GenomicSEM Modelling of Diverse Executive Function GWAS Improves Gene Discovery

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Abstract:

Previous research has supported the use of factor scores as the gold-standard in measuring executive function. However, for logistical reasons genome-wide association studies (GWAS) of executive function have largely eschewed factor scores in favour of singular task measures. As low correlations have traditionally been found between individual executive function (EF) tests, it is unclear whether these GWAS have truly been measuring the same construct. In this study, we addressed this question by performing a factor analysis on summary statistics from nine GWAS of EF taken from four studies, using GenomicSEM. Models were able to capture the classic three factors of inhibition, working memory, and set-shifting, although set-shifting and inhibition could be merged without negatively impacting model fit. Furthermore, the GWAS performed on a common factor model identified 63 new genomic risk loci beyond what was found in the constituent GWAS reaching genome-wide significance, resulting in 18 newly mapped EF genes. The majority of these have previous associations with brain morphology but no established associations with cognitive performance. These results help to clarify the underlying genetic structure of EF and support the idea that EF GWAS are capable of measuring genetic variance related to latent EF constructs even when not using factor scores. Furthermore, they demonstrate that GenomicSEM can combine GWAS with divergent and non-ideal measures of the same phenotype to improve statistical power.

Introduction:

Executive function (EF) covers the higher-order cognitive processes used to engage in goal-directed behaviour (Ahmed & Miller, 2011, Welsh et al., 2006). It has a role in promoting academic achievement (St Clair-Thompson & Gathercole, 2006; Best et al., 2011; Deer et al., 2020) and health behaviours, (Reimann et al., 2020), and has been implicated across a wide variety of psychiatric diagnoses including ADHD (Brown, 2009; Marije Boonstra et al., 2005), schizophrenia (Johnson, Selfridge & Zalewski, 2001; Wobrock et al., 2009; Orellana & Slachevsky, 2013) and depression (Fossati et al., 2002; Letkiewicz et al., 2014; Cotrena et al., 2016). Multiple twin studies have suggested that EF is fully heritable at the latent variable level in adolescents (Friedman et al., 2008; Engelhardt et al., 2015), seemingly violating the supposed 'law' of behavioural genetics that no trait is 100% heritable (Plomin & Deary, 2015). Although twin studies do support an increased role for environment in predicting EF during adulthood (Friedman et al., 2016; Gustavson et al., 2018; Morrison et al., 2021), they still support additive genetic effects as the primary source of stability in EF over time. Furthermore, twin studies show that genes can explain much of the association between EF and psychiatric diagnoses (Harden et al., 2020), stressful life events (Morrison et al., 2021), and math and reading ability (Daucourt et al., 2020). Thus, understanding the relation between EF and outcomes of interest requires a strong understanding of the role that genes play in EF development.

A key piece of theory underlying our understanding of EF is the unity-diversity model, which is the most well-cited model of EF in the literature (Miyake et al., 2000). This model holds that EF is comprised of the three separable factors known as inhibition, updating, and shifting, which share common variance known as common EF. This model has been subsequently revised to a bifactor model, consisting of a common EF factor onto which all items load as well as orthogonal updating-specific and shifting-specific factors (Miyake & Friedman, 2012; Friedman & Miyake, 2017). Notably, this model lacks an inhibition specific factor, as the authors argue there is no inhibition-specific variance. This model has important implications for the measurement of EF, as it has been argued that on a theoretical level, an EF test measuring only EF is impossible. This is because EF is only engaged when directing cognitive resources towards specific tasks, which carry their own cognitive

demands that are also captured in task performance (Miyake and Friedman, 2012). The need to eliminate this so-called 'task impurity', as well as measurement error, has led to the best-practice recommendation that EF be measured by multiple EF tests combined into a latent variable model like unity-diversity through CFA or similar methods (Friedman & Miyake, 2017). Importantly, latent EF factors typically outperform individual EF tests in predicting other outcomes of interest (Harden et al., 2020; Gustavson et al., 2022), and produce stronger correlations for EF assessments performed in different contexts (Freis et al., 2023), emphasizing the value of this measurement model. However, there is little-to-no agreement upon a gold-standard set of EF tasks for researchers to use, either when building these factor scores or as single-test measures. A literature review of empirical studies of EF published between 2008 and 2013 identified 109 tasks used for assessment throughout the field, of which 53 were used in multiple studies (Baggetta & Alexander, 2016). The use of such a diverse array of tests might not be an issue if they were highly correlated measures, however this is not the case. Perhaps owing to task impurity, the individual EF tests used in CFAs typically correlated below 0.4, with several showing no significant correlation (Lehto et al., 2003; Miyake et al., 2000). Despite these issues, single-task measurement of EF remains popular in clinical research, a methodological challenge meta-analyses often have to contend with (Andrews et al., 2021; Khoury et al., 2015; Lund et al., 2022; Power et al., 2021). Researchers cannot be sure that correlations with single-test EF measures are actually due to EF, nor that the results will replicate when performed with different EF measures, making the interpretation of any EF study using such measures challenging.

These issues are problematic for genome-wide association studies (GWAS) of EF, where the logistics of the large cohorts required for sufficient statistical power pressures researchers into using abbreviated test batteries that are quicker and easier to administer. As a consequence, marked heterogeneity exists in the approaches to measuring EF phenotypes used in GWAS. Across the 7 GWAS of EF as measured through cognitive tests that could be identified in the literature, only two, trail-marking part B and backwards digit span, were used in more than one study (Ibrahim-Verbaas et al., 2016; Zhang et al. 2018; Donati, Dumontheil, and Meaburn, 2019; Wendel et al., 2021; Hatoum et al, 2022; Dueker et al., 2023; Arnatkeviciute et al., 2023). As these GWAS have largely been performed on separate, weakly-correlated tests rather than latent factors, it is difficult to determine if they are measuring constructs similar to those found elsewhere in EF literature or even in other GWAS. One notable exception is a study conducted in the UK Biobank, which is both the largest GWAS of EF to date (N> 400000) and the only such study to use a factor score (Hatoum et al, 2022). However, the UK Biobank cognitive test battery was not designed to measure EF, with their suitability to do so being based on a post-hoc analysis of their correlations with common reference EF tests (Fawns-Ritchie & Deary, 2020). The battery included only two traditional EF tasks, the trail-making task and a backwards digit span. As a consequence of these limitations, the factor analysis derived from the UK Biobank's cognitive tests was only able to capture common EF, and the subsequent polygenic score was not a predictor of the updating or shifting-specific factors (Hatoum et al, 2022). And while the polygenic score was able to predict an impressive 9% of the common EF factor (Hatoum et al., 2022), this is still far below the heritability implied by twin studies of EF (Friedman et al., 2008; Engelhardt et al., 2015), even considering the limitations of SNP heritability. But larger GWAS meta-analyses cannot be performed with measurement of the phenotype so fractured. Further, measurement error reduces statistical power in GWAS (Liao et al., 2014, van der Sluis et al., 2010), which may account for the failure of EF GWAS not using factor scores to find any significant associations. There is thus good reason to think measuring EF through latent factors will improve the quality of EF GWAS above and beyond what is possible simply by increasing sample size of single-test measures.

GenomicSEM provides a powerful tool to address both the need for latent variables and larger sample sizes in EF GWAS. This method allows for the analysis of multiple GWAS using summary statistics, using them to build a genetic covariance matrix using Linkage Disequilibrium-score regression (LDSC) (Bulik-Sullivan et al., 2015), analogous to the covariance matrix employed by traditional structural equation modelling (Grotzinger et al., 2019). Therefore, rather than requiring building a CFA from multiple EF tests administered to the same participants, GenomicSEM allows a CFA to be built from GWAS of single-test measures without requiring participant overlap. Furthermore, once a model is accepted, GenomicSEM enables users to run a multivariate GWAS on the specified latent factors, using only the summary statistics used to build the model rather than individual-level genetic data. This is accomplished by fitting a structural equation model for each SNP in the analysis, using the SNP effects included in the genetic and sampling covariance matrices to estimate the influence of each SNP on the latent factors (Grotzinger et al., 2019). Thus, EF GWAS ostensibly measuring the same EF component but unsuitable for meta-analysis due to their use of different measures can be combined at the latent factor level, providing an alternative path for increasing sample size while also addressing task impurity. GenomicSEM does not model shared variance due to environment, which is an important limitation of the method compared to traditional SEM. However, this also provides a method of addressing concerns about correlations between tests representing a form of measurement error (Willoughby et al., 2014; Willoughby et al., 2016; Camerota et al., 2020), which should not appear at the genetic level across distinct samples.

The present study represents the first effort to model multiple latent EF factors in GenomicSEM, as well as the first EF model to use GWAS summary statistics taken from different samples. The purpose of the present study will therefore be to examine the factor structure of the currently available EF GWAS, determining the extent to which EF measures from separates studies load onto common constructs. Furthermore, where such common constructs are found, we aim to use Genomic SEM to perform GWAS on the latent factors, to increase statistical power for gene discovery beyond that of the constituent GWAS and allowing for the creation of polygenetic scores of EF factors that should be more predictive of latent EF factors than those derived from the individual studies.

Method:

Summary Statistics

A literature search was conducted in order to identify GWAS of EF suitable for inclusion in GenomicSEM. Inclusion criteria were EF measured by a cognitive test that showed statistically significant SNP heritability in LDSC (Bulik-Sullivan et al., 2015). As ethnically diverse samples are currently incompatible with GenomicSEM (Grotzinger et al., 2019), samples also needed to be either conducted in a solely European sample or have a European subsample available to meet inclusion criteria. The summary statistics which met inclusion criteria are presented in Table 1. While summary statistics for the Wisconsin Card Sorting Test (Zhang et al. 2018), the PsyCourse Study's Trail Making Part B and Backwards Digit Span, (Wendel et al., 2021) and the CHARGE consortium's Trail-Making Part B were also obtained, these failed to show significant SNP heritability in LDSC and so were excluded from further analysis. In addition to their factor score GWAS statistics, Hatoum et al. (2022) made available summary statistics for GWAS of the individual tests that contributed to it. As these tests should in theory tap different EF domains, we used these separate summary statistics when building our model. RsIDs for Arnatkeviciute et al. (2023) were obtained using bedops (Neph et al., 2012). Results for the UK Biobank's Symbol Digit Substitution Test, the CHARGE consortium's

Stroop test and the Stop-Signal test were reverse-coded so all positive loadings would correspond to better task performance.

Table 1: GWAS summary statistics for EF test variables used in the present study

Paper	**Cohort**	**Test**	**EF Component Tapped**	**Sample Size**
Hatoum et al, 2022	UK Biobank	Trail-Making Part B	Shifting	93024
		Backwards Digit Span	Working Memory	81701
		Symbol-Digit Substitution (SDST)	Shifting	84125
		Pairs Matching	Shifting	81701
		Prospective Memory	Inhibition	162335
Ibrahim-Verbaas et al, 2016	Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium	Letter Digit Substitution Test/ Digit Symbol Substitution Task (DSST)	Shifting	32070
		Stroop	Inhibition	12866
Donati, Dumontheil, and Meaburn, 2019	Avon Longitudinal Study of Parents and Children (ALSPAC)	Working Memory Principal Component*	Working Memory	4611
Arnatkeviciute et al, 2023	Meta-analysis (unnamed consortium)	Stop-Signal Reaction Time (SSRT)	Inhibition	11715

* The Working Memory Principal Component contained loadings from the N-back, Counting Span, Digit Vigilance, and Dual Tasks.

Factor structure

We assigned each set of GWAS summary statistics loadings onto one of three EF factors- inhibition, working memory, or shifting. Available data were insufficient to distinguish updating from other forms of working memory, so a general working memory factor took the place of updating in our model. While many of the tests presented in Table 1 have long been recognized in the literature as tapping specific EF subcomponents, Hatoum et al.'s (2022) GWAS of the UK Biobank included nonstandard tests for which their capacity to measure EF was established post-hoc based on correlations with standard EF reference tests (Fawns-Ritchie & Deary, 2020). As the reference tests

used tap different EF subcomponents (shifting for Trail Making Part B, working memory for Backwards Digit Span, and complex EF for Tower Test) we used the relative difference in correlations with these tests as reported in that paper to assign the nonstandard UK Biobank tests to specific EF domains. Symbol-Digit substitution correlated strongly with the Trails reference tests ($r = -0.558$, $p < .001$) and only weakly with Backwards Digit Span ($r = 0.177$, $p < .05$), indicating that it may contain significant shifting-specific variance. The Charge consortium also included a similar GWAS combining Letter Digit Substitution and Digit Symbol Substitution, although they used it as a processing speed test (Ibrahim-Verbaas et al, 2016). While this is a common interpretation in the literature, some studies have also supported a relationship between substitution tasks and set shifting, including when measured through Trails B (Jehu et al., 2021; Knowles et al., 2015; Lessov-Schlaggar et al., 2007). As such, while we assigned both digit substitution GWAS to set shifting, we also included an orthogonal factor which loaded these GWAS alone, in order to minimize variance due to processing speed captured by our shifting factor. Pairs matching correlated modestly with Trails B ($r = 0.277$, $p < .001$) but had no significant correlation with Backwards Digit span ($r = -0.122$) suggesting a weaker but still shifting-specific EF component. Prospective memory had modest correlations with all EF reference tests (Backwards Digit Span $r = 0.265$ $p < .01$, Trails B -0.306, $p < .001$) consistent with literature finding prospective memory to be associated with multiple EF domains (Kerns, 2000; Shum et al., 2008; Yang et al., 2011). However, we theorized that the task would be most strongly related to inhibition, which was not represented in the reference tests. The UK Biobank's prospective memory task is event-based, a classification which previous research has suggested is most strongly related to inhibition (Mahy et al., 2014; Schnitzspahn et al., 2013; Yi et al., 2014; Zuber et al., 2019). Furthermore, the task is conceptually similar to inhibition tasks such as stop-signal and Go/No-Go, both of which are reaction tasks in which a response is inhibited upon receiving a certain signal (Raud et al., 2020). For the prospective memory task, the reaction is to simple onscreen instructions (e.g. 'touch the blue square'), with the inhibition signal being a previously given set of countermanding instructions (e.g. 'When you are told to touch the blue square, touch the orange circle'). While the perception of the signal is dependent upon the participant's prospective memory, responding appropriately to it nevertheless has clear inhibitory demands.

The working memory principal component extracted from the ALSPAC cohort (Donati et al. 2019), while in some ways similar to a CFA approach, comes with issues which require a more nuanced interpretation. PCA is not hypothesis-driven, and analyses all variance in the terms rather than only their shared variance. Consequently, the working memory principal component did not only load onto tasks with obvious working memory demands, but instead had loadings on the Digit Vigilance and Dual Tasks, which are respectively tasks of sustained and divided attention (Donati et al., 2019). In an earlier version of their analysis, the authors also found loadings from the stop-signal task variables at both age 10 and 15 onto their working memory principal component (Donati et al., 2019). While these variables were removed due to their loading onto multiple components, they nevertheless indicated that the principal component they identified as working memory shared variance with the stop-signal task, possibly indicating that it captured variance due to inhibition or some other shared cognitive process. The authors of that paper offered a similar explanation for the principal component they identified as inhibition showing no SNP heritability, suggesting that this may be due to there being no genetic variance unique to inhibition (Donati et al., 2019). Perhaps as a result of these features, in our preliminary analysis the ALSPAC working memory component showed a relationship to prospective memory that could not be accounted for either through shared working memory demands or common EF variance more broadly. As such, we accounted for this correlation through a correlated error term, declining to assign an interpretation without sufficient conceptual clarity.

Analysis

Analysis was conducted in GenomicSEM (Grotzinger et al., 2019). Models were tested using the absolute fit thresholds proposed in the original GenomicSEM paper, with CFI values of ≥0.95 considered good fit and ≥0.90 considered acceptable fit (Kenny, 2014), and values of SRMR of <0.05 considered good fit and <0.10 considered acceptable fit (Hoyle, 1995). The genetic covariance matrix was obtained using LDSC (Bulik-Sullivan et al., 2015); genetic correlations are presented in Table 2. Our initial hypothesis was that the data would fit a unity-diversity three-factor model of set shifting, inhibition, and working memory. We tested both the standard version of this model and a version including an orthogonal factor for substitution task -specific variance. We also tested all possible combinations of models merging two EF factors together. Finally, bifactor models, which added an orthogonal common EF factor to the previously described models, were also tested, both including or eliminating inhibition-specific variance.

The accepted model was run through the user-specified GWAS function in GenomicSEM, regressing SNPS onto each of the latent factors. As this resulted in no significant GWAS associations, a common factor model was also run using the common factor GWAS function in GenomicSEM. The genetic covariance matrix was smoothed due to significant differences in *n* between samples, and SNPs which showed a difference of more than 1 in Z-score between the pre- and post-smoothed genetic covariance matrices were removed from the results. LDSC (Bulik-Sullivan et al., 2015) was used to obtain intercepts and genetic covariance with other psychiatric phenotypes, including Hatoum et al.'s (2022) full-sample EF and processing speed (taken form the UK Biobank's snap game) summary statistics, as well as summary statistics for educational attainment (Okbay et al., 2022), cognitive ability (Lee et al., 2018), and 9 different disorders taken from the psychiatric genetics consortium (Arnold et al., 2018; Demontis et al., 2023; Forstner et al., 2021; Grove et al., 2019; Howard et al., 2019; Mullins et al., 2021; Trubetskoy et al., 2022; Watson et al., 2019; Yu et al., 2019). In line with the approach taken by Hatoum et al. (2022) variance shared between our EF factors, cognitive ability (Lee et al., 2018), and processing speed was controlled for using multiple regression, allowing us to examine the correlations between variance unique to our factors and outcomes of interest. GWAS results were entered into FUMA/MAGMA (Watanabe et al., 2017) to obtain functional annotations and gene mappings.

Results:

Table 2 presents genetic correlations for all summary statistics which met inclusion criteria by showing significant SNP heritability in LDSC. With the exception of Stop-Signal, all summary statistics showed multiple significant genetic overlaps with other measures of EF, indicating that they tap a common phenotype.

Table 2: Genetic correlation between GWAS summary statistics

	UKB Trails	UKB Pairs	UKB SDST	UKB Digit	UKB P. Memory	CHARGE DSST	CHARGE Stroop	ALSPAC WM	Stop-Signal
UKB Trails	0.1141 (0.0082)	**0.7097 (0.0445)**	**0.7133 (0.0466)**	**0.6685 (0.047)**	**0.3358 (0.0569)**	**0.5832 (0.0663)**	**0.3873 (0.1108)**	**0.4237 (0.1151)**	-0.1003 (0.1235)
UKB Pairs		0.3765 (0.0163)	**0.6571 (0.0409)**	**0.439 (0.0339)**	**0.3331 (0.0461)**	**0.5568 (0.0559)**	**0.2358 (0.0772)**	**0.324 (0.0789)**	0.0614 (0.0945)
UKB SDST			0.1564 (0.0094)	**0.3224 (0.0442)**	**0.2257 (0.0506)**	**0.8745 (0.0717)**	**0.3596 (0.0986)**	**0.3136 (0.1125)**	0.2078 (0.1232)

UKB Digit		0.1433 (0.0091)	**0.2328 (0.0514)**	**0.3836 (0.0605)**	**0.4496 (0.1077)**	**0.6427 (0.109)**	-0.0349 (0.1317)
UKB P. Memory			0.0368 (0.0035)	**0.3206 (0.077)**	**0.2728 (0.1326)**	**0.4875 (0.1459)**	0.1959 (0.1684)
CHARGE DSST				0.156 (0.0178)	**0.5018 (0.1355)**	**0.3977 (0.1579)**	**0.4738 (0.173)**
CHARGE Stroop					0.1035 (0.0336)	-0.2293 (0.2989)	-0.3916 (0.301)
ALSPAC WM						0.279 (0.1097)	0.5458 (0.3198)
Stop-Signal							0.0489 (0.0272)

SNP heritabilities are presented along the diagonal. **Bolded** correlations are significant at $p < 0.05$. Standard deviations in parentheses. UKB = UK Biobank, Trails = Trail-Making Part B, SDST = Symbol Digit Substitution, Digit = Backwards Digit Span, P. Memory = Prospective Memory, DSST = Digit Symbol Substitution, WM = Working Memory Principal Component.

Confirmatory factor analysis

Fit statistics for our CFAs are presented in Table 3. All bi-factor models failed to converge and so are not reported. During modelling, the Stop-Signal Reaction Time measure failed to significantly load onto any factor to which it was assigned. As it also did not significantly correlate with any other measure except for the CHARGE consortium's DSST, it is excluded from all models presented here. The three-factor model met acceptable fit thresholds by CFI but failed to do so for SRMR. After the addition of the orthogonal substitution-task factor, the resulting model fit improved significantly, resulting in good fit by CFI and acceptable fit by SRMR, as well as a statistically significant improvement over both the common factor and previous three-factor model by $\chi2$ and AIC. The substitution-task factor also correlated with the UK Biobank's processing speed measure (Hatoum et al, 2022) at 0.82 (±0.08, $p < 0.001$), confirming that it was primarily capturing processing speed-specific variance. For models which combined executive function factors together, only shifting=inhibition was not a significantly worse fit. As it was a more parsimonious model, a significant improvement by AIC, and not significantly different by $\chi2$, shifting=inhibition was accepted and used for the GWAS.

Table 3: Confirmatory factor analysis model results for the genomic structure of EF.

Model	**χ^2**	**df**	**χ^2 p-value**	**AIC**	**CFI**	**SRMR**
Common Factor Model	167.227	20	2.996601e-25	199.227	0.9190672	0.1298758
Three Factor Correlated	139.129	16	1.066886e-21	179.129	0.9323142	0.1050022
Three-Factor with Substitution-specific variance	43.47783	12	1.873677e-05	91.47783	0.9826962	0.09313937
Inhibition = Shifting	*43.95965*	*15*	*0.000111575*	*85.95965*	*0.9840805*	*0.09124558*
Inhibition = Working Memory	65.84484	15	2.428626e-08	107.8448	0.9720499	0.1110163
Working Memory = Shifting	116.0682	16	3.120142e-17	156.0682	0.9449911	0.1095364

Endorsed model in italics. All bifactor models failed to converge and so are not presented.

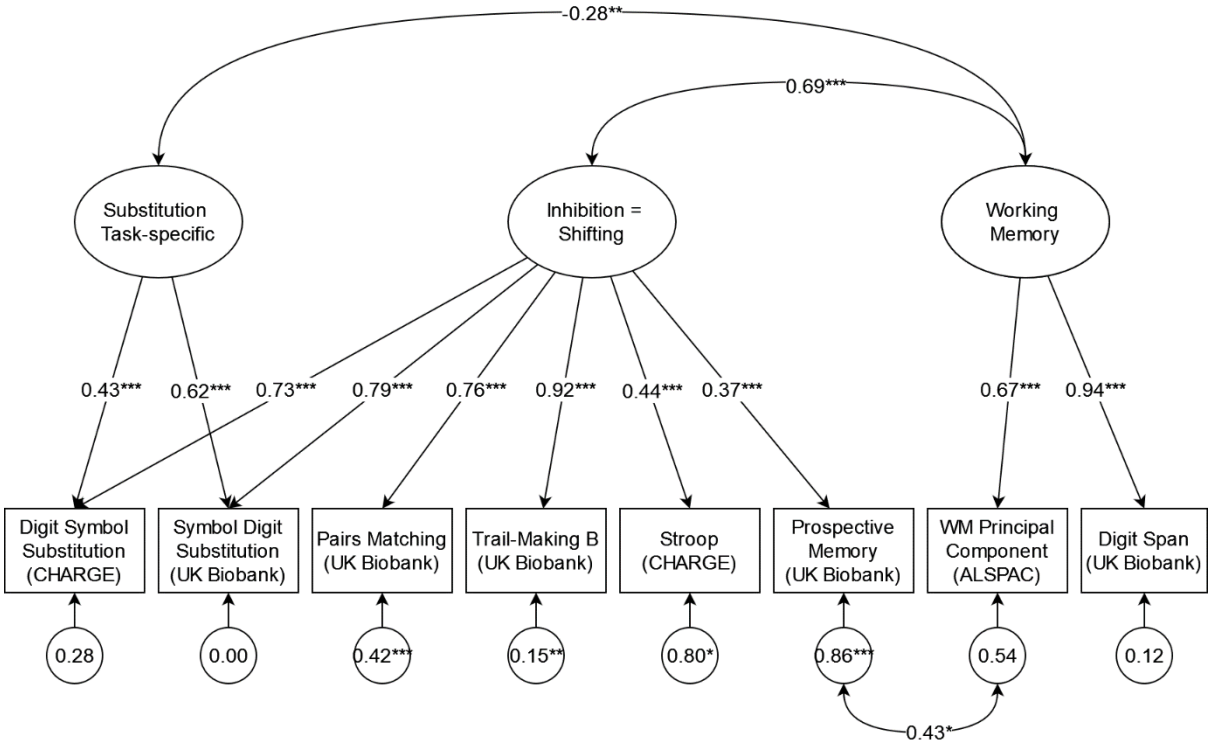

Figure 1: Standardised results for the accepted confirmatory factor analysis model of EF GWAS. *p < .05, ** p < .01, *** p < .001

GWAS

Table 4 presents a brief summary of our GWAS results. As only the common factor model produced genome-wide significant hits, results for the accepted model are not reported. We also present a summary of the subset of our results which were not found in previous EF GWAS. Full FUMA and MAGMA results are available in supplementary tables S1 -S10, and include lead and independent significant SNPS, genomic risk loci, identified genes and GWAS Catalog mappings, both with and without overlaps with previous EF GWAS.

Table 4: Summary of GWAS Results for the Common Factor Model, with and without overlaps with previous EF GWAS

GWAS	Genomic Risk Loci	Lead SNPs	Independent Significant SNPs	Mapped Genes	Top Gene
Common Factor	80	88	187	254	*EXOC4*
Novel Results	62	68	136	18	*SLC6A4*

LDSC

LDSC results for the common factor model as well as our latent inhibition = shifting and working memory factors are presented in Table 5. For the purpose of comparison, we also present the results of full sample common EF taken from the UK Biobank (Hatoum et al., 2022), which differs from the

genetic correlations presented in their original paper as larger GWAS of the presented phenotypes have since been made available.

Table 5: Genetic correlations between executive function and other cognitive phenotypes

	Common Factor	Inhibition= Shifting	Working Memory
cEF (UK Biobank)	**1.0079 (0.0464)**	**0.4249 (0.0466)**	*0.0944 (0.0416)*
Processing Speed	**0.3154 (0.0248)**	**0.3242 (0.039)**	**-0.1753 (0.0402)**
Educational Attainment	**0.3638 (0.0235)**	-0.0279 (0.0341)	**0.2282 (0.0352)**
Cognitive Performance	**0.7417 (0.0348)**	0.0366 (0.0401)	**0.3607 (0.0437)**
ADHD	**-0.2378 (0.0305)**	-0.0424 (0.0491)	-0.0747 (0.0499)
Autism	0.0191 (0.0416)	-0.0901 (0.0627)	0.1153 (0.061)
Schizophrenia	**-0.3543 (0.0279)**	**-0.307 (0.0402)**	**0.1463 (0.039)**
Bipolar Disorder	**-0.2794 (0.0286)**	**-0.2293 (0.0481)**	*0.1053 (0.05)*
Anxiety	**-0.2643 (0.0681)**	*-0.2893 (0.1085)*	0.1448 (0.1009)
Anorexia Nervosa	**0.1558 (0.039)**	**0.2074 (0.0573)**	-0.1595 (0.0608)
Major Depressive Disorder	**-0.1771 (0.0248)**	*-0.125 (0.0437)*	0.04 (0.043)
Obsessive-Compulsive Disorder	*-0.1632 (0.0588)*	*-0.2543 (0.0995)*	0.1842 (0.1066)
Tourette Syndrome	-0.0485 (0.044)	-0.1447 (0.0804)	0.119 (0.0831)

Bolded results are statistically significant after adjusting for multiple testing. Italicized results are nominally significant at $p < 0.05$. Standard errors in parentheses.

Table 6 presents genetic association results after adjusting for overlap with GWAS of cognitive performance and processing speed, using summary statistics from Lee et al. (2018) and Hatoum et al. (2022), respectively.

Table 6: Genetic correