic correlation in terms of cognitive ability. These findings were consistent with the above loci results and suggested that the extracted CPS factor differed from other reported traits used in previous GWAS studies. The high correlation between the CPA component and the general cognitive factor might be because the general cognitive ability was a common factor extracted from the accuracy of various cognitive tasks[10,21,22].

Cognitive processing speed and accuracy exhibited distinct associations with neuroimaging phenotypes

To explore potential brain structures associated with CPA and CPS, we calculated their genetic correlations with brain volume, cortical thickness, as well as fractional anisotropy (FA) and mean diffusivity (MD)-weighted white matter tract measurements (A total of 408 phenotypes[26], Supplementary Data 8). 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 and Supplementary Data 8), and CPS showed more limited correlations with the brain volumes, primarily in the left lateral ventricle (Supplementary Fig. 2), left anterior occipital, and right medial orbital areas ($r_g = 0.11$ to 0.27, FDR corrected $p < 0.05$; Fig. 2a and Supplementary Data 8). 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, Supplementary Data 8).

For white matter phenotypes, CPS demonstrated strong correlations with the FA in 11 tracts ($r_g = -0.15$ to -0.11, FDR corrected $p < 0.05$; Fig. 2c, Supplementary Data 8), and the MD in 8 tracts ($r_g = 0.10$ to 0.14, FDR corrected $p < 0.05$; Fig. 2d). Those tracts mainly included the bilateral anterior corona radiata, superior longitudinal fasciculus, superior frontal-occipital fasciculus, and corpus callosum. In contrast, none of the white matter tracts were significantly correlated with CPA. Moreover, genetic correlations of CPS with mean FA in bilateral corpus callosum, which is the major cross-hemisphere pathway, were significantly higher than those for CPA ($z = 3.56$ and 3.28, $p < 0.0006$; Supplementary Data 9). This may suggest that connections between the left and right hemispheres of the brain are particularly important for cognitive processing speed.

Genetic correlations between cognitive processing speed and accuracy and health-related traits

We tested the genetic correlations between the two factors and 40 traits related to mental health[19,27–36], encompassing socioeconomic status (2), risk behaviors (15), psychiatric disorders (10), personality (5), and sleep (9). Among these, 11 traits exhibited significant genetic correlations with CPS ($r_g = -0.55$ to 0.09, Bonferroni corrected $p < 0.05$), while 27 traits showed significance for CPA ($r_g = -0.38$ to 0.60, corrected $p < 0.05$). Notably, part of these correlations (18 traits) differed significantly between the two factors ($z = -9.71$ to 8.39, corrected $p < 0.05$; Fig. 3 and Supplementary Data 10). Because a shorter response time means higher cognitive processing speed, the genetic correlation with CPS was negated when compared with those of CPS in Fig. 3, and the original values for these analyses can be found in Supplementary Data 10. For the majority of these traits, the absolute values of genetic correlation were higher with CPA than CPS, except for some,

such as playing computer games ($r = 0.55$ vs. 0.30, $z = 6.48$, $p < 5e^{-8}$) and bipolar disorders ($r = -0.25$ vs. -0.13, $z = 3.54$, $p < 5e^{-4}$). These results underscored the significant associations between general cognitive functions and health-related phenotypes, revealing more prominent roles of CPA for various risk behaviors compared to CPS.

Mendelian randomization revealed a significant causal relationship between the two factors and psychiatric disorders

We investigated the causal relationship between the two latent factors and nine psychiatric disorders through a two-directional two-sample Mendelian randomization (MR[14,15]) analysis (Supplementary Data 11–12). In the forward MR analysis, we observed a significant causal influence of CPS on schizophrenia ($b = 2.31$, $se = 0.32$, $p < 10^{-12}$), along with a significant causal influence of CPA on schizophrenia ($b = -2.07$, $se = 0.55$, $p < 0.0002$). In the reverse MR analysis, a significant causal influence of major depressive disorder (MDD) on CPS ($b = 0.005$, $se = 0.0009$, $p < 10^{-7}$) was found, as well as schizophrenia exerting a causal influence on both CPS ($b = 0.027$, $se = 0.003$, $p < 10^{-24}$) and CPA ($b = -0.018$, $se = 0.003$, $p < 10^{-7}$). Sensitive analyses validated the above causal results including other four MR methods (Fig. 4), leave-one-out analyses (Supplementary Fig. 3), and assessment for pleiotropy (Supplementary Data 12).

Annotation analysis revealed distinct neurobiological substrates underlying cognitive processing speed and accuracy

We performed annotation analyses on the GWAS summary statistics of CPS and CPA using the MAGMA software[37] in the FUMA platform[38]. Notably, 513 and 445 significant genes were identified for CPS and CPA, respectively (Supplementary Data 13-14, Bonferroni-corrected $p < 0.05$). Enrichment analysis revealed one significant Gene Ontology (GO) term[39] for CPS, namely, postsynaptic membrane ($b = 0.30$, $se = 0.035$, Bonferroni-corrected $p < 0.05$, Fig. 5a, Supplementary Data 15). Additionally, two significant terms were identified for CPA, namely, the generation of neurons and neurogenesis ($b = 0.032$ and 0.031, $se = 0.028$ and 0.026, Bonferroni-corrected $p < 0.05$, Fig. 5a, Supplementary Data 16).

We further tested how the significant genes were expressed in GTEx 54 general tissues[40] for CPS and CPA. Similar tissues were enriched in both factors, particularly brain-related tissues and the pituitary as expected (Fig. 5b and Supplementary Data 17). Moreover, we found the mRNA expression of CPS-related genes was significantly higher during late infancy stages, a key developmental stage for white matter myelination that may support the processing speed ($b = 0.08$, $se = 0.026$, $p < 0.0006$, Fig. 5c, Supplementary Data 18), while no significant results were observed for the mRNA expression of CPA-related genes across developmental periods.

In the cell-type-specific analysis[40], both factors showed significant enrichment in Gamma-aminobutyric acid (GABA)-related cell types in the fetal prefrontal and midbrain, as well as in hybrid neurons in the human cortex. Furthermore, the CPS-related genes exhibited significant enrichment in inhibitory lysosome-associated membrane protein 5 (LAMP5) in the lateral geniculate nucleus (LGN) and GABA in the hippocampus. In contrast, the CPA-related

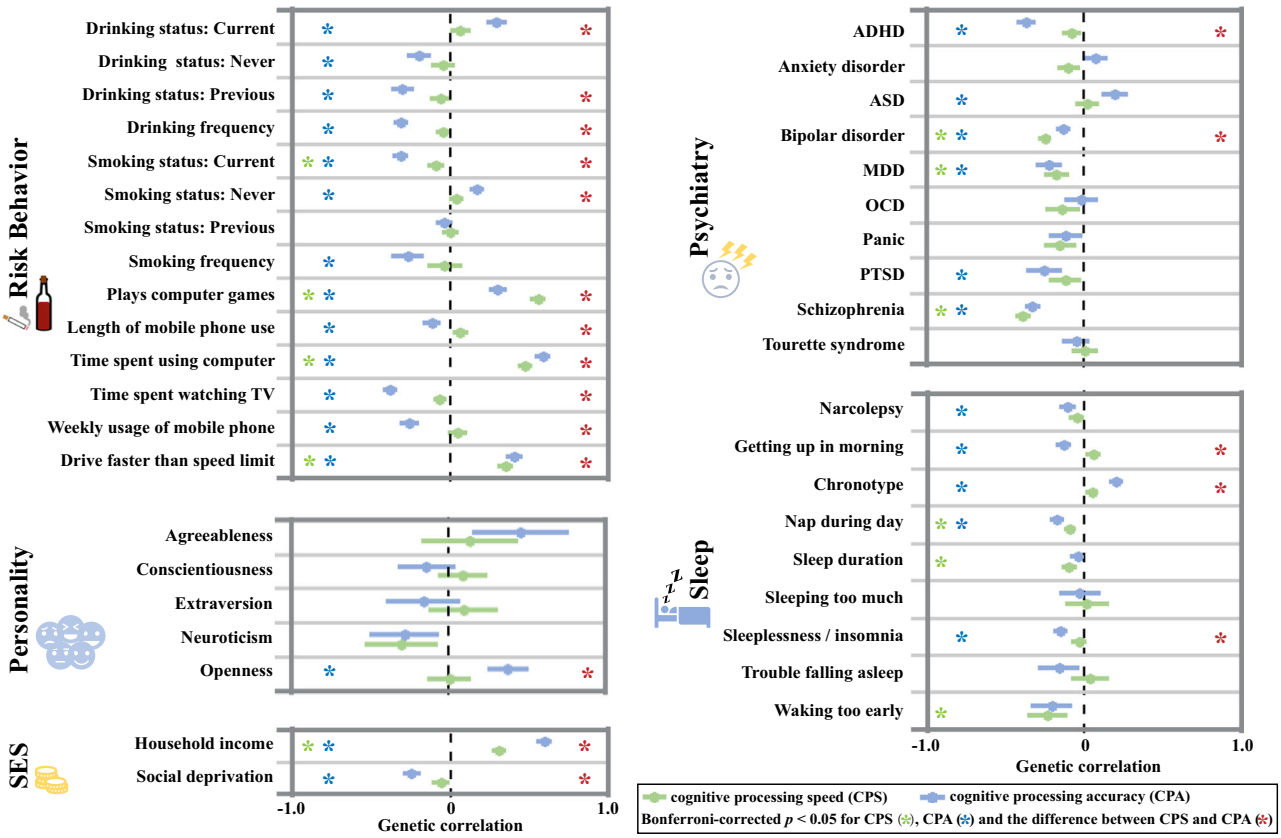

Fig. 3 | Genetic correlations between the two factors and 40 mental health-related traits. The traits were classed into five categories including risk behaviors (e.g. smoking, drinking, screen exposure, and driving, $n = 32{,}614$ to 455,838), personality ($n = 20{,}669$), socioeconomic status (SES, $n = 392{,}422$), psychiatric disorders ($n = 5910$ to 123,787), and sleep-related phenotypes ($n = 57{,}215$–455,848). See Supplementary Data 10 for the details of the sample size used in these analyses. The forest plot indicates the estimation (dot) and standard error (line) of the genetic correlations between each trait 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. The error band indicates the estimation ± 95%CI of the genetic correlation. Z-test was utilized to obtain the two-sided p-values. Significant results were defined as Bonferroni corrected $p < 0.05$. See Supplementary Data 10 for the exact p-values.

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genes showed significant enrichment in GABAergic cells in the prefrontal cortex at 16 gestational weeks (GW16) and in excitatory neurons in the psychENCODE developmental dataset (Fig. 5d and Supplementary Data 20). These findings suggested that the two components had both common and distinct elements at the cellular level.

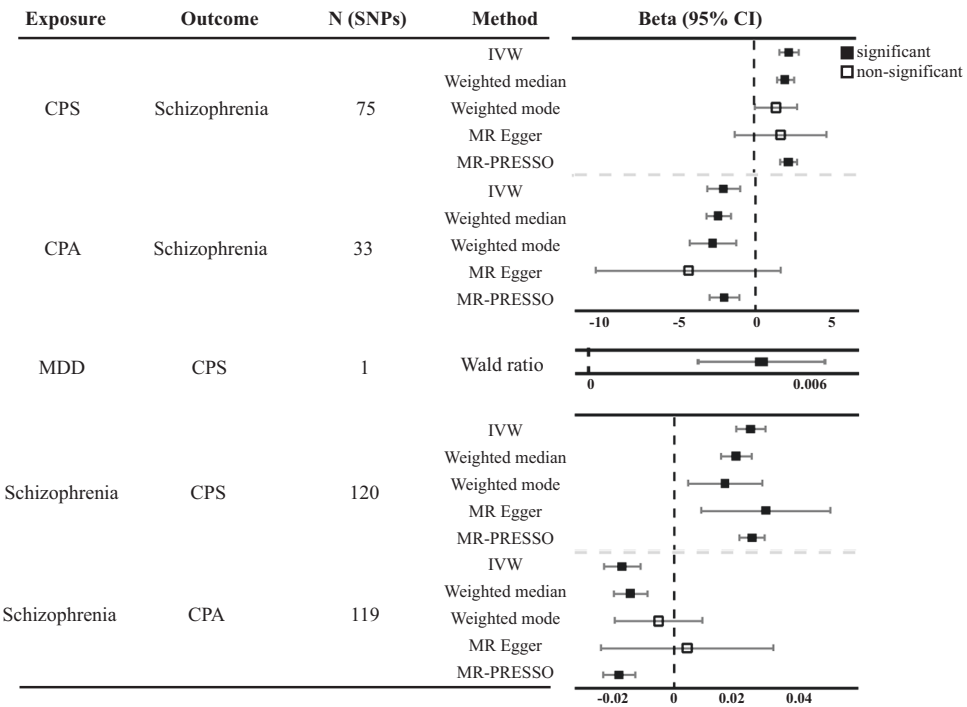

Fig. 4 | Causalities in the two-sample two-direction Mendelian randomization analyses between the CPS/CPA and psychiatric disorders. The forest plot showed significant causalities in the solid square with different estimation methods. Effective sample size was 92983 and 57604 for MDD and Schizophrenia, respectively. CPS cognitive processing speed, CPA cognitive processing accuracy. The error band indicates ± 95% CI of the causal effect in the Mendelian randomization analyses. Significant results were defined as Bonferroni corrected $p < 0.05$. See Supplementary Data 12 for the exact p-values.

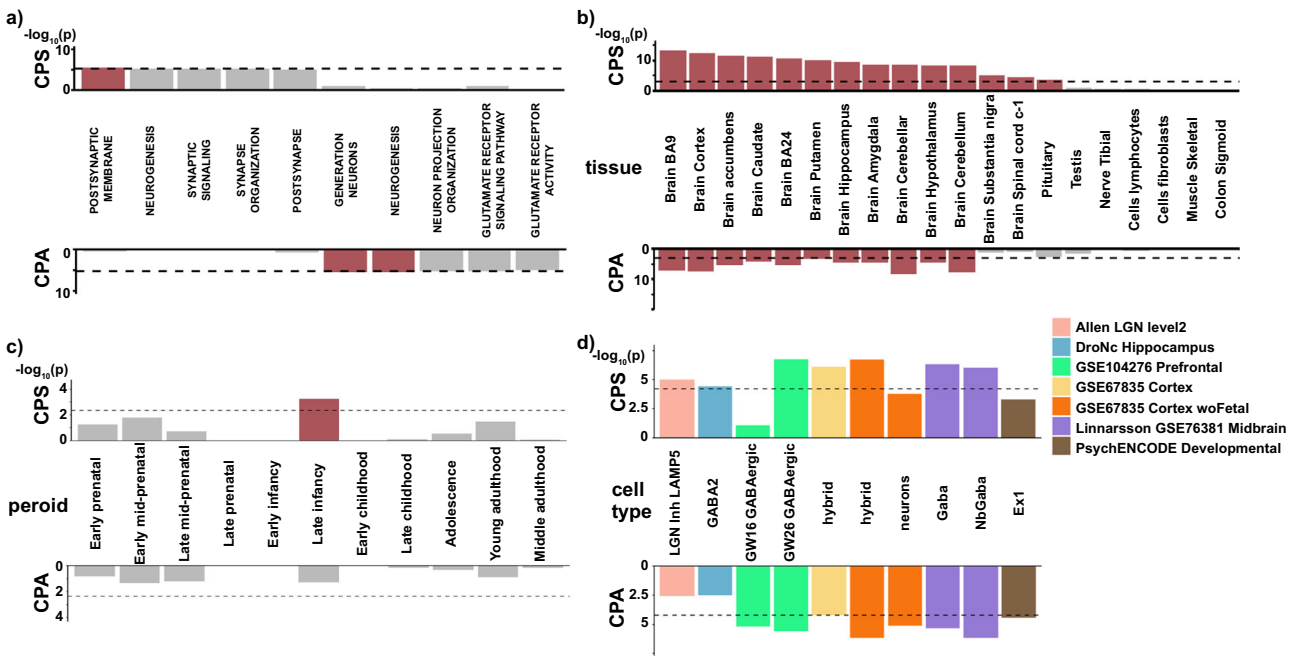

Fig. 5 | Results of the annotation analysis for cognitive processing speed and accuracy. a The top 5 results of the MAGMA gene-set analysis for the two factors separately (full results were shown in Supplementary Data 15–16). **b** The top 20 results of GTEx tissue-specific enrichment analysis (full results were shown in Supplementary Data 17). **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 corrected $p < 0.05$. 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.

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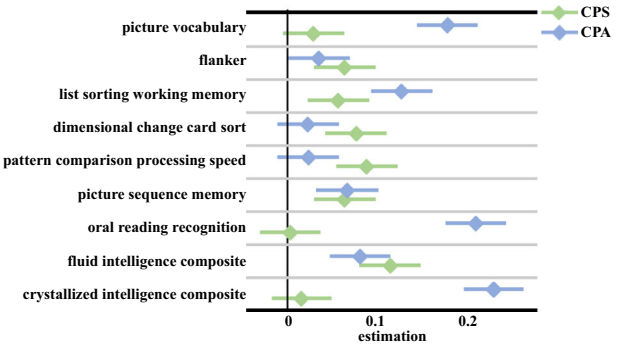

Fig. 6 | Polygenic score analysis of the two factors on the multiple cognitive abilities in young adolescents. The forest plots showed the estimation of the effects of PGS scores on all 7 cognitive abilities and 2 composite cognitive scores in the ABCD datasets ($n = 4968$). The x-axis indicates the estimation of the regression coefficient in the linear mixed-effects model and the error band indicates the estimation ± 95%CI.

The polygenic score analysis revealed the genetic variation of cognitive processing speed and accuracy was significantly associated with cognitive development in young adolescents

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 $p < 0.05$, Supplementary Data 20). Considering the high correlation between CPA and CPS, we further included the PGS scores of both 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 and Supplementary Data 20). For the composite scores, we revealed that PGS for CPS was significantly associated with the fluid intelligence composite ($b = -0.114$, $se = 0.017$, $p < 10^{-10}$) 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 showed a weaker association with the fluid intelligence composite ($b = 0.081$, $se = 0.017$, $p < 10^{-5}$, Fig. 6 and Supplementary Data 20). These findings demonstrated the separation of the two gene scores in relation to fluid and crystallized intelligence tasks and highlighted their substantial contributions to the development of diverse cognitive abilities in children.

Discussion

Using genomic SEM, we segregated two latent factors, namely, cognitive processing speed and accuracy that deciphered independent dimensions of general cognitive function. Notably, the CPS factor exhibited distinctions from previously identified cognitive phenotypes, while the CPA factor demonstrated similarity to general cognitive ability. Genetic correlations based on neuroimage phenotypes revealed that microstructural variations in white matter tracts underpinned CPS but not CPA. Health-related traits, including screen exposure, drinking, smoking, and sleep status, exhibited differential genetic correlations with CPS and CPA. We further demonstrated a significant causal relationship between these cognitive factors and psychiatric conditions (e.g., schizophrenia), implying a crucial covariation between cognitive ability and mental health. In addition, enrichment analysis highlighted diverse neurobiological annotations for these two factors, suggesting unique neural mechanisms underlying them. Lastly, the PGS score of the two cognitive factors could significantly explain the individual variations in multiple cognitive abilities in young adolescents, unveiling the important contributions of the two factors to normal cognitive development.

Before delving into our results, it's crucial to examine the relationship between the two latent factors and prior studies to avoid confusion in cognitive terminology. For CPS, our review identified two types of similar measurements in previous studies: one focused on general processing speeds from multiple tasks[7,9] and the other on reaction time tasks alone[5,6,11,12]. The former, with a limited sample size ($n = 1311–32,070$), identified a single effective SNP (rs17518584), which did not survive the threshold in our study ($p = 4.73 e^{-5}$). The latter, despite large sample sizes ($n = 282,217–432,297$), showed inconsistent results across studies. Utilizing a GWAS summary with the most significant SNPs from these studies, we found a moderate genetic correlation between reaction time with the latent factor of CPS ($r_g = 0.55$), signifying a different genetic basis between the CPS and simple reaction time. Concerning CPA, our analysis may not yield new elements compared to general cognitive ability but provided an independent measure in contrast to CPS. Notably, our current study employed different cognitive tasks compared to previous studies[10,22,24,25], yet the results exhibited a high level of correlation, supporting the reliability of the extracted components using genomic structural equation modeling.

We performed a comprehensive analysis that revealed distinct neuroimaging and genetic features underlying the two factors. A notable difference is that the CPS but not the CPA exhibits a significant correlation with white matter fibers. This finding aligns with prior imaging-behavior studies that demonstrated a significant link between fluid intelligence and white matter microstructure[41–43]. Given the pivotal role of these white matter fibers as information highways in the brain, higher integrity or myelination (higher FA) of fiber tracts might enhance information processing speed[44]. Annotation analyses further revealed significant enrichment during late infancy, a critical period for white matter myelination development[45]. The significantly associated fibers mainly included the superior longitudinal fasciculus, superior frontal-occipital fasciculus, corona radiata, and corpus callosum. The dorsal association fibers such as the superior frontal-occipital fasciculus connect the occipital and frontal lobes, serving as an important bridge between visual processing and executive functions, thus could be an important basis for the cognitive processing speed in vision-based tasks[46,47]. The corpus callosum is the largest interhemispheric commissure and an important pathway for information processing between the two hemispheres. Previous studies have also reported associations between the myelination of the corpus callosum and processing speed in healthy adults[48]. As for the cortical cortex, CPS-related regions were located in the anterior and dorsal occipital lobes, which may reflect that CPS is more dependent on basic sensory abilities. While 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[49,50].

Previous studies have reported a notable genetic correlation between the *g* factor and various traits, including vascular-metabolic and neuropsychiatric aspects[5]. Extending these findings, our study identified a significant correlation between CPA/CPS and several health-related behaviors, such as screen exposure and sleep status. For most health-related traits, the correlations were negative, meaning higher cognitive abilities were associated with healthier lifestyles or states (lower alcohol and smoking frequency or lower risk of psychiatric disorders). There were some exceptions such as computer use, playing computer gaming, and ASD. The positive link between

computer use and intelligence may be because most jobs today, especially mental jobs, rely on computers. The high correlation between computer games and CPS may be because video games benefit cognitive processing speed[51,52], but more causal evidence is needed to verify this point. The positive correlation between ASD and cognitive ability was also reported in the previous study[20,53], which we thought was an interesting result, but the mechanism is not well studied yet. Future studies may be able to delve deeper into the genetic pleiotropy between neurological disease and cognitive ability.

Furthermore, we established a significant causal relationship between these cognitive factors and psychiatric disorders. In particular, we found a bidirectional causal interaction between schizophrenia and both CPA/CPS. Deficits in multiple cognitive domains, especially cognitive processing speed, are a core clinical feature of schizophrenia[54,55]. Our finding also supported the hypothesis of schizophrenia for general cognitive impairment[56]. In addition, other Mendelian randomization analyses have reported causal associations between white matter microstructure and schizophrenia[57]. Therefore, one may speculate a complex interaction between schizophrenia, brain white matter, and cognitive processing speed.

Several limitations should be noted in interpreting our results. First, the cognition-related traits used in the present study were limited and lacked the phenotypes for sensorimotor or language abilities. The inclusion of more comprehensive cognitive tasks may lead to more representative estimates of general cognitive abilities at the time of factor extraction. Second, 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. Third, we only estimated the genetic correlation but not the causal relationship between general cognitive ability and other health-related traits, which was due to the sample overlap between the datasets. Therefore, whether cognitive ability leads to a healthy lifestyle (or vice versa) still needs further evidence.

In summary, through the genomic SEM, we found that two latent cognitive factors underlined multiple cognitive phenotypes, namely cognitive processing speed and accuracy. Those two factors showed distinct neuroimaging signatures, genetic architecture, and associations with health-related traits. The findings not only delineate the diverse neurobiology associated with general cognitive abilities but also shed light on their connections with brain health and a broad spectrum of cognitive development.

Methods

GWAS datasets

We utilized GWAS summary statistics on cognitive abilities obtained from a previous investigation[19], which employed fastGWA to analyze 2173 traits across 456,422 individuals in the UK Biobank. This dataset provided 14 cognition-related traits with sample sizes ranging from 24,713 – 455,496, detailed in Supplementary Data 2. These traits predominantly originated from seven cognitive tasks, including fluid intelligence/reasoning, numeric memory, pairs matching, prospective memory, reaction time, symbol digit substitution, and trial-making tests. 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).

GenomicSEM analyses

We employed the GenomicSEM[13] package in R (version 4.2.2) to perform factor analyses on the 14 cognitive traits. First, we preprocessed the 14 GWAS summary statistic files using the munge function. 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 the MHC regions. Subsequently, we applied the Linkage Disequilibrium Score Regression (LDSC[20]) method to calculate a genetic covariance matrix (S) and a sampling covariance matrix (V). An exploratory factor analysis with two factors and Promax rotation was performed on the S matrix to examine the separation between the two factors. These two factors, namely, cognitive processing speed (CPS) and cognitive processing accuracy (CPA), effectively distinguished components related to speed and accuracy, accounting for 58% of the genetic variation (Supplementary Data 3). In a follow-up step, a confirmatory factor analysis (CFA) with the two factors demonstrated a good model fit with $\chi^2(69) = 1125$, Akaike Information Criteria (AIC) = 1197, Comparative Fit Index (CFI) = 0.9992, and Standard Root Mean Square Residual (SRMR) = 0.0736. Finally, we standardized the 14 cognition-related GWAS summary data using the sumstats function and used the userGWAS function to estimate the significant SNPs for CPA/CPS factors. We estimated the QSNP heterogeneity statistic for the two factors and removed the SNPs showing significant effect ($p < 5e^{-8}$), resulting in 3750 SNPs removed in the CPA factor and 404 SNPs removed in the CPS factor.

We found that in the data-driven model mentioned above, the CPS factor loaded on some measurements related to accuracy. Therefore, 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 (Supplementary Fig. 4), 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 (Supplementary Data 7) and found that the genetic correlations were similar between the two models.

