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Genome-wide Association Study Shows That Executive Functioning Is Influenced by GABAergic Processes and Is a Neurocognitive Genetic Correlate of Psychiatric Disorders

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ABSTRACT

BACKGROUND: Deficits in executive functions (EFs), cognitive processes that control goal-directed behaviors, are associated with psychopathology and neurologic disorders. Little is known about the molecular bases of individual differences in EFs. Prior candidate gene studies have been underpowered in their search for dopaminergic processes involved in cognitive functioning, and existing genome-wide association studies of EFs used small sample sizes and/or focused on individual tasks that are imprecise measures of EFs.

METHODS: We conducted a genome-wide association study of a common EF (cEF) factor score based on multiple tasks in the UK Biobank (n = 427,037 individuals of European descent).

RESULTS: We found 129 independent genome-wide significant lead variants in 112 distinct loci. cEF was associated with fast synaptic transmission processes (synaptic, potassium channel, and GABA [gamma-aminobutyric acid] pathways) in gene-based analyses. cEF was genetically correlated with measures of intelligence (IQ) and cognitive processing speed, but cEF and IQ showed differential genetic associations with psychiatric disorders and educational attainment.

CONCLUSIONS: Results suggest that cEF is a genetically distinct cognitive construct that is particularly relevant to understanding the genetic variance in psychiatric disorders.

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Deficits in executive functions (EFs), cognitive control processes that regulate thoughts and actions during goal-directed behavior (1), characterize many brain disorders. They are associated with almost all psychiatric disorders, leading some to suggest that EF deficits are a transdiagnostic risk factor for psychopathology (2–5). Recent work using single nucleotide polymorphism (SNP) effects from large genome-wide association studies (GWASs) to estimate genetic correlations suggests that cognition-psychopathology associations may be partially genetic in origin (6–8). These studies have primarily focused on general cognitive ability (g) or IQ, the cognitive construct with the largest GWAS sample sizes. However, adult phenotypic and twin studies suggest that a common EF (cEF) factor capturing variance shared across diverse EF tasks is distinguishable from IQ at the phenotypic and genetic levels and predicts behavior over and above IQ (1,9,10). Here, we conducted a GWAS of a cEF factor score generated from UK Biobank (UKB) data (11) to discover the molecular underpinnings of cEF. We then tested the hypotheses that cEF is genetically separable from IQ and cognitive processing speed and is the cognitive dimension most relevant for understanding genetic variation underlying psychopathology.

EFs are a family of cognitive functions (12) that include response inhibition, interference control, working memory updating and capacity, and mental set-shifting (1). Because EFs are control processes, EF tasks involve processes that are being controlled (e.g., visual processing) in addition to the control processes of interest (e.g., biasing attention toward task-relevant information) (13). These noncontrol processes contribute to individual differences in performance on specific tasks, leading to the task impurity problem (13). Thus, GWAS loci and molecular processes associated with individual EF tasks may capture cognitive processes other than EFs. Individual EF tasks can also show low reliability (13), decreasing power for association tests. The task impurity and reliability problems can be reduced by extracting common variance across multiple EF tasks with a cEF factor (9,14,15).

Five independent twin studies have shown that across samples and ages, cEF is moderately to highly heritable (46%–100%) (14–17) and highly phenotypically and genetically stable across time (10,18). However, little is known about the

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molecular underpinnings of cEF. Most historical perspectives from the candidate gene (19) and animal (20) literature argued that neurocognitive function is supported by metabotropic processes, particularly the slow neuromodulator effects of dopaminergic systems, although candidate gene associations often fail to replicate in large, well-powered GWASs (21). Work in humans and monkeys suggests that fast ionotropic processes influence EFs, particularly the excitatory neurotransmitter glutamate (via activation of anti-NMDA receptors) (22). Fast inhibitory GABAergic (gamma-aminobutyric acidergic) processes have also been studied in relation to EFs, particularly tasks that require response inhibition, interference control, and selection (23). Existing GWASs of EFs have had insufficient power to test hypotheses regarding these molecular mechanisms. To date, the largest GWASs of EFs and processing speed (24,25) focused on individual neurocognitive tasks (study *N*s = 1311–32,070) and collectively identified only 2 genome-wide significant variants.

In contrast, GWASs of IQ have been conducted with large sample sizes and yielded numerous associations (6–8). These associations may improve understanding of cEF, which correlates moderately with IQ (9,26); however, cEF and IQ are not genetically identical, at least not in adults. In young adult and middle-aged twin samples (9,14), phenotypic and genetic correlations of cEF with IQ are moderate (*r*s = 0.53–0.68; r_gs = 0.57–0.59) and significantly lower than 1.0. Importantly, IQ genetically correlates with variance specific to working memory processes in addition to cEF (9,14), suggesting that IQ variation is supported by both cEF and working memory–specific abilities in adults. Phenotypic literature also suggests that EFs show discriminant predictive validity in behavioral problems when controlling for IQ (27). Genetic correlations derived from GWASs provide an opportunity to evaluate whether cEF may capture distinct genetic variance from IQ and show stronger a relationship with psychopathology.

Here, we report a GWAS of a phenotypic cEF factor score based on the commonality of 5 EF tasks assessed at multiple occasions in the UKB (*n* = 427,037). We also conducted a GWAS of factor scores for IQ (verbal-numerical reasoning) (*n* = 216,381) and cognitive processing speed (*n* = 432,297) for comparison. We validated the factors by demonstrating that polygenic scores (PGSs) for cEF and IQ based on these GWASs differentially predicted multiple EF latent variables and IQ in deeply phenotyped young adult samples. We hypothesized that the genetic correlation of cEF with IQ would be substantial but significantly lower than 1.0 and that cEF would be genetically associated with psychopathology when controlling for IQ and speed.

METHODS AND MATERIALS

Participants

Participants were 501,826 individuals in the UKB study (11,28) who had completed at least 1 cognitive assessment at the time that the data were released to us (Table S1 in Supplement 2). We restricted genetic analyses to 427,037 individuals of European ancestry as determined by principal component (PC) analysis (mean age = 56.849 years, SD = 8.009; 54% female) whose genotypes were imputed to the Haplotype Reference Consortium (29), 1000 Genomes, and UK10K reference panels by the UKB (28).

Measures

The cognitive measures (Figure 1; Supplemental Methods in Supplement 1) included 1 classic neuropsychological EF task, the Trail Making Test, and the following 4 other cognitive tasks: symbol digit substitution, backward digit span, prospective memory, and pairs matching. A validation study of the UKB cognitive measures (30) showed that these tasks correlate with reference measures in ways that suggest that they include executive components, as discussed in detail in Supplemental Methods in Supplement 1. We reasoned that a common factor extracting shared variance across these tasks and the Trail Making Test would be similar to the cEF factors that have been examined in smaller studies (10,15,16,18). We also included measures of IQ (the fluid intelligence/reasoning test) and speed (the "Snap" game reaction time).

Analytic Procedures

Factor Scores. We focused on a phenotypic cEF factor score, which was possible because the tasks used in our model were all from the same UKB sample. Using a phenotypic factor score (vs. a genetic factor with genomic structural equation modeling [GenomicSEM]) has the following advantages: 1) its interpretation is consistent with similar factors estimated in the phenotypic literature, and 2) the result is a score that we can return to UKB for use in other phenotypic and genetic studies. Figure 2A presents the correlations among the cognitive measures (see Table 1 for genetic correlations). We used Mplus for the confirmatory factor analysis used to obtain the cEF scores (Figure 2B). Model fit was good (comparative fit index = 0.980, root-mean-square error of approximation = 0.009) (see Table S2 in Supplement 2 for fit statistics of all structural equation models). We also calculated IQ and speed factor scores using relevant measures from UKB (see Supplemental Methods in Supplement 1).

Genetic Analyses. We followed the same procedure for GWASs of the cEF, speed, and IQ factor scores. We ran a test of association using BOLT-LMM (31), controlling for age, age^2, sex, the first 10 European PCs, the first 10 global PCs, batch, and site. We tested the consistency of the cEF results by conducting GWASs in 2 UKB subsamples; participants in the densely assessed sample (*n* = 93,024) completed at least the Trail Making Test, a classic neuropsychological EF task that has been used to tap cEF factors in prior studies (10,15), whereas the sparsely phenotyped sample consisted of the remaining individuals who completed at least 1 neurocognitive task and were unrelated to people in the densely phenotyped sample (*n* = 256,135).

Genome-wide results were entered in the FUMA/MAGMA (32) pipeline (33), linkage disequilibrium score (LDSC) regression (34), and PrediXcan (35) to characterize the results. We calculated genetic correlations of cEF with psychiatric, personality, neurologic, and health-related outcomes via LD Hub (36) with the GWAS summary statistics from the full sample.

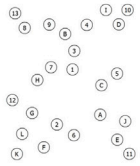
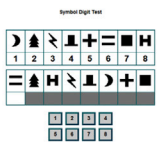
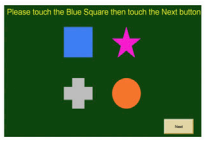
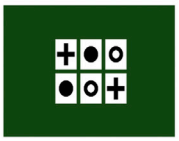
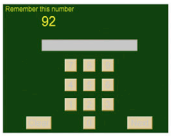
Measure	N	Description	Illustration	Cognitive Construct Tapped
Trail Making Test[a]				
Online	104,050	The alphanumeric condition (shown here) requires participants to join 25 circles enclosing numbers and letters (1-13, A-L) in alternating order (1-A-2-B…). Total time is compared to a control condition requiring joining 25 circles enclosing the numbers 1-25 in ascending order.		cEF: Requires avoiding the prepotent tendency to join stimuli in ascending order and switch between 2 sets of stimuli. Regressing out the control condition removes variation due to basic motor and processing speed.
Symbol Digit Substitution[b]				
Online	117,785	Given a top grid with 8 symbols above digits 1-8, indicate the digits that go with the rearranged symbols in the lower grid. Complete as many grids as possible in 1 minute.		cEF and Speed: Although often used as a processing speed measure, also requires EF to avoid the prepotent tendency to enter numbers in order and to update symbol–number pairings across grids.
Prospective Memory[c]				
Initial visit	171,309	Before other cognitive tests, participants were told they would be asked to touch a blue square at the end of the games, but that they really are supposed to touch the orange circle. After all the tests they were shown four shapes and asked to touch the blue square.		cEF: Requires memory for a goal that must be used to override the more salient current instruction.
Repeat visit	20,314			
Imaging visit	15,880			
Pairs Matching[d]				
Initial visit	484,340	Memorize an array of 6 or 12 cards with symbols (3 or 6 pairs). Once the cards were face down, try to select matching pairs from the array. If a correct pair was selected, it disappeared. Continue until all pairs are identified.		cEF: Requires working memory maintenance and updating ability as incorrect pairs are revealed.
Repeat visit	20,085			
Imaging visit	15,472			
Online	114,828			
Backward Digit Span (called "numeric memory" by UKB)[e]				
Initial visit	50,116	Recall numbers with increasing numbers of digits (from 2-12) in reverse order.		cEF: Requires working memory maintenance and manipulation.
Imaging visit	4,237			
Online	111,086			
Intelligence (called "fluid intelligence/reasoning" by UKB)[f]				
Initial visit	165,486	Answer as many of 13 questions as possible in 2 minutes.		IQ: Taps knowledge and verbal/numerical reasoning.
Repeat visit	20,115			
Imaging visit	15,450			
Online	120,030			
Speed (called "snap game" by UKB)[g]				
Initial visit	165,486	View 2 cards at a time for 2 seconds, press a button as quickly as possible when they matched. Task included 5 practice pairs and 7 scored pairs.		Speed: Assesses simple processing speed.
Repeat visit	20,115			
Imaging visit	15,450			

Figure 1. Descriptions of cognitive measures used to obtain factor scores. See Supplemental Methods in Supplement 1 for additional details and Table S1 in Supplement 2 for descriptive statistics. [a]Dependent measure was the unstandardized residual of the $\log_{10}$-transformed time in seconds to correctly complete the alphanumeric set after regressing out the $\log_{10}$-transformed numeric path time; [b]Dependent measure was the number of symbol digit matches made correctly in 1 minute; [c]Dependent measure was a categorical variable coded as 1 for correct and 0 for incorrect on first try; [d]Dependent measure was the sum of the $\log_{10}$-transformed number of incorrect matches + 1 in the 6- and 12-card rounds; [e]Dependent measure was the maximum number of digits remembered correctly; [f]Dependent measure was the number of correct answers; [g]Dependent measure was the $\log_{10}$-transformed mean time in milliseconds to correctly identify matches across 7 pairs, excluding pairs with times <50 ms (anticipatory responses) and >2000 ms (responses that occurred after cards had disappeared). Scores were reversed in models so higher numbers indicated faster speed. cEF, common executive function; UKB, UK Biobank.

A Phenotypic Correlations

	Trails	SymDig	PM1	PM2	PM3	Pairs1	Pairs2	Pairs3	PairsO	Digit1	Digit3	DigitO
Trails												
SymDig	0.34											
PM1	0.20	0.24										
PM2	0.22	0.25	0.71									
PM3	0.22	0.24	0.52	0.69								
Pairs1	0.19	0.25	0.28	0.22	0.19							
Pairs2	0.18	0.26	0.24	0.23	0.22	0.23						
Pairs3	0.19	0.28	0.19	0.21	0.19	0.23	0.22					
PairsO	0.22	0.27	0.18	0.22	0.20	0.23	0.24	0.24				
Digit1	0.25	0.19	0.29	0.31	0.21	0.19	0.16	0.05	0.14			
Digit3	0.27	0.25	0.12	0.21	0.18	0.18	0.15	0.16	0.16	0.57		
DigitO	0.24	0.23	0.16	0.21	0.19	0.13	0.13	0.13	0.15	0.43	0.50	

B Confirmatory Factor Analysis Model

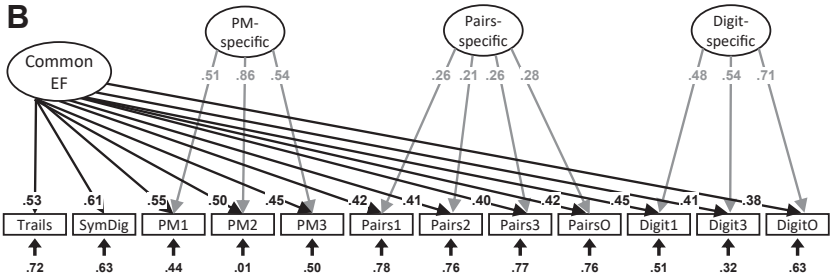


Figure 2. Development of a cEF factor across cognitive tasks in the UK Biobank. **(A)** Correlations taken from Mplus. **(B)** Confirmatory factor analysis model used to extract factor scores. Ellipses indicate latent variables; rectangles indicate observed variables. Numbers on arrows are standardized factor loadings, and numbers at the end of arrows are residual variances. All parameters were statistically significant ($p < .05$). Task names with 1 indicate first assessment, 2 repeat assessment, 3 imaging visit assessment, and O online follow-up. Directionality was reversed for some variables so that for all variables, higher scores indicate better performance. cEF, common executive function; digit, digit span; Pairs, pairs matching; PM, prospective memory; SymDig, symbol digit substitution (online); Trails, Trail Making Test (online).

We used multitrait-based conditional and joint analysis (within the genome-wide complex trait analysis–generalized summary-data-based Mendelian randomization family of methods) (37) using GWAS summary data to discover SNP effects that were related to cEF above and beyond IQ and vice versa (per SNP). We then ran the same FUMA/MAGMA pipeline on the resulting summary statistics to discover what biological pathways remained after accounting for the other cognitive ability.

We used GenomicSEM (38) to evaluate genetic multiple regression models using our factor scores to predict individual outcomes and psychopathology factors. We also used

Table 1. Heritability (Diagonal) and Genetic Correlations (Off-Diagonal) Between cEF Indicators and cEF Factor Scores

Measure	Symbol Digit	Pairs Matching	Digit Span	Prospective Memory	Trail Making	Dense cEF	Sparse cEF	Full cEF
Symbol Digit	0.1245 (0.0079)							
Pairs Matching	0.6603 (0.0271)	0.0713 (0.003)						
Digit Span	0.3226 (0.0345)	0.4420 (0.0263)	0.1337 (0.0069)					
Prospective Memory	0.4479 (0.0414)	0.5982 (0.0348)	0.4539 (0.0355)	0.0527 (0.0039)				
Trail Making	0.7126 (0.0322)	0.7085 (0.0317)	0.6530 (0.0293)	0.5927 (0.0463)	0.1136 (0.0084)			
Dense Sample cEF	0.8428 (0.0138)	0.8580 (0.0207)	0.6653 (0.0214)	0.6416 (0.0365)	0.9274 (0.0133)	0.1894 (0.0105)		
Sparse Sample cEF	0.7031 (0.0307)	0.9831 (0.0074)	0.5580 (0.0259)	0.7052 (0.0308)	0.7771 (0.0381)	0.9230 (0.0286)	0.0696 (0.0038)	
Full Sample cEF	0.7683 (0.0178)	0.9527 (0.0047)	0.6164 (0.0178)	0.7046 (0.0255)	0.8452 (0.0215)	0.9629 (0.0106)	0.9892 (0.0073)	0.0906 (0.0038)

The heritability of each measure is shown on the diagonal. The lower diagonal contains the genetic correlations of each indicator and cEF factor scores in the densely phenotyped (dense), sparsely phenotyped (sparse), and full samples, as estimated by linkage disequilibrium score regression. Standard errors are in parentheses. When there were multiple assessments of the same task (pairs matching, digit span), the measure is the average of the *z* scores for all assessments, except for the categorical prospective memory task, for which the measure used for this table is the first assessment.

cEF, common executive function.

GenomicSEM to run a confirmatory factor analysis and GWAS using the individual cEF task GWAS summary statistics, then evaluated its similarity to our cEF factor GWAS by assessing the genetic correlation, overlapping genome-wide signal, and consistency of SNP effects. We did not compute a GWAS for IQ or speed in GenomicSEM, given that they included fewer indicators and are not the primary focus of this study.

PGS Analyses. We used the UKB GWAS summary statistics to calculate PGSs for cEF and IQ in 2 twin samples (39) (see Supplemental Methods in Supplement 1). PGSs were generated with summary best linear unbiased predictor analyses, using all SNPs with the –score function in PLINK (version 1.90b4.4) (40).

RESULTS

GWASs of cEF Factor Score

We found 129 lead ($r^2 < 0.1$) and 299 independent ($r^2 < 0.6$) SNPs in 112 distinct loci that were significantly associated with cEF in the full sample (Figure 3; Figures S1 and S2 in Supplement 1; Tables S3–S9 in Supplement 2). The SNP with the lowest p value (rs12707117, $\beta = -0.012$, $p = 2.1 \times 10^{-26}$) is an expression quantitative trait locus in cerebellar tissue mapped to *EXOC4*. Q-Q plots (Figure S1 in Supplement 1) showed departure from expected p values under the null hypothesis for the full sample and the subsamples ($\lambda_{full} = 1.6946$, $\lambda_{dense} = 1.311$, $\lambda_{sparse} = 1.3101$), but the low LDSC intercepts (full = 1.0381, dense = 1.0128, sparse = 1.0238) suggest that this inflation reflects polygenicity rather than confounding stratification.

The SNP heritability (SNP-h^2) of cEF estimated via BOLT-REML was 0.104 (SE = 0.002) and via LDSC was 0.091 (SE = 0.0038) (see Table 1). Although the LDSC SNP-h^2 for the densely and sparsely phenotyped subsamples differed as expected (see Supplemental Methods in Supplement 1), their genetic correlation ($r_g = 0.923$) confirmed that they measured substantially overlapping constructs (see Supplemental Results in Supplement 1 for further comparisons). Therefore, the analyses that are described subsequently use the full sample.

Comparison to GenomicSEM Analysis

To evaluate the similarity of our results across methods, we used GenomicSEM to run a genetic confirmatory factor analysis and GWAS using the 5 individual cEF task GWAS summary statistics (see Supplemental Results in Supplement 1). The genetic correlation between the factor score cEF and GenomicSEM cEF was 0.996 (SE = 0.0009), suggesting very high overlap in the genetic signal across the 2 approaches.

Of the 299 independent ($r^2 < 0.6$) genome-wide significant SNPs for our phenotypic factor score, only 3 showed evidence that they were not mediated by the GenomicSEM cEF factor (i.e., they were task-specific variants) (see Supplemental Results in Supplement 1). These results confirm that our GWAS of the phenotypic factor score is appropriate; thus, we only present the results of our cEF phenotypic factor GWAS.

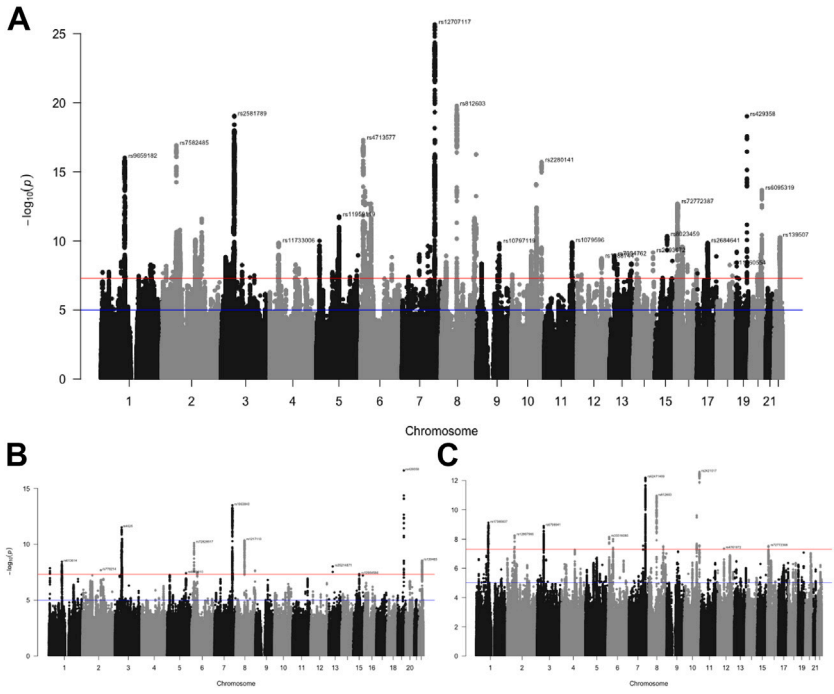


Figure 3. Manhattan plots for genome-wide association studies of common executive functioning factor score. **(A)** Results in the full sample, **(B)** results in the densely phenotyped sample, and **(C)** results in the sparsely phenotyped sample. Each dot is a single nucleotide polymorphism, chromosomes are organized on the x-axis, and the y-axis represents the negative $\log_{10}$ of the p value for each single nucleotide polymorphism.

Genetic Separability of cEF and IQ

cEF factor scores phenotypically correlated with IQ factor scores ($r = 0.35$, $p < .001$) and speed factor scores ($r = 0.28$, $p < .001$). IQ and speed factor scores weakly correlated with each other ($r = 0.17$, $p < .001$), demonstrating divergence at the phenotypic level. SNP-h^2 estimated via BOLT-REML for IQ was 0.242 (SE = 0.003) and for speed was 0.094 (SE = 0.002). LDSC correlations indicated that the IQ factor scores were highly genetically correlated with IQ measures used in prior GWASs (6,7): $r_g = 0.9639$ (SE = 0.0046) to $r_g = 0.9817$ (SE = 0.0043).

Genetic Correlation. The LDSC genetic correlation between cEF and IQ was 0.743 (SE = 0.013, $p = 1.00 \times 10^{-221}$), which was significantly lower than 1.0 ($p = 1.4 \times 10^{-59}$). Similarly, the BOLT-REML genetic correlation was 0.766 (SE = 0.007, $p < \times 10^{-300}$); the 95% CI (0.752–0.778) did not include 1.0. These SNP-based genetic correlations reflect the genetic separability of cEF and IQ and are similar to those from twin-based r_g estimates of IQ and cEF ($r_g = 0.69$) for this age range (14).

GWAS of cEF Conditioned on IQ. Owing to the moderate to high genetic correlation between cEF and IQ, we anticipated that statistical power would be lower for conditional GWAS from multitrait-based conditional and joint analysis. Consistent with this expectation, we identified 41 lead SNPs that were significantly associated with cEF when conditioned on IQ (Figure S3 in Supplement 1; Table S10 in Supplement 2). Notably, the *EXOC4* variant remained significantly associated with cEF, as did *APOE*. We identified 17 lead SNPs significantly associated with IQ, conditioning on cEF (Table S11 in Supplement 2). These results indicate that there are specific genetic effects for cEF and IQ.

PGS Analyses. We created PGSs of cEF and IQ in 2 young adult twin samples that were deeply phenotyped on multiple EF latent variables (cEF, updating-specific, and shifting-specific factors) and Full Scale IQ (FSIQ). To maximize power and minimize the number of tests, we created the model shown in Figure 4, which integrates FSIQ data and the multiple waves of EF data in line with our previously published twin models of these data (16,18). We restricted the PGS analysis to individuals of European ancestry (based on the first 3 PCs), resulting in a final N of 916 (Table S12 in Supplement 2 provides results for less conservative ancestry restrictions).

Controlling for its shared variance with the IQ PGS ($r = 0.607$, SE = 0.027), the cEF PGS predicted the cEF latent variable (standardized $\beta = 0.171$, $p = .014$, partial $r = 0.136$), but not the updating-specific and shifting-specific latent variables or FSIQ (βs = −0.068 to 0.078, ps > .101, partial rs = −0.053 to 0.050). The standardized beta for predicting the cEF latent variable in the twin samples was similar to those we found for predicting the cEF factor scores across the independent UKB subsamples (βs = 0.095–0.145) (see Supplement 1). Thus, the cEF PGS shows a similar association with the deeply phenotyped cEF latent factor as it does with the UKB cEF factor score from which it was derived, supporting the conclusion that they tap similar constructs.

Conversely, controlling for its shared variance with the cEF PGS, the IQ PGS predicted FSIQ ($\beta = 0.149$, $p = .003$, partial $r = 0.121$) as well as the updating-specific latent variable ($\beta = 0.147$, $p = .046$, partial $r = 0.119$), but not the cEF or shifting-specific latent variables (βs = −0.037 to 0.003, ps > .591, partial rs = −0.030 to 0.007). The association of the IQ PGS with the updating-specific latent variable is consistent with prior adult twin studies showing that IQ is genetically related to working memory–specific latent variables over and above its association with cEF (9,14). These results further support the conclusion that the cEF and IQ factors in UKB are tapping similar constructs as those assessed in these carefully phenotyped young adult twin samples.

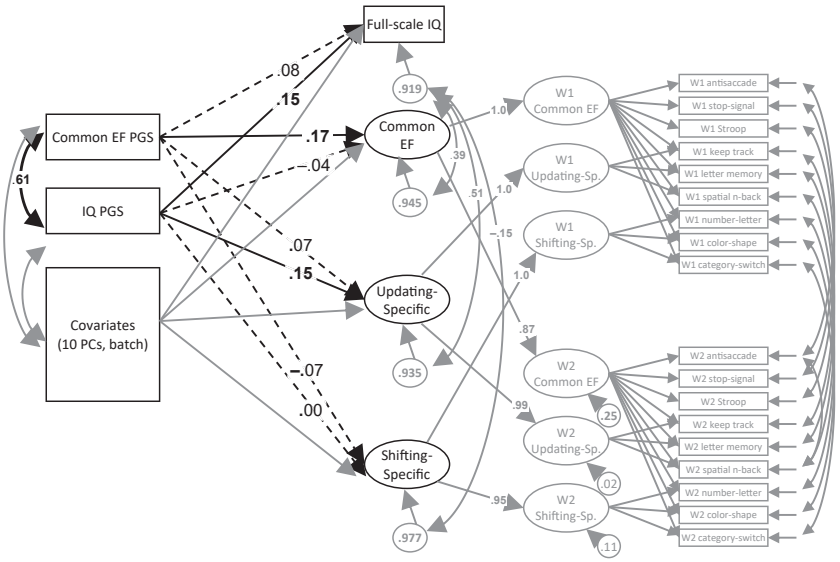


Figure 4. Analysis model of PGSs predicting EF latent variables and Full Scale IQ in Colorado twin data. Paths of primary interest are shown in black with thicker lines. Solid lines and boldface type indicate $p < .05$; dashed lines indicate $p > .05$. Analyses were limited to twins with European ancestry based on the first 3 PCs ($n = 916$ with genetic data). The 3 EF latent variables were based on 9 laboratory tasks at W1 (LTS age 17, $n = 571$; CTS age 21, $n = 298$), and on 9 tasks at W2 (LTS only at age 23, $n = 555$). Full Scale IQ was based on 11 Wechsler Adult Intelligence Scale subtests in the LTS (age 16, $n = 584$), and 4 Wechsler Abbreviated Scale of Intelligence subtests in the CTS (age 21, $n = 297$). Age, sex, and age × sex were regressed out of each measure within each sample and wave prior to analysis. CTS, Community Twin Sample; EF, executive function; LTS, Longitudinal Twin Study; PC, principal component; PGS, polygenic score; W, wave.

Genetic Separability of cEF and IQ Is Key for Psychiatric Dysfunction

LDSC correlations using published GWAS summary statistics indicated that the cEF factor score was significantly negatively genetically correlated (Bonferroni correction $\alpha = 0.0012$ for 41 traits) with all psychiatric disorders except autism spectrum disorder, anxiety, and obsessive-compulsive disorder (Figure 5A; Table S13 in Supplement 2). Although 95% confidence intervals of cEF and IQ r_gs did not overlap for 5 of the 11 psychiatric traits, they did overlap for neuropsychiatric symptoms, personality, sleep, biometric traits, and most substance use measures.

Multiple regressions using GenomicSEM (Figure 5B; Table S14 in Supplement 2) indicated that after controlling for speed and IQ, cEF remained significantly negatively associated with most psychopathologies, except attention-deficit/hyperactivity disorder, but was no longer positively associated with educational attainment. After controlling for speed and cEF, IQ had a significant negative association only with attention-deficit/hyperactivity disorder and had significant positive associations with anorexia nervosa, autism spectrum disorder, bipolar disorder, obsessive-compulsive disorder, and Psychiatric Genomics Consortium (PGC) cross-disorder. Together, these results suggest that the genes specific to cEF and those specific to IQ have different influences on the pathogenesis of psychiatric traits.

To formally test the hypothesis that common psychiatric disorders are more genetically related to cEF than IQ, we estimated a GenomicSEM model in which the cEF, IQ, and speed factor scores predicted 4 genetic psychopathology factors: internalizing, externalizing, and 2 thought disorder factors (psychosis and compulsive disorders) (Figure 6A) ($\chi^2_{59} = 397.333$, comparative fit index = 0.955, standardized root-mean-square residual = 0.077) (see Supplemental Methods in Supplement 1 for details on this model). cEF was significantly negatively associated with the internalizing and both the psychosis and the compulsive thought disorder factors (βs = −0.304 to −0.617), but not the externalizing factor ($\beta = 0.053$), controlling for IQ and speed. In contrast, controlling for cEF and speed, IQ was significantly negatively associated with the externalizing factor ($\beta = -0.359$), but was not significantly associated with the internalizing factor ($\beta = 0.081$) and was positively related to both the psychosis and compulsive thought disorder factors (βs = 0.167–0.565).

Figure 6B highlights results for traits that show the opposite pattern (individual models also shown in Figure 5; Table S14 in Supplement 2): IQ was significantly positively related to educational attainment and childhood IQ, controlling for cEF and speed (βs = 0.79–0.86, $p < 7.4 \times 10^{-9}$); there

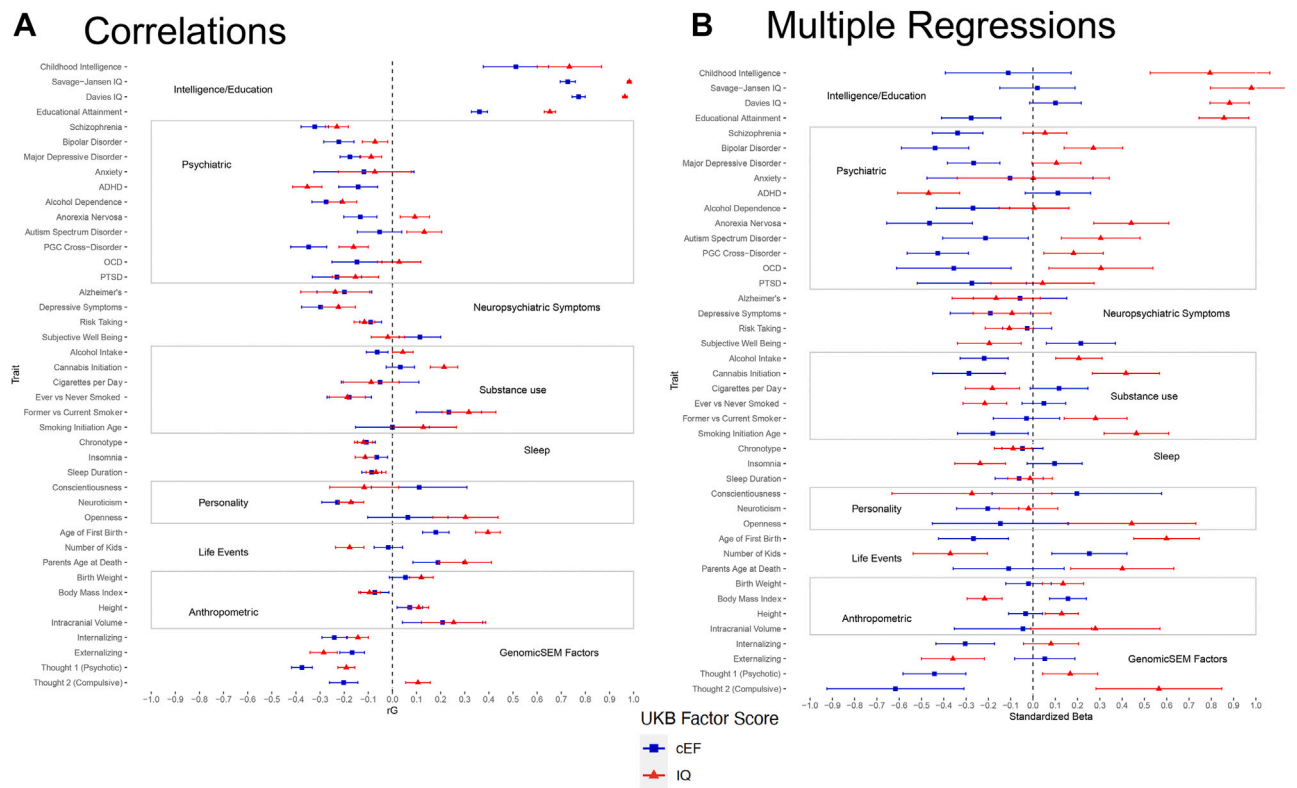


Figure 5. Genetic associations of cEF and IQ factor scores in the UKB with psychiatric, behavioral, and health traits. **(A)** Genetic correlations, estimated with linkage disequilibrium score regression; **(B)** standardized partial regression coefficients from GenomicSEM for cEF controlling for the genetics of IQ and speed, and for IQ controlling for the genetics of cEF and speed. Bars indicate 95% confidence intervals. ADHD, attention-deficit/hyperactivity disorder; cEF, common executive function; OCD, obsessive-compulsive disorder; PGC, Psychiatric Genomics Consortium; PTSD, posttraumatic stress disorder; SEM, structural equation modeling; UKB, UK Biobank.

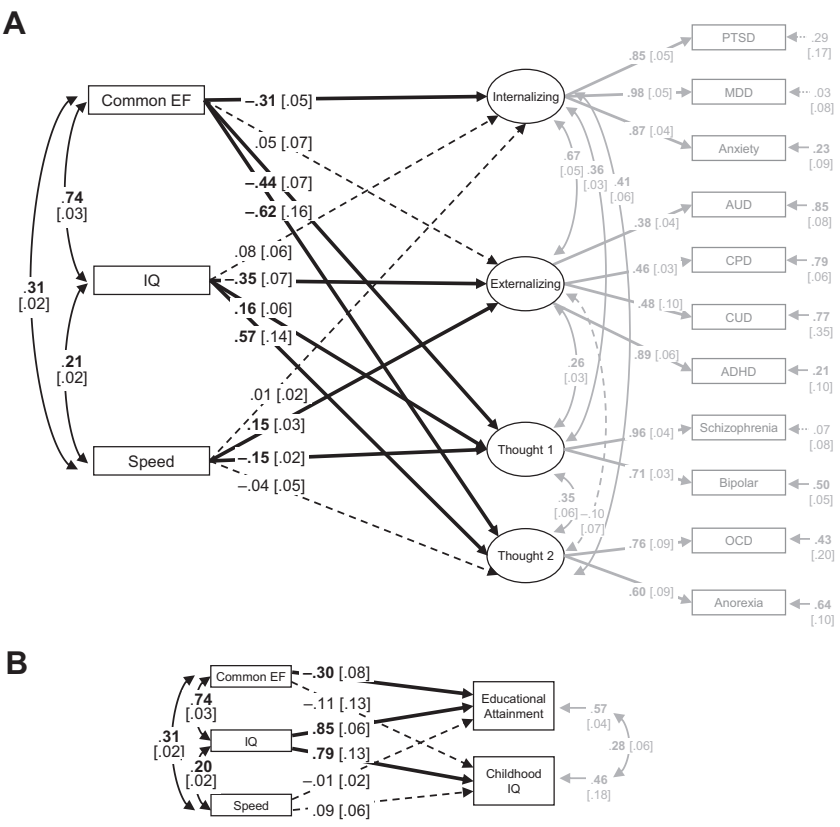


Figure 6. GenomicSEMs. **(A)** cEF, IQ, and speed factor scores predict 4 correlated psychopathology factors; **(B)** cEF, IQ, and speed factor scores predict IQ-related traits. Ellipses indicate latent variables; rectangles indicate observed variables. Numbers on single-headed arrows are fully standardized factor loadings or regression coefficients, numbers on curved double-headed arrows are correlations, and numbers at the ends of arrows are residual variances. Boldface type and solid lines indicate $p <$ .05; dashed lines indicate $p >$ .05. ADHD, attention-deficit/hyperactivity disorder; anorexia, anorexia nervosa; AUD, alcohol use disorder; cEF, common executive functioning; CPD, cigarettes per day; CUD, cannabis use disorder; GenomicSEM, genomic structural equation modeling; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.

was a weaker (educational attainment $\beta = -0.27$, $p = 3.0 \times 10^{-4}$) or a null (childhood IQ ($\beta = -0.11$, $p = .411$) association with cEF controlling for IQ and speed. The cEF genetic association with educational attainment changed from significantly positive to significantly negative after controlling for IQ. cEF showed negative genetic correlations with several disorders that are positively genetically correlated with IQ and educational attainment, such as anorexia nervosa, autism spectrum disorder, and bipolar disorder (37); it may be that genetic variance unique to lower cEF reflects a part of this genetic risk for these disorders that is positively associated with education, leading to this negative partial genetic correlation with higher cEF.

Genetic Associations With cEF Implicate GABAergic and Synaptic Molecular Pathways

In MAGMA, we identified 319 genes significantly associated with cEF in the full sample (Bonferroni $\alpha = 0.05/18597 = 2.689 \times 10^{-6}$), 21 of which were consistent across the smaller and densely and sparsely phenotyped subsamples. The strongest association was again *EXOC4* (Figure S4 in Supplement 1; Table S16 in Supplement 2).

Using gene-set analyses of this gene list, we found 12 associated gene sets (post–Bonferroni correction), all of which could be summarized under the following 3 broad pathways: potassium channel activity, synaptic structure, or GABA receptor activity (Figure 7A; Table S17 in Supplement 2). Suggestive associations of additional pathways (corrected $p < .1$) also implicated synaptic, potassium channel, and ionotropic pathways. To account for some genes appearing in multiple associated pathways, we conducted a conditional gene-set analysis accounting for overlap in genes among the top pathways (41), excluding the Gene Ontology (42,43) terms "synapse," "$GABA_A$ gene," and "voltage-gated potassium channel" pathways because of multicollinearity. Results indicated that the Gene Ontology terms "GABA receptor complex" and "regulation of synapse structure or activity" pathways were associated with cEF over and above other discovered pathways. See Supplemental Results in Supplement 1 for genetic pathway analyses of the cEF multitrait-based conditional and joint analysis, GWAS, and gene expression analyses.

Genetic Associations With cEF Do Not Strongly Implicate Dopaminergic Pathways or Replicate Candidate Genes

Test of Hypothesized/Popular Pathways. While there were 10 nominally significant pathways from a priori–hypothesized categories (dopaminergic, glutaminergic, and GABA pathways), the effect sizes were highest for GABA (Figure 7B). For glutaminergic pathways, the strongest association was NMDA receptor activation, a finding that is supported by previous research (22). Dopaminergic genes showed the weakest evidence for association among hypothesized pathways.

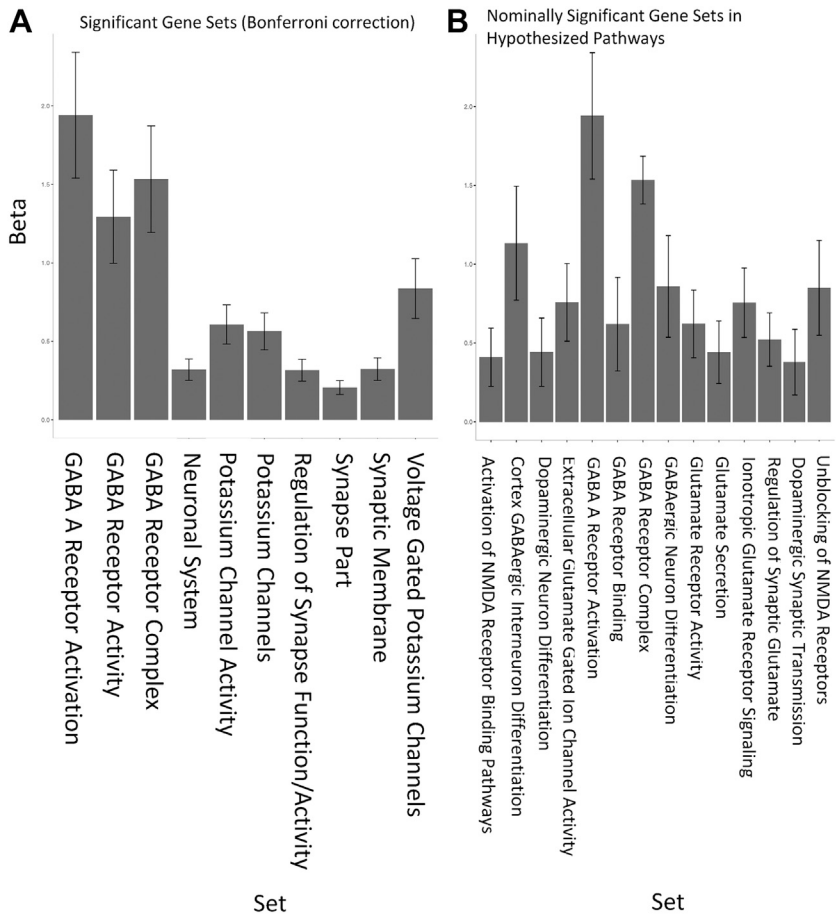


Figure 7. Associated gene-set categories from MAGMA gene-set analysis. Signal Gene Ontology term and curated gene set enrichment for single nucleotide polymorphism influencing common executive function factor score as the MAGMA gene enrichment beta and standard error. **(A)** Gene sets significantly associated after Bonferroni correction for 10,651 tests ($\alpha = 4.7 \times 10^{-6}$). **(B)** Gene sets in hypothesized pathways that were nominally significant. Bars indicate standard errors. GABA, gamma-aminobutyric acid.

Candidate Gene Analysis. We found little evidence that the most popular candidate gene polymorphisms (19) were related to cEF at levels above chance. COMT val/met (rs4680), the most-studied candidate gene polymorphism for EFs, was not significant at the genome-wide level ($\beta = -0.002$, $p = .021$). Previously studied polymorphisms of *DRD2* (rs1079596: $\beta = 0.010$, $p = 1.3 \times 10^{-10}$; rs2075654: $\beta = 0.010$, $p = 1.4 \times 10^{-100}$) were genome-wide significant; however, the effect sizes are much smaller than previously reported (44). Using MAGMA to determine the degree of association of historical EF candidate genes themselves as opposed to the most-studied specific polymorphisms within them (19), only *DRD2* was associated with cEF ($p = 1.15 \times 10^{-12}$, all genewise summary statistics are available in Table S16 in Supplement 2).

DISCUSSION

We conducted a GWAS of a cEF factor score in the UKB that minimized the task impurity problem and incorporated existing knowledge of the factor structure of EFs. Our results suggest that genetic influences on cEF involve variation within fast ionotropic and synaptic pathways, in particular GABAergic pathways, rather than the commonly studied metabotropic and dopaminergic pathways. We demonstrated cEF's genetic overlap with IQ but also found important differences between them, as shown through differential associations with education and psychiatric disorders.

In line with twin literature (9,14), this study supports the importance of cEF as a cognitive dimension that is partially genetically related to IQ and speed in adulthood. Although there was a high genetic correlation between cEF and IQ (LDSC $r_g = 0.743$), this correlation was significantly lower than 1.0, indicating some specific variance. This separability has important implications for understanding cognitive aspects of psychopathology. Controlling for IQ and speed, cEF remained significantly negatively genetically associated with the internalizing disorder and the compulsive and psychotic thought disorder factors, whereas IQ was not. In contrast, after controlling for their genetic overlap, IQ remained strongly positively associated with education and childhood IQ, while cEF was not.

Although cEF and IQ showed genetic separability in their associations with these outcomes when controlling for one another, it is important to remember that they show more similar patterns when considered separately. Consistent with the hypothesis that low cEF is a transdiagnostic risk factor for psychopathology (the *p*-factor) (2–5), cEF negatively correlated with all 4 psychopathology factors. EF also positively

correlated with educational attainment. Similarly, IQ negatively correlated with all but the compulsive thought disorder factor and positively correlated with educational attainment. In some multiple regressions, relationships became nonsignificant, which suggests that the variance unique to cEF or IQ is not related to the outcome; e.g., it appears that the genetic variance in externalizing disorders that is related to cEF overlaps entirely with IQ, whereas the variance unique to cEF is related to the other psychopathology factors. This particular result was unexpected but may be consistent with prior findings that externalizing psychopathology is particularly associated with working memory (45), which includes updating-specific abilities that are related to IQ but not to cEF (see Figure 4). In other cases, relationships with cEF or IQ even slightly reversed (e.g., educational attainment and cEF) in the multiple regressions compared with the correlational models. Such suppression effects suggest that although the variance shared with IQ is positively related to educational attainment, the variance unique to cEF or IQ is actually negatively related. Again, this result was not expected but is intriguing if replicated, as are similar reversals in the relationship of IQ to some psychiatric disorders such as bipolar disorder.

The current results extend those of a recently published GenomicSEM GWAS on a genetic *g* factor (46), which focused on a singular dimension of cognitive ability that included EF, IQ, and speed tasks. Our follow-up analyses of this genetic *g* model (see Supplemental Results in Supplement 1) suggest that some of their reported relationships with educational and mental health outcomes were not fully mediated by the genetic *g* factor. Our results characterize the heterogeneity of these relationships with EF, IQ, and speed, providing a different and complementary perspective to the focus on commonality (46). Both commonality and uniqueness of cognitive abilities are important to consider in relation to psychopathology (8).

Multiple lines of evidence suggested the importance of GABA to cEF variation. We found little evidence that dopaminergic processes genetically relate to individual differences in cEF, outside the *DRD2* gene; other monoamine (dopamine and serotonin) candidate genes were not associated with cEF despite very high power to detect previously reported associations. Together, our findings strongly implicate a key role of fast synaptic communication mechanisms underlying the inheritance of cEF, rather than the slow neuromodulatory processes that are often hypothesized in the literature.

Altered GABAergic functioning is also associated with cognitive deficits in psychiatric illnesses (47–49), consistent with our finding that cEF was genetically correlated with nearly all psychiatric disorders. These results are in line with past literature, suggesting that cEF is broadly genetically associated with psychopathology (2). Disruption to the excitatory/inhibitory neurotransmission balance related to GABAergic processes may explain such transdiagnostic associations with cognitive deficits, particularly EFs (47,48,50).

These results should be interpreted in the context of several limitations. First, attaining the large sample sizes needed for GWASs necessitates minimal phenotyping that might be both shorter and less detailed than gold standard measures of a construct (21). The UKB cognitive battery was not designed to tap cEF. This battery contained 1 classic neuropsychological EF task, the Trail Making Test; the other cognitive measures are not commonly used to assess EFs. However, as described in Figure 1, these tasks do have EF demands. Indeed, a validation study (30) suggested that these bespoke UKB tests correlated similarly or more strongly with reference EF tests (e.g., a tower test) as they did with reference tests for the intended constructs (e.g., memory) (see Supplemental Methods in Supplement 1 for more discussion). Our factor analytic approach enabled us to extract this shared EF variance. We reasoned that a common factor extracting shared variance across these tasks and the Trail Making Test would be closely related to the cEF factors examined in smaller studies (10,15,16,18), 2 of which also used the Trail Making Test (10,15). Indeed, PGSs based on the cEF and IQ factors differentially predicted gold standard EF latent variables and FSIQ in independent, deeply phenotyped young adult samples. However, keeping in mind that different conceptualizations of similar constructs can lead to different results, our findings may be interpreted with caution until there are larger samples with a more complete set of gold standard EF tasks.

Second, our IQ measure was a factor score based on repeated administrations of the UKB's fluid intelligence/reasoning task. This test, which was also included in a recent GWAS of *g* factor (7), includes items that require reasoning and is genetically strongly correlated (r_g = 0.87) (46) with matrix pattern recognition, a classic fluid IQ measure. In the UKB, it shows a different pattern of association with age compared with other UKB cognitive measures, leading some to suggest that it may tap crystallized IQ instead of, or in addition to, fluid IQ (51,52). However, in an independent sample (30), it showed a similar association with cross-sectional age as other UKB cognitive measures and also correlated most strongly with tests of working memory and nonverbal reasoning, leading the authors to suggest that it may be more fluid than was suggested by Hagenaars *et al.* (52). Given these mixed patterns, this measure's genetic associations with cEF and other outcomes may be most appropriately compared with the literature on general IQ (indeed, we examined its relationship to FSIQ in our PGS analysis).

Although we would have preferred to use multiple IQ measures just as we used multiple EF measures, there were not additional IQ measures with sufficient sample sizes. The potential concern that our comparisons of IQ to cEF may be unbalanced is allayed by the following 3 facts: 1) our IQ measure was genetically highly genetically correlated (r_gs = 0.96–0.98) with prior large GWASs of IQ (6,7) that assessed IQ with factor scores as well as the same UKB measure we used; 2) cEF was not uniformly more genetically related to outcomes compared with IQ, but these 2 traits showed differential prediction of psychopathology and educational outcomes; and 3) the PGSs for these factors showed comparable effect sizes (β = 0.17 vs. 0.15) when predicting their gold standard counterparts in the Colorado twin samples, and the IQ PGS also predicted the updating-specific factor (β = 0.15) in these samples, in line with prior findings that the updating-specific factor is genetically related to IQ (9,14).

Finally, because the UKB sample is made up overwhelmingly of participants of European ancestry, we restricted our analysis to European samples to avoid confounds owing to population stratification. Although it is possible and perhaps likely that the molecular underpinnings of cEF generalize to

non-European populations, further work is needed to replicate these observations in diverse populations of sufficient sizes and similar phenotypes.

Conclusions

cEF is heritable and highly polygenic, with a clear indication for a role of synaptic, GABAergic, and ionotropic pathways. cEF is genetically related to, but separable from, IQ, and cEF is robustly related to genetic risk for general psychopathology even controlling for its genetic overlap with general IQ and speed.

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ASH ran the genome-wide association analysis and analyses with summary statistics along with ECM and CLM. ASH, CLM, and NPF wrote the manuscript. NPF sponsored the research, generated the phenotype in the UKB, and conducted the polygenic score analyses along with CEB-B. LME organized the raw genotype data from the UKB as well as the genotype data in the twin samples. MCK, LME, AER, ML, and RHCP provided advice and assistance with analyses and manuscript preparation. All authors contributed to the final written version of the manuscript.

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This research was completed using the UKB under application No. 24795. Summary statistics for GWASs will be available upon publication of this work through the GWAS catalog or available upon request. All results run on FUMA have been made publicly available through that platform. cEF results can be accessed via FUMA (cEF full sample: https://fuma.ctglab.nl/browse/65, cEF densely phenotyped sample: https://fuma.ctglab.nl/browse/66, cEF sparsely phenotyped sample: https://fuma.ctglab.nl/browse/67). Full results for the IQ and speed GWAS are also available on FUMA (IQ: https://fuma.ctglab.nl/browse/114, Speed: https://fuma.ctglab.nl/browse/118). All biological results for cEF-specific and IQ-specific GWAS can be downloaded here (cEF-specific: https://fuma.ctglab.nl/browse/116, IQ-specific: https://fuma.ctglab.nl/browse/117).

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ARTICLE INFORMATION

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