GWAS of Over 427,000 Individuals Establishes GABAergic and Synaptic Molecular Pathways as Key for Cognitive Executive Functions

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Abstract

Executive functions (EFs) are top-down cognitive control mechanisms that direct goal-orientated behaviors. EF deficits are associated with psychopathology and neurological disorders, but little is known about the molecular bases of EF individual differences. Existing genome-wide association studies (GWAS) of EFs used small sample sizes and/or individual tasks, which are mixtures of higher and lower order cognitive mechanisms. To remedy these limitations, we conducted a GWAS of a "Common EF" (cEF) factor based on multiple tasks in the UK Biobank (N=93,027-427,037), finding 299 independent loci. Gene-based analysis found synaptic, potassium channel and GABA pathways associated with cEF. cEF genetically correlated with almost all psychiatric traits and with behavioral and health outcomes. These patterns of genetic correlations were different than those previously found for intelligence. Our results suggest that cEF is neurologically complex and that fast-neuronal processes form a basis for genetically influenced cognitive outcomes in health and psychiatric dysfunction.

Introduction

Neurocognitive executive functioning (EF), or the ability to control and influence one's thoughts and actions to achieve goal-orientated behaviors[1], varies continuously across the general population[2]. EF is correlated with, but distinguishable from, a general intelligence factor at the phenotypic and genetic levels, and predicts behavior over and above intelligence[3]. Further, EF is an important construct in clinical neuroscience, and EF deficits are associated with multiple neurological and behavioral disorders, including Alzheimer's disease[4], vascular dementia[5], lateral sclerosis[6], and almost all psychiatric disorders, including schizophrenia[7], depression[8], ADHD[9], antisocial personality disorder[10], sleeping dysfunction[11], and suicidal ideation[12]. Because of these broad associations, it has been argued that EF deficits are a common risk factor across all psychiatric symptoms[1,13,14]. Furthermore, EF is associated with clinical outcomes within disorders. Among schizophrenia patients, lower scores on EF tasks relate to worse daily functioning[15], higher rates of hospitalization, and higher symptom severity[16], and EF predicts better daily functioning among Alzheimer's patients[17]. Thus, EF differs between cases and controls and, for some disorders, relates to degree of disorder impairment.

Past twin and family studies have established that EF is highly heritable in childhood[18], early adulthood[3] and middle age[19], and the genetic variance underlying EF reflects the same genes across multiple time points[20]. Furthermore, twin studies have shown that EF relates genetically to several different psychiatric disorders[13] and behavioral dimensions of health, like sleep[11]. However, little is known about the molecular underpinnings of EF in humans. Most historical perspectives from the candidate gene[21] and animal[22] literature have argued that neurocognitive function is supported by metabotropic processes, in particular the slow neuromodulator effects of the dopaminergic systems. However, recent work in humans with the

drug ketamine[23] has argued that fast ionotropic processes probably influence neurocognitive ability, in particular, the excitatory neurotransmitter glutamate (via activation of NMDA receptors)[23]. Fast inhibitory GABAergic processes have also been studied in relation to EFs, but are often neglected in the literature[24]. Unfortunately, no GWAS of EF has had sufficient power to compare these mechanisms. To date, the largest GWAS of neurocognitive tasks included 1,311 to 32,070 individuals (depending on the task) and found a single genome-wide significant association for a processing speed task[25]. It is likely that larger samples will be required to discover and differentiate the molecular pathways associated with EF in the general population. As these different mechanisms implicate different pathways for medication targets and overlap with brain disorders, further discovery of these pathways is needed.

Furthermore, all previous molecular genetic studies have measured EF using individual tasks, such as response inhibition, working memory maintenance, updating, mental set shifting, etc. However, because EFs are control processes, each task includes a mixture of “common” EF (cEF) and the lower-level cognitive processes on which each individual EF task operates[2]. These lower-level processes can contribute to individual differences in performance on specific tasks, leading to the "task impurity problem”[2]. This task impurity implies that GWAS hits and molecular processes associated with individual EF tasks may be imperfect proxies of cEF, diluting or obscuring results one would find on cEF itself.

Past work has demonstrated that across multiple cognitive tasks, a cEF factor can be derived to capture the variance shared across EF tasks and remove task-specific processes to solve this task impurity problem[2]. This should increase the effect sizes of associations with cEF[2] and aid in the interpretation of discoveries, which can be tied into the broader literature on cEF. For example, past research suggests psychiatric outcomes are more strongly related to cEF itself

rather than specific EF components, such as working memory updating or task shifting[1,13,14]. Finally, given the separability of intelligence and cEF[3], it is likely that there are unique biological systems acting on cEF apart from those shared with intelligence.

This study is the first to examine a GWAS of cEF with a factor based on multiple cognitive tasks, and it is the largest GWAS sample for any cognitive ability to date. We generated a cEF factor score in the UK Biobank (UKB) sample of over 427,000 individuals of European ancestry based on the commonality of five EF tasks across multiple measurement occasions. We generated a cEF score in the entire sample but also conducted analyses separately in two UKB subsamples, differing in which specific EF measures were collected, in order to ensure consistency of effects across different missingness patterns. The specific goals of our investigation were (1) to catalogue the specific SNPs associated with cEF; (2) to characterize the genetic and molecular pathways underlying cEF; and (3) to understand the degree to which the association between cEF and psychiatric health and wellness is due to shared genetic factors, including whether this pattern is different from past studies of intelligence.

Results

SNP associations and Annotations in the Full Sample

Using confirmatory factor analysis we obtained a factor score of cEF in the full UKB sample of 427,037 individuals. We used this score to conduct a GWAS in the full sample as our main analysis (see Online Methods for generation of model, and Figure 1 for full model). Because the actual *n* for each EF task varied by ascertainment, due to some individuals being part of a more densely measured online sample (see Table 1 for descriptive statistics of indicators, and Table 2 for genetic correlations among indicators), we also tested consistency in

genetic effects by conducting GWAS in two UKB subsamples. First, we conducted a GWAS of the cEF factor score in the more densely measured sample of 93,024 individuals who had the trail-making task and completed an additional online battery (the "dense" sample) of cognitive tasks; we chose this sample based on the trail-making task because trail-making has been used as an indicator of cEF in past genetic studies of cEF and the sample containing trail-making had more dense measurement[18,19]. Our second UKB sample was individuals who completed at least one neurocognitive task and were part of the UKB but did not complete the trail-making task and were unrelated to people measured on the online cognitive battery (n=256,135, the "sparse" sample). All genome-wide results and their annotations for this study can be accessed, including SNP wise effects, gene-wise p-values and pathways, via FUMA (https://fuma.ctglab.nl/browse/65 for the full sample, https://fuma.ctglab.nl/browse/66 for the dense sample, and http://fuma.ctglab.nl/browse/67 for sparse sample results).

We found 299 independent loci significantly associated with cEF in the full sample analysis, using BOLT to run a linear mixed model test of association controlling for age, age^2, sex, first 20 principal components, and batch and site (Figures 2 & S6, & S1-S7). Consistent with these results BOLT-REML estimated SNP-heritability of cEF to be 0.104 (se=0.002). The most significantly associated SNP mapped to *EXOC4* and is an eQTL in cerebellar tissue (β=-.012, p = 2.1e-26). Q-Q plots (supplemental Figure S1) show departure from expected p-values under the null hypothesis for all three samples (lambda_full =1.6946, lambda_dense=1.311, lambda_sparse=1.3101), but low LD-score regression intercepts (Full = 1.0381, Dense = 1.0128, Sparse = 1.0238) which suggests that this inflation reflects high polygenicity of cEF, rather than confounding stratification. Of these associated loci, we identified 334,554 cis-eQTLs within relevant brain tissues. However, not all gene expression was due to cis-eQTLs, as Circos plots

showed 1,329 possible long-range regulatory connection between SNPs, giving credence to the importance of regulatory variation in cEF gene expression. Of particular interest, some of the longest-range connections between SNPs were found on chromosome 17 between C17 (cytokine gene) and LRRC37A2 (Table S6 & Figure S2). These analyses show the high biological complexity of cEF, as cEF is highly polygenic, and this polygenicity and related to a very complex expression profile characterized by both long- and short-range patterns of regulatory expression. Because of the staggering number of eQTLs and the complex pattern of long-range regulatory processes, further analyses looked for convergence across gene-based and tissue-based approaches.

Comparison of the densely- and sparsely-phenotyped subsamples

SNP-heritability of the dense subsample was higher than the sparse subsample (LDSC[26] h^2=.19, se=0.014 and $h^{2=}$.07, se=0.0039, respectively). Nevertheless, both samples appear to measure the same cEF construct, albeit with varying levels of precision, because they were highly genetically correlated (LDSC-based *r*G=0.918, se=0.029). Despite the three-fold smaller sample size in the dense sample, we identified the same number of genome-wide significant loci in both samples (34 independent loci in each, 7 of which were shared between both samples; Supplemental Table S1 & S8-S19), suggesting greater measurement precision in the dense subsample and that adequate measurement of phenotypes is an important aspect of discovering cEF-associated loci. However, the larger number of identified loci when using the combined dataset, demonstrates the statistical power gained from utilizing our factor-based approach to leverage the entire sample. Therefore, we focus our remaining discussion on analyses of the full sample.

Gene-Based Analysis

Gene-Wise Analysis. To discover individual genes associated with cEF, we ran a gene-wise test of association by aggregating effects of all SNPs within 10kb of each gene using the FUMA/MAGMA pipeline. We identified 319 genes significantly associated (Bonferroni α= 0.05/18597 = 2.689e-6) with cEF in the full sample, 21 of which were consistent across the dense and sparse subsamples, with the strongest association again being *EXOC4* (Figure S4, Supplemental Tables 20-22). Inflation of gene-based *p*-values (Q-Q plots in supplemental Figure S3) is likely due to polygenicity, as described above.

Gene-Set Analyses. To discover specific molecular pathways that are most strongly associated with cEF, we performed a gene-set analysis of "Curated Gene Sets" and "GO terms" pathways identified in Msigdb v5.2[27] using MAGMA (5,917 gene-sets tested), with gene-level *p-values* from gene-wise analysis as input. Post-Bonferroni correction, we found 12 associated gene-sets, all of which could be summarized under three broad pathways: potassium channel activity, synaptic structure, or GABA receptor activity (Figure 3A). Suggestive associations of additional pathways, which did not exceed the multiple-testing threshold, also implicated synaptic, potassium channel and ionotropic pathways as being associated with cEF.

To follow up on this analysis we ran a conditional gene-set analysis[28] to investigate which pathways remained significant after accounting for the other top pathways. In this analysis, we excluded the "synapse" GO term pathway, the "$GABA_A$ gene" set pathway, and "voltage-gated potassium channel" pathways due to multicollinearity, as these are supersets of, or overlapped completely with, other significant pathways (particularly "GABA receptor complex" and "voltage-gated potassium channel activity"). The GO terms for "GABA receptor complex" and the GO terms for "regulation of synapse structure or activity" remained significantly associated conditioning on all other significant pathways, meaning that genes

specifically in these molecular pathways have independent and strong contributions to genetic variation in cEF.

Based on the current molecular literature[23], it is possible that glutaminergic and dopaminergic pathways are involved in cEF variation, but we probably lacked statistical power to discover them due to our conservative multiple comparison threshold (genetic pathways are not independent, so a Bonferroni over-corrected). We hypothesized *a priori* that genes in dopaminergic, glutaminergic and GABA pathways would be enriched and extracted the effects of these MBsig pathways that were above nominal significance (but did not meet Bonferroni significance). While there are 10 nominally significant glutaminergic and dopaminergic pathways, the effect sizes and significance values are highest for GABA (Figure 3B). Some glutaminergic pathways were nominally significant. The strongest association was NMDA receptor activation, which is the main pathway targeted by ketamine and previously supported[23]. Finally, dopaminergic genes showed the weakest evidence for association of pre-hypothesized pathways, with only two pathways nominally associated with cEF. Together, these results suggest a strong association of GABA in cEF individual differences, but we cannot completely rule out glutaminergic pathways. Dopaminergic pathways showed the weakest evidence of pre-hypothesized pathways.

We attempted to find converging evidence for GABAergic function using cell-type specific gene expression in three human brain tissues (that were publicly available through FUMA, see supplemental Figure S5 for full discovery results from single-cell type enrichment), specifically the human cortex, the hippocampus and the frontal cortex. We found our GWAS to be significantly enriched in genes specifically expressed in GABA2 cells in the hippocampus, GABAergic neurons in the prefrontal cortex (though this was specific to 26 weeks of gestation)

and hybrid and neurons cells in the whole human cortex (across age), post-Bonferroni correction (within tissue for all cell-types of that tissue).

Gene-Property Analysis. Genes can be differentially expressed in particular tissue types. We used the results of the gene-wise analysis as input for MAGMA/FUMA to conduct gene-property analysis by tissues across 30 broad and 53 specific human tissues in the GTEx sample to ascertain which tissues associated variants were likely influencing gene expression in. After Bonferroni correction, only the brain and pituitary broad tissues were implicated, whereas all 13 specific brain tissues were associated except the substantia nigra and spinal cord-c1 (supplemental Figure S6). No other tissues were implicated.

Transcriptional Profiling. To examine the transcriptional profile across the implicated brain tissues (all GTEx tissues excluding the substantia nigra and the spinal cord c-1), we used PrediXcan[29] to predict brain transcription patterns that lead to improved cEF from our SNP summary statistics and tissue-specific eQTL expression associations from the GTEx sample's[30] 11 associated brain tissues. We found 441 brain tissue-specific transcripts (of 4,324 possible) associated with cEF, post-Bonferroni correction (supplemental Table S23 and Online Figure S7). We then entered this transcriptional profile in the connectivity Map (cMAP)[31]. After filtering for transcripts found in multiple tissues, 78 were also associated with transcriptional changes after exposure to perturbagens in the cMAP. Thirty-three perturbagens mimicked the cEF transcriptional profile (supplemental Table S24). Of note, 3 of the top 15 substances have previous psychiatric and cognitive applications: nicergoline[32], an anti-dementia drug that is shown to be effective in a broad array of behavioral and cognitive disorders in old age; nortriptyline[33], a first-generation tricyclic antidepressant; and chlorpromazine[34], a typical anti-psychotic that is prescribed to treat severe cases of schizophrenia, bipolar, OCD, and depression.

Candidate Gene and Candidate Gene Polymorphism Analysis

Similar to other recent studies on schizophrenia and major depression[35–37], we found no evidence that the most popular candidate gene polymorphisms (those reviewed by [21]) were related to cEF at levels above chance. No polymorphism that is historically studied in the candidate gene literature was genome-wide significant and in the same direction as hypothesized. Likely the most studied candidate gene polymorphism, COMT val/met (rs4680), was not significant at the genome-wide level (β = -.002, p=.021) and was in the opposite direction of effect as what was hypothesized in the candidate gene literature. The popular polymorphisms of the DRD2 gene were genome-wide significant, but in the *opposite direction* as hypothesized by the candidate gene literature (rs1079596: β = 0.010, p=1.3e-10; rs2075654: β = 0.010, p=1.4e-10).

We also used MAGMA to derive combined *p-values* from GWAS summary statistics to determine the degree of association of historical cEF candidate genes (as opposed to the most-studied specific polymorphisms within them), again derived from ref [21]. Only DRD2 was associated with cEF (p=1.15E-12).

Analysis of cEF Full Sample Summary Statistics

Genetic Correlations. We used LD Score regression through LDhub[38] to estimate the genetic correlation between cEF and other major behavioral and neurological phenotypes, many of which have been associated with EF phenotypically and/or genetically in the literature. To summarize briefly, cEF was significantly associated (above Bonferroni correction α = .0011) with all psychiatric disorders (except anorexia, which was nominal, and autism, which was non-significant), all education and intelligence variables and neuroticism. cEF did not show a strong

pattern of association with neurological disorders. We found moderate and nominally significant genetic correlations of cEF with numerous other cognitive, psychiatric, and personality traits (Fig. 4, Supplemental Table S25).

We also examined the genetic correlation of cEF with intelligence, given prior literature suggesting a close relationship[3,39,40]. We estimated the genetic correlation between cEF and intelligence (using summary statistics from Sniekers et al. 2017[41]) to be .71 (se=.0215); this correlation was greater than zero, p=1.00e-221 but also significantly less than 1, p= 1.4e-59), consistent with cEF being genetically separable from intelligence. This SNP-based genetic correlation is similar to those from twin-based rG estimates of IQ and EF (.5 in young adults[3], .69 in middle age[40], and 1 in children[39]). Moreover, cEF was more strongly genetically correlated with bipolar disorder and schizophrenia than was intelligence[42] and the 95% confidence intervals in genetic correlation between cEF and these disorders and intelligence and these disorders did not overlap (Scz-IQ = -.2122 & CI=.049, Scz-EF=-.3457 & CI=.043, BiP-IQ=.0562 & CI=.080, BiP-EF = -.3161 & CI=.067).

Discussion

We discovered and characterized the molecular genetic processes that influence top-down cognitive control (in humans). The genetics of Common Executive Functioning (cEF) are highly complex, as we found 299 independent significant loci associated with cEF. However, the genetic pattern of our results was categorized by genes influencing fast ionotropic and synaptic pathways, in particular GABAergic process, rather than the commonly studied metabotropic and neuronal pathways. Finally, it is likely these fast-synaptic processes influencing cEF could further elucidate mechanisms of psychiatric disorders, as cEF is genetically correlated to all forms of psychiatric distress.

This study used gene-set and cell-type-specific analysis to discover (and test) molecular pathways underlying cEF. We found GABA activity from multiple lines of evidence, and cell-type-specific analyses implicated GABA in both the cortex and hippocampus. Further, GABAergic pathways were the most associated molecular pathways tested and influence cEF above and beyond other neurotransmitter pathways. Finally, synaptic and ionotropic pathways were more strongly associated with cEF than the traditionally studied metabotropic and dopaminergic pathways. Together, the consistency in our findings strongly implicates 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. Interestingly, while there is some past support for GABAergic pathways, of the associated neurotransmitters in the literature, GABA is often neglected[24]. Thus, investigating genetic variation in GABA pathways is a promising future direction to understand top-down cognitive processes and their correlates.

We also hypothesized that glutamate, in particular NMDA receptor agonism, would influence cEF. While several of these pathways were nominally significant, none reached Bonferroni significance, though many were close and this threshold was conservative. As sample sizes of EF tasks increase, we expect GWAS to implicate glutaminergic as well as GABAergic function.

We found little evidence for the most popular cEF molecular theories. Namely, little evidence was found that dopaminergic processes relate to the inherited vulnerability to cEF deficit. It is possible that alterations in dopaminergic function are a consequence, rather than an inherited cause, of cEF performance. Importantly, the dopaminergic candidate genes that are currently used in the neurocognitive and imaging literature[21] were not associated with cEF, despite very high power to detect previously reported associations. This work suggests that

researchers should shift from studying EF using dopaminergic and serotonergic processes to GABA (and perhaps glutaminergic) processes.

We attempted to localize where in the brain these molecular patterns may be most important. In contrast to the widely held belief that EF is a frontal brain phenomenon, the molecular pathways underlying cEF that we detected are almost entirely neurological and likely not confined to one brain region. In addition to the frontal-parietal brain regions classically associated with EF, this work is consistent with imaging studies that have suggested associations between cEF and lower-order brain areas, particularly the cerebellum[43], as this was our most enriched brain area in a gene-property analysis. In this study, the strongest signal came from a variant mapped to *EXOC4*, which influences exocytic vesicles docking to the plasma membrane. The sentinel variant is an eQTL in the cerebellum, and we found significant eQTL enrichment (across the genome) for the cerebellum and a number of other non-cortical brain regions. It is possible that the associations of these regions are due to the need for repeated deliberate action in cognitive abilities, that likely evolved from basic motor processes controlled by the cerebellum[44].

It is likely that the molecular processes underlying cEF are influential in psychiatric dysfunction. We found novel genetic associations with schizophrenia, bipolar disorder, alcohol dependence, Alzheimer's disease, educational attainment, age of first birth, and parents age of death. We also replicated genetic association of cEF with depression[45] and ADHD[46]. These results are in line with past literature, suggesting cEF is a broad risk factor for psychopathology[1,13]. Finally, as recent genome-wide association studies[47] of schizophrenia and medical drug repurposing of bipolar, depression, and anxiety[48] medications have implicated drugs targeting GABAergic processes, it is likely these processes of cEF would be good targets of intervention for the top-down cognitive deficits seen in psychiatric disorders.

While there is substantial and significant overlap between our cEF factor and intelligence, there is some separability based on a genetic correlation significantly below unity. Further, this genetic correlation is likely to be inflated given that previous meta-analyses of intelligence, upon which the genetic correlations were estimated, included cohorts with EF tasks[41,42]. In addition, past work on general intelligence did not discover GABA activity or synaptic pathways (that we found associated with cEF) and, instead, found pathways associated with neurogenesis and neuron development (though the sample size was smaller)[42]. Finally, the separability of cEF and intelligence is reflected in differential correlations with outcomes of interest. cEF genetically correlates more strongly (non-overlapping 95% CIs) with schizophrenia, bipolar disorder, than intelligence (when compared to the results published in Savage, Jensen et al.[42]), whereas, intelligence is more genetically correlated with educational attainment, head size, autism, openness to experience, and smoking behaviors than cEF[41,42]. Thus, in line with twin literature[3], cEF is related to but genetically distinct from intelligence, and this distinction may be key to understanding the cognitive component of psychopathology in particular.

Though most lines of evidence herein implicate cEF as a potential target of intervention, there have been very few (human) studies that have attempted to target cognitive deficits in psychiatric disorders[49]. With our summary statistics as input, we used gene-sets, gene-property analysis and transcriptional profiles to prioritize drug relabeling. Our analyses point to several pharmaceuticals as possible targets for addressing the cognitive deficits in psychiatric disorders. Specifically, nicergoline, nortriptyline, and chlorpromazine induce transcriptional profiles similar to higher cEF and are known to cross the blood-brain barrier. Interestingly, all three drugs have been used to treat a broad array of psychiatric conditions, are older classes of psycho-pharmaceuticals with less specific drug targets, and treat disorders related to EF. Additionally,

all three of these drugs have some modest evidence in favor of their efficacy. For example, nicergoline has been shown to improve glucose uptake and cell firing of ionotropic neurotransmitters[50], so drugs with a similar profile may be a useful area of future investigation. Past work in depressed elderly individuals found improved cognitive abilities and reduced depression symptoms with exposure to nortriptyline[33]. Finally, low doses of chlorpromazine have been shown to improve "cognitive inhibition" in healthy individuals[34]. More work should be done to see how these drugs may influence cognitive abilities, particularly in clinical psychiatric populations.

There are a number of limitations. First, almost all bioinformatic follow-up depended on tissue-based analysis from the GTEx sample. While this sample is the richest source of eQTL data to date, a lack of generalizability from this population would affect our results as well. Further, to the extent that there is a strong genetic correlation in expression across tissues, we expect signal from the multiple correlated brain tissues, and while we used tissue-specific expression, this does not mean we can draw strong conclusions about which tissues are implicated above and beyond one another. Finally, although it is typical in GWAS to focus on European samples, we cannot draw strong conclusions about how well these molecular underpinnings will generalize to non-European populations.

Conclusion

cEF is heritable and highly polygenic, with clear indication for a role of synaptic, GABAergic, and ionotropic pathways. Some of these processes reflect a shared genetic influence on cEF and psychiatric disorders and may be viable pharmacological targets. We establish here a molecular profile of neurocognitive ability that helps clarify the neuro-molecular underpinnings

of individual differences that capture the top-down component of psychiatric dysfunction and well-being.

References Cited

1. Hatoum, A. S., Rhee, S. H., Corley, R. P., Hewitt, J. K. & Friedman, N. P. Do executive functions explain the covariance between internalizing and externalizing behaviors? *Dev. Psychopathol.* 1–17 (2017). doi:10.1017/S0954579417001602

2. Miyake, A. *et al.* The unity and diversity of executive functions and their contributions to complex 'Frontal Lobe' tasks: a latent variable analysis. *Cogn. Psychol.* **41,** 49–100 (2000).

3. Friedman, N. P. *et al.* Individual differences in executive functions are almost entirely genetic in origin. *J. Exp. Psychol. Gen.* **137,** 201–25 (2008).

4. Lafleche, G. & Albert, M. S. Executive function deficits in mild Alzheimer's disease. *Neuropsychology* **9,** 313–320 (1995).

5. McGuinness, B., Barrett, S. L., Craig, D., Lawson, J. & Passmore, A. P. Executive functioning in Alzheimer's disease and vascular dementia. *Int. J. Geriatr. Psychiatry* **25,** n/a-n/a (2009).

6. Abe, K. *et al.* Cognitive function in amyotrophic lateral sclerosis. *J. Neurol. Sci.* **148,** 95–100 (1997).

7. Minzenberg, M. J., Laird, A. R., Thelen, S., Carter, C. S. & Glahn, D. C. Meta-analysis of 41 Functional Neuroimaging Studies of Executive Function in Schizophrenia. *Arch. Gen. Psychiatry* **66,** 811 (2009).