Genetic correlation

We estimated the genetic correlation in the context of the factor model between the two factors (i.e. CPS and CPA) and various traits, including previously reported cognitive phenotypes ($n = 9$; reaction time[5]; common executive function[11]; two general intelligence[10,22]; educational attainment[10]; cognitive and noncognitive skills[24]; cognitive and noncognitive performance[25]), brain structure ($n = 408$[26]), socioeconomic status ($n = 2$, household income and social deprivation[19]), risk behaviors ($n = 15$[19]), psychiatric disorders ($n = 10$[28–36,58]), personality ($n = 5$[27]), and sleep ($n = 9$[19]). False Discovery Rate (FDR) correction was applied in brain structure considering the small effect size and large number of the phenotypes while Bonferroni correction was applied on other phenotypes. For a comprehensive understanding of these traits, a detailed description was provided in Supplementary Data 7 and 10. For the brain structure phenotypes, we used the cortical brain volume, cortical thickness of 148 cortical regions, and the mean fractional anisotropy (FA), and diffusivity (MD) value along the 48 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 $p < 0.05$).

The comparison of genetic correlation between CPS and CPA 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, and se is the standard error of the estimate. The comparison of effect sizes between the two factors in the subsequent analyses followed a similar formula.

Annotation analyses
All analyses in this section were conducted using the FUMA platform[38], and Bonferroni corrections were applied to account for multiple tests in all subsequent analyses.

Leading SNPs
The leading SNPs for CPS/CPA were chosen based on a significance threshold of p-value < $2.5e^{-8}$, a window size <250 kb, and two criteria for defining leading SNPs: a linkage disequilibrium (r^2) threshold of 0.6 and a lead SNP definition threshold of 0.1. The reference panel used was 1000 G Phase 3 European.

SNP-to-gene mapping
This analysis was conducted using the default parameters in the FUMA processes, without the application of any optional SNP filtering.

Gene-set analysis
Gene-set analysis was conducted using MAGMA, covering a total of 10,526 gene sets categorized into three classes of Gene Ontology (GO[39]) terms—biological processes, molecular function, and cellular components. The gene sets were obtained from MsigDB (v7.0[59,60]).

MAGMA expression analysis
We utilized MAGMA[37] to investigate whether genes associated with the two factors (i.e. CPS and CPA) exhibited selective expression in the BrainSpan gene expression data[61] and GTEx tissue data[61]. The BrainSpan data covered 11 developmental periods spanning from early prenatal to middle adulthood and the GTEx tissue data encompassed 54 different tissue types.

Cell type analysis
We utilized the cell type function[40] within the FUMA platform to assess whether genes associated with CPS /CPA demonstrated specificity in certain cell types based on human brain expression datasets.

Two-sample Mendelian randomization analysis
In the two-sample MR analyses[14,15], instrumental SNPs for exposures were selected using the clump function in PLINK software (v1.9). Genomic data from the European superpopulation in the 1000 Genomes Project[62] served as the linkage disequilibrium (LD) reference, with a restriction to bi-allelic SNPs and a minor allele frequency > 0.1. LD pruning parameters were set at $r^2 = 0.001$, window size = 10,000 kilobase pairs, and a p-value threshold of $5e^{-8}$ for exposures. Subsequently, SNPs significantly associated with outcomes or three potential cofounders (alcohol intake frequency, smoking frequency, and household income, $p < 5e^{-8}$) were removed. Data harmonization was achieved using the harmonise_data function in the TwoSampleMR v0.5.6 R package, ensuring consistent allele usage for genetic variant association estimation. The primary analysis method employed was the Inverse Variance-Weighted (IVW[63]) regression with multiplicative random effects. For the significant results with the IVW method, we conducted four other methods to assess the robustness of the results including weighted median method, weighted mode, MR-Egger, and MR-PRESSO[64]. The Wald ratio method[65] was used when only one instrument was available. MR-Egger regression[66] and MR-PRESSO test were applied to evaluate potential directional pleiotropy bias, and a leave-one-out analysis was performed to check for the influence of individual SNPs on the causal association.

To prevent sample overlap between the two factors and the GWAS summary for psychiatric disorders, only the dataset without the UK Biobank sample was considered. The analysis included nine psychiatric disorders: attention deficit hyperactivity disorder (ADHD[29]), anxiety disorder[67], autism spectrum disorder (ASD[30]), bipolar disorder (BD[34]), major depressive disorder (MDD[32]), obsessive-compulsive disorder (OCD[31]), panic disorder[58], schizophrenia[36], and Tourette syndrome (TS[35]). For subsequent analyses, the two factors were initially treated as exposures (forward MR) and then as outcomes (inverse MR). Bonferroni corrections were applied for the multiple tests.

ABCD datasets
Genotype data. The polygenic scores (PGS) analysis[16] of CPS and CPA defined based on the primary results were applied to the genetic data from the Adolescent Brain Cognitive Development (ABCD) study (v4[18,68]). The ABCD data used in this study included genetic data[69] and cognitive scores[17] collected at the baseline, from 11,875 children aged 9 and 10 from 21 research sites across the United States between October 2016 and October 2018. All study procedures received approval from institutional review boards at individual sites, and written consent was obtained from parents, with verbal assent from the children[70].

We referred to the previous methods in the related paper[71,72] to estimate population stratification and combined the pre-imputed genotype data with the 1000 Genome Phase 3 data (https://www.internationalgenome.org/). We used the first five principal components to identify population clusters using UMAP, resulting in 7 broad populations including Africans, Americans, Bengali, Finnish Europeans, Non-Finnish Europeans, East Asians, and South Asians. For the PGS analyses, only non-Finnish Europeans ($n = 6161$) were included. Post-imputation quality control measures were implemented, eliminating SNPs with low minor allele frequencies (MAF < 0.01), poor imputation ($r^2 < 0.3$), high missingness (>0.05), and those failing the Hardy-Weinberg disequilibrium test ($p < 10^{-6}$). Finally, 11,540,083 autosomal SNPs were retained for the subsequent analysis.

Cognitive variables. Cognitive ability was evaluated using nine age-corrected standard scores obtained from the NIH Toolbox[17,73]. These scores encompassed picture vocabulary, flanker, pattern comparison processing speed, picture sequence memory, oral reading recognition, list sorting working memory, dimensional change card sort, fluid intelligence composite, and crystallized intelligence composite.

We excluded preterm-born infants with gestational age <37 weeks and randomly excluded one participant from each pair with a closed gene relationship (pi-hat > 0.1875) estimated with individual genotype data using PLINK (v1.9). We also excluded individuals with incomplete data (e.g. cognitive scores and demographic data). Finally, 3843 subjects (mean age: 9.92 ± 0.61 years, 2039 males) remained in the following PGS analysis.

PGS analysis. PRScs (https://github.com/getian107/PRScs)[16] 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. 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.

Reporting summary
Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability
The GWAS summary statistics are available following the corresponding reference, the main data comes from the Psychiatric Genomics

Consortium (https://pgc.unc.edu/for-researchers/download-results/), Oxford Brain Imaging Genetics Server (https://open.win.ox.ac.uk/ukbiobank/big40/), GWAS Catalog (https://www.ebi.ac.uk/gwas/home), and fastGWA summary statistics for UKB imputed data (https://yanglab.westlake.edu.cn/data/ukb_fastgwa/imp/). The ABCD data (https://nda.nih.gov/abcd) are not openly available due to data privacy laws, but access can be obtained upon application at NDA website (https://nda.nih.gov/abcd/request-access). The genetic data of the 1000 Genomes project is available online (https://www.internationalgenome.org/). The GWAS results of the CPS and CPA generated in this study have been deposited in the GWAS Catalog (CPS: GCST90446168: https://www.ebi.ac.uk/gwas/studies/GCST90446168 and CPA: GCST90446169: https://www.ebi.ac.uk/gwas/studies/GCST90446169), noted that the effective sample size for the factors reported in the data was calculated following the method on the GenomicSEM website (https://github.com/GenomicSEM/GenomicSEM/wiki/5.-Multivariate-GWAS).

Code availability

Code used to create the two factors is available at https://github.com/zjuwulab/GenomicSEM-CognitiveProcessing. Other softwares or packages used in this study include MATLAB (v2018a), R (v4.2.2), GenomicSEM (https://github.com/GenomicSEM/GenomicSEM), TwoSampleMR (v0.1.2), Plink (v1.90b7), and FUMA.

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Author contributions

M.L., X.D., and D.W. conceptualized the study; M.L. and Y.C. designed the analytic approach; M.L. and X.D. analyzed the data and visualized the results; M.L. and D.W. wrote the manuscript; Z.C. and X.X. helped in the analyses; X.X., and Z.Z. helped in the writing.

Competing interests

The authors declare no competing interests.

Additional information

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