8. Friedman, N. P., du Pont, A., Corley, R. P. & Hewitt, J. K. Longitudinal Relations Between Depressive Symptoms and Executive Functions From Adolescence to Early

Adulthood: A Twin Study. *Clin. Psychol. Sci.* **6,** 543–560 (2018).

9. Boostra, A.M., Oosterlaan, J., Sergeant, J. A. & Buitelaar, J. K. Executive functioning in adult ADHD: a meta-analytic review. *Psychol. Med.* **35,** 1097–1108 (2005).

10. Friedman, N. P., Rhee, S. H., Ross, J. M., Corley, R. P. & Hewitt, J. K. Genetic and environmental relations of executive functions to antisocial personality disorder symptoms and psychopathy. *Int. J. Psychophysiol.* (2018). doi:10.1016/J.IJPSYCHO.2018.12.007

11. Friedman, N. P., Corley, R. P., Hewitt, J. K. & Wright, K. P. Individual Differences in Childhood Sleep Problems Predict Later Cognitive Executive Control. *Sleep* **32,** 323–333 (2009).

12. Brick, L. A. *et al.* Overlapping genetic effects between suicidal ideation and neurocognitive functioning. *J. Affect. Disord.* **249,** 104–111 (2019).

13. Martel, M. M. *et al.* A General Psychopathology Factor (P Factor) in Children: Structural Model Analysis and External Validation Through Familial Risk and Child Global Executive Function. *J. Abnorm. Psychol.* (2016). doi:10.1037/abn0000205

14. Snyder, H. R., Miyake, A. & Hankin, B. L. Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. *Front. Psychol.* **6,** 328 (2015).

15. Bowie, C. R. *et al.* Predicting Schizophrenia Patients' Real-World Behavior with Specific Neuropsychological and Functional Capacity Measures. *Biol. Psychiatry* **63,** 505–511 (2008).

16. Johnson-Selfridge, M. & Zalewski, C. Moderator Variables of Executive Functioning in

Schizophrenia: Meta-Analytic Findings. *Schizophr. Bull.* **27,** 305–316 (2001).

17. Boyle, P. A. *et al.* Executive Dysfunction and Apathy Predict Functional Impairment in Alzheimer Disease. *Am. J. Geriatr. Psychiatry* **11,** 214–221 (2003).

18. Engelhardt, L. E., Briley, D. A., Mann, F. D., Harden, K. P. & Tucker-Drob, E. M. Genes Unite Executive Functions in Childhood. *Psychol. Sci.* **26,** 1151–1163 (2015).

19. Gustavson, D. E. *et al.* Genetic and Environmental Influences on Verbal Fluency in Middle Age: A Longitudinal Twin Study. *Behav. Genet.* **48,** 361–373 (2018).

20. Friedman, N. P. *et al.* Stability and change in executive function abilities from late adolescence to early adulthood: A longitudinal twin study. *Dev. Psychol.* **52,** 326–40 (2016).

21. Barnes, J. J. M., Dean, A. J., Nandam, L. S., O'Connell, R. G. & Bellgrove, M. A. The Molecular Genetics of Executive Function: Role of Monoamine System Genes. *Biol. Psychiatry* **69,** e127–e143 (2011).

22. Robbins, T. W. Chemical neuromodulation of frontal-executive functions in humans and other animals. *Exp. Brain Res.* **133,** 130–138 (2000).

23. Stoet, G. & Snyder, L. H. Effects of the NMDA Antagonist Ketamine on Task-Switching Performance: Evidence for Specific Impairments of Executive Control. *Neuropsychopharmacology* **31,** 1675–1681 (2006).

24. Sarter, M. & Bruno, J. P. The neglected constituent of the basal forebrain corticopetal projection system: GABAergic projections. *Eur. J. Neurosci.* **15,** 1867–1873 (2002).

25. Ibrahim-Verbaas, C. A. *et al.* GWAS for executive function and processing speed suggests

involvement of the CADM2 gene. *Mol. Psychiatry* **21,** 189–197 (2016).

26. Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47,** 291–295 (2015).

27. Subramanian, A. *et al.* Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc. Natl. Acad. Sci. U. S. A.* **102,** 15545–50 (2005).

28. de Leeuw, C. A., Stringer, S., Dekkers, I. A., Heskes, T. & Posthuma, D. Conditional and interaction gene-set analysis reveals novel functional pathways for blood pressure. *Nat. Commun.* **9,** 3768 (2018).

29. Gamazon, E. R. *et al.* A gene-based association method for mapping traits using reference transcriptome data. *Nat. Genet.* **47,** 1091–1098 (2015).

30. GTEx Consortium, T. Gte. The Genotype-Tissue Expression (GTEx) project. *Nat. Genet.* **45,** 580–5 (2013).

31. Lamb, J. *et al.* The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. *Science* **313,** 1929–35 (2006).

32. Saletu, B., Garg, A. & Shoeb, A. Safety of nicergoline as an agent for management of cognitive function disorders. *Biomed Res. Int.* **2014,** 610103 (2014).

33. Doraiswamy, P. M. *et al.* Does Antidepressant Therapy Improve Cognition in Elderly Depressed Patients? *Journals Gerontol. Ser. A Biol. Sci. Med. Sci.* **58,** M1137–M1144 (2003).

34. Beech, A., Powell, T. J., McWilliam, J. & Claridge, G. S. The effect of a small dose of

chlorpromazine on a measure of ‘cognitive inhibition’. *Pers. Individ. Dif.* **11,** 1141–1145 (1990).

35. Farrell, M. S. *et al.* Evaluating historical candidate genes for schizophrenia. *Mol. Psychiatry* **20,** 555–562 (2015).

36. Johnson, E. C. *et al.* No Evidence That Schizophrenia Candidate Genes Are More Associated With Schizophrenia Than Noncandidate Genes. *Biol. Psychiatry* **82,** 702–708 (2017).

37. Border, R. *et al.* No Support for Historical Candidate Gene or Candidate Gene-by-Interaction Hypotheses for Major Depression Across Multiple Large Samples. *Am. J. Psychiatry* **176,** 376–387 (2019).

38. Bulik-Sullivan, B. *et al.* An atlas of genetic correlations across human diseases and traits. *Nat. Genet.* **47,** 1236–1241 (2015).

39. Engelhardt, L. E. *et al.* Strong Genetic Overlap Between Executive Functions and Intelligence. *J. Exp. Psychol. Gen.* **145,** 1141 (2016).

40. Gustavson, D. E. *et al.* Genetic and environmental architecture of executive functions in midlife. *Neuropsychology* **32,** 18–30 (2018).

41. Sniekers, S. *et al.* Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. *Nat. Genet.* **49,** 1107–1112 (2017).

42. Savage, J. E. *et al.* Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat. Genet.* **50,** 912–919 (2018).

43. Reineberg, A. E. & Banich, M. T. Functional connectivity at rest is sensitive to individual differences in executive function: A network analysis. *Hum. Brain Mapp.* **37,** 2959–75 (2016).

44. Buckner, R. L. The Cerebellum and Cognitive Function: 25 Years of Insight from Anatomy and Neuroimaging. *Neuron* **80,** 807–815 (2013).

45. Friedman, N. P., du Pont, A., Corley, R. P. & Hewitt, J. K. Longitudinal Relations Between Depressive Symptoms and Executive Functions From Adolescence to Early Adulthood: A Twin Study. *Clin. Psychol. Sci.* **6,** 543–560 (2018).

46. Young, S. E. *et al.* Behavioral Disinhibition: Liability for Externalizing Spectrum Disorders and Its Genetic and Environmental Relation to Response Inhibition Across Adolescence. *J. Abnorm. Psychol.* **118,** 117–130 (2009).

47. Gaspar, H. A. & Breen, G. Drug enrichment and discovery from schizophrenia genome-wide association results: an analysis and visualisation approach. *Sci. Rep.* **7,** 12460 (2017).

48. Ettinger, A. B. & Argoff, C. E. Use of Antiepileptic Drugs for Nonepileptic Conditions: Psychiatric Disorders and Chronic Pain. *Neurotherapeutics* **4,** 75–83 (2007).

49. Millan, M. J. *et al.* Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat. Rev. Drug Discov.* **11,** 141–168 (2012).

50. Miccheli, A. *et al.* [1-13C]Glucose entry in neuronal and astrocytic intermediary metabolism of aged rats: A study of the effects of nicergoline treatment by 13C NMR spectroscopy. *Brain Res.* **966,** 116–125 (2003).

Table 1. Descriptive Statistics for Cognitive Measures Used to Obtain Factor Scores

Measure	*N*	Mean	SD	Min	Max	Skewness	Kurtosis
Trail making							
Online[a]	104,050	0.00	0.11	-0.44	0.44	0.48	0.73
Numeric[b]	104,052	1.57	0.14	1.14	2.87	0.65	0.67
Alphanumeric[b]	104,050	1.80	0.15	1.31	2.87	0.49	0.46
Symbol-digit substitution							
Online	117,785	19.76	5.11	0	40	-0.40	0.54
Prospective Memory[c]							
Initial visit	171,309	0.24	--	--	--	--	--
Repeat visit	20,314	0.15	--	--	--	--	--
Imaging visit	15,880	0.12	--	--	--	--	--
Pairs Matching[d]							
Initial visit	484,340	0.76	0.37	0.00	2.22	0.39	0.56
Repeat visit	20,085	0.70	0.34	0.00	2.06	0.33	0.55
Imaging visit	15,472	0.66	0.33	0.00	2.00	0.35	0.61
Online	114,828	0.83	0.37	0.00	2.31	0.39	0.26
Digit Span							
Initial visit	50,116	6.69	1.34	2	12	-0.32	0.84
Imaging visit	4,237	6.80	1.24	2	11	-0.20	0.68
Online	111,086	6.92	1.49	2	11	-0.38	1.09

Note. Descriptive statistics and sample information for each task loading on the common executive functioning (cEF) factor from the UKBiobank sample. N includes European and non-European descent in the UKBiobank.
[a]Unstandardized residual of the log10-transformed alphanumeric path time after regressing out the log10-transformed numeric path time; only this score was used in the model.
[b]Log10-transformed total times in seconds to complete the numeric and alphanumeric paths; these variables were not used in the confirmatory factor analysis model but were used to obtain the residualized trails measure used in the model.
[c]Categorical variable coded as 1 for correct and 0 for incorrect on first try. The mean described proportion correct. Dashes indicate that other descriptive statistics were not calculated.
[d]Sum of the log10-transformed number of incorrect matches +1 in the 6- and 12-card rounds.

Table 2. Genetic Correlation between common EF indicators and common EF samples

	Symbol Digit	Pairs Memory	Digit Span	Prospect. Memory	Trail Making	Trails+ cEF	Trails- cEF	Full cEF
Symbol Digit	**0.1245 (0.0079)**							
Pairs Memory	0.6603 (0.0271)	**0.0713 (0.003)**						
Digit Span	0.3226 (0.0345)	0.442 (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)	0.653 (0.0293)	0.5927 (0.0463)	**0.1136 (0.0084)**			
Trails+ sample cEF	0.8428 (0.0138)	0.858 (0.0207)	0.6653 (0.0214)	0.6416 (0.0365)	0.9274 (0.0133)	**0.1894 (0.0105)**		
Trails- sample cEF	0.7031 (0.0307)	0.9831 (0.0074)	0.558 (0.0259)	0.7052 (0.0308)	0.7771 (0.0381)	0.923 (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 (0.0039)**

Note. Lower diagonal matrix representing the genetic correlation and standard error of each indicator and common executive functioning (cEF) factor scores in theTrails+, Trails-, and full samples. as estimated by LD score regression. The heritability of each measure is shown on the diagonal.

A Phenotypic Correlations

	Trails	SymDig	PM1	PM2	PM3	Pairs1	Pairs2	Pairs3	PairsO	Digit1	Digit3
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

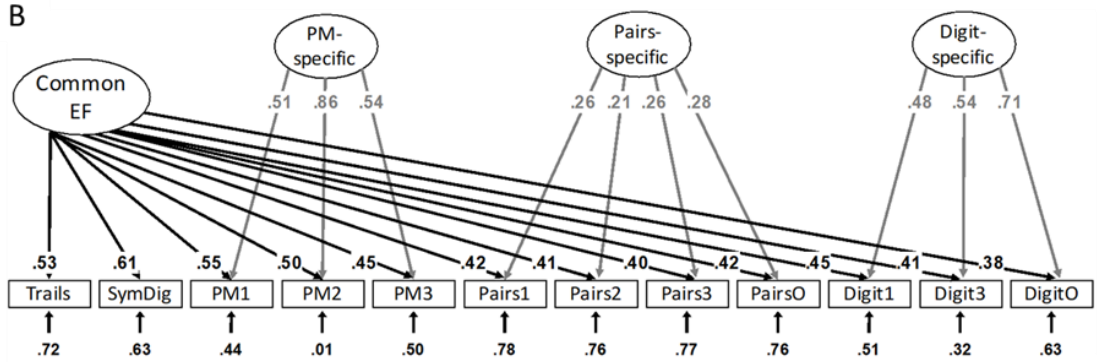

Figure 1. Justification for a common executive functioning (cEF) factor across cognitive tasks in the UK Biobank: (A) Correlations taken from Mplus; (B) Confirmatory factor analysis model used to extract factor scores. Ellipses indicate latent variables; rectangles indicate observed variables. Numbers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

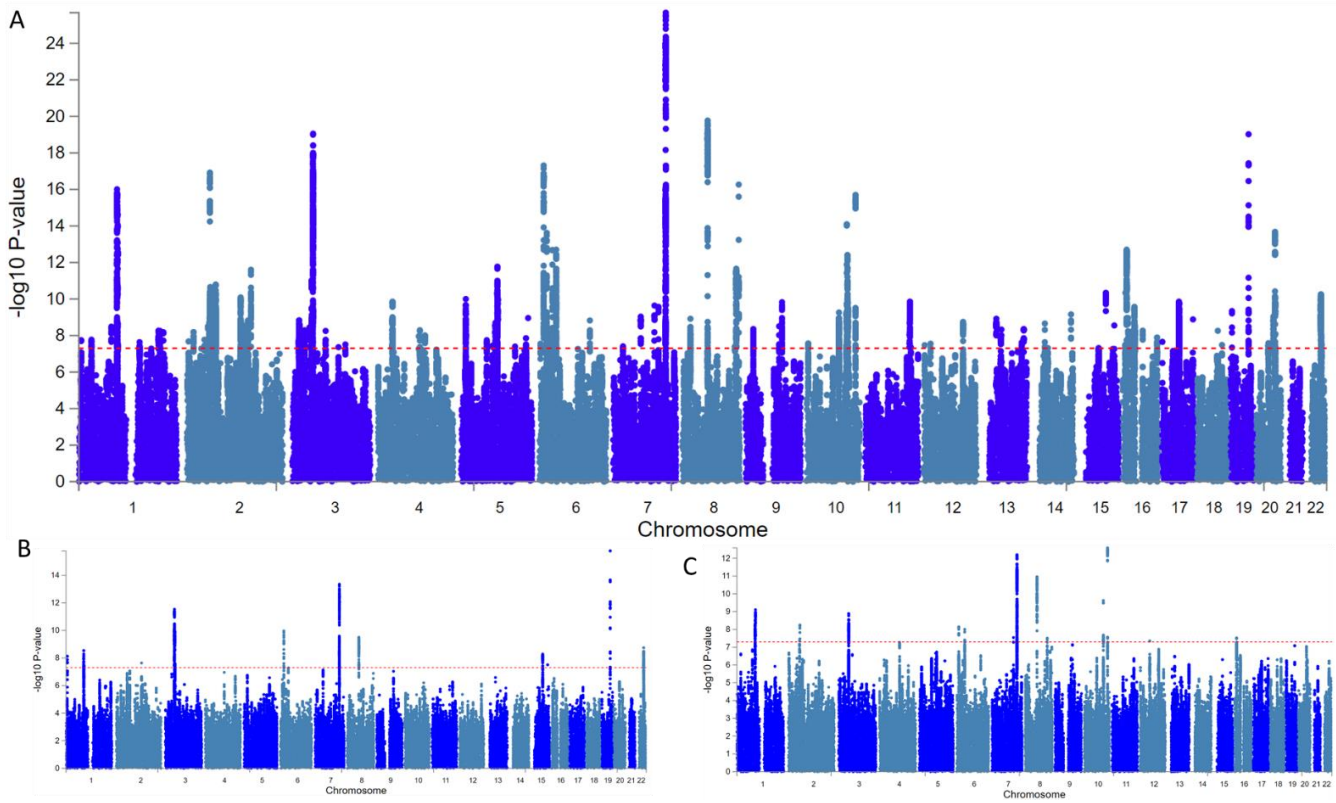

Figure 2. Manhattan plots for GWAS of common executive functioning (cEF) in the full sample (Panel A), the densely-phenotyped sample (Panel B), and the sparsely-phenotyped sample (Panel C). Each dot is a SNP, chromosomes are organized on the x-axis, y-axis represents the negative log10 of the p-value per SNP.

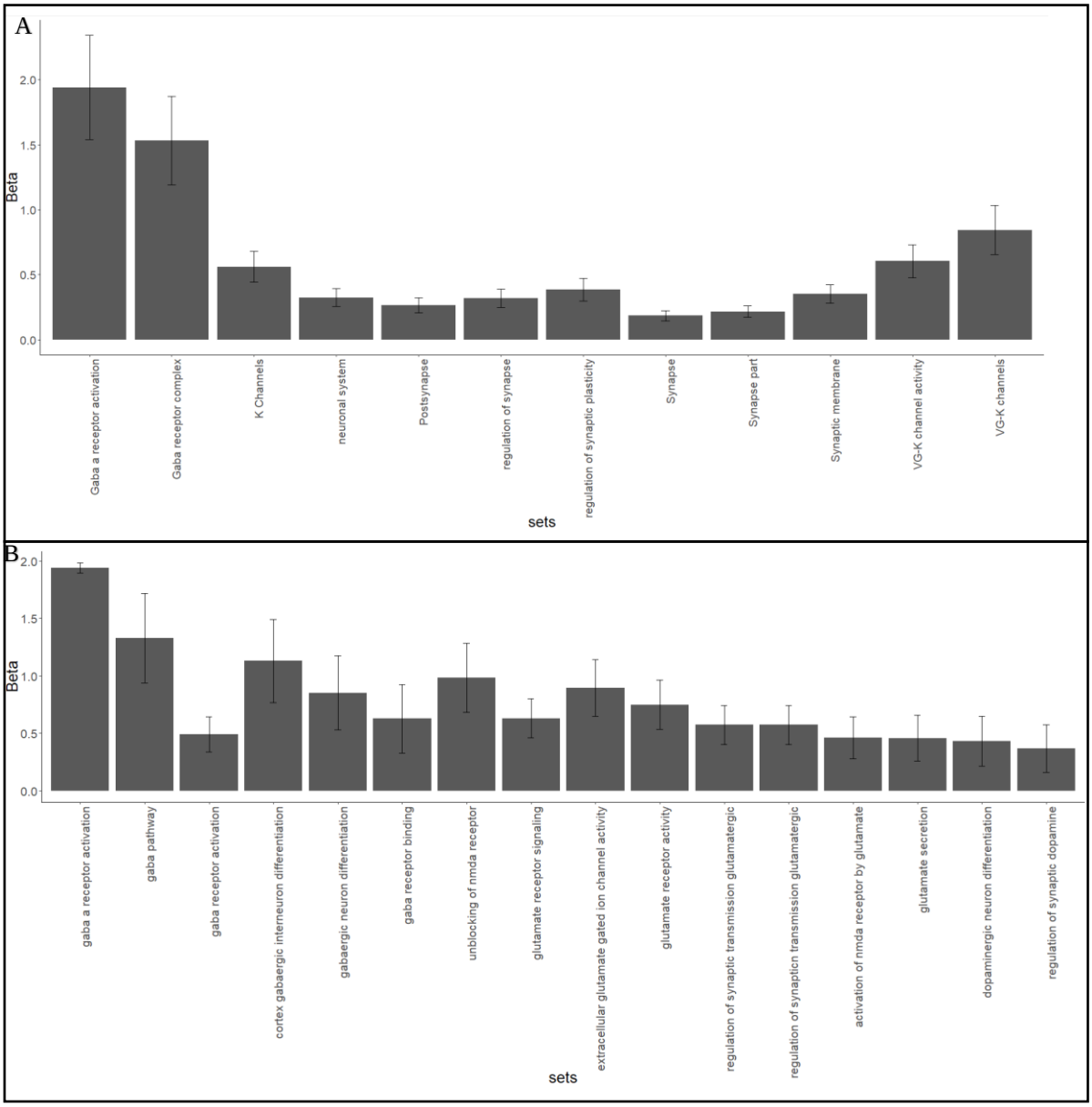

Figure 3. Associated Gene-set Categories from MAGMA Gene-Set Analysis. Signal GO term and curated gene set enrichment for SNPs influencing common executive functioning (cEF) as the MAGMA gene enrichment beta and standard error. (A) Gene-sets significantly associated post Bonferroni corrected alpha for 10,651 tests $\alpha = 4.7E\text{-}06$. (B) Gene-sets in hypothesized pathways that were nominally significant. VG = voltage-gated.

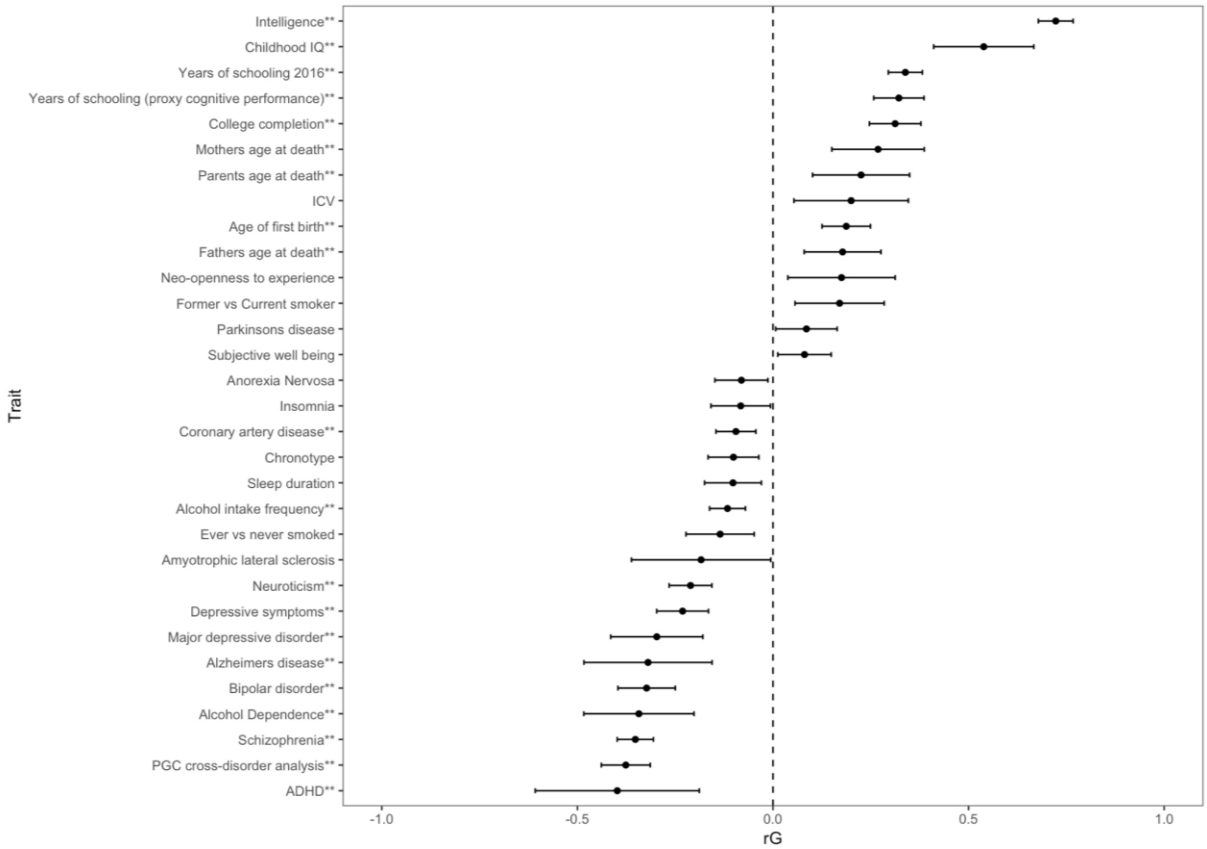

Figure 4. Genetic correlations between common executive functioning (cEF) and psychiatric, behavioral and health traits using LD score regression. Bars indicate 95% confidence intervals. All results significant at nominal significance $p < .05$. ** represents significance below Bonferroni correction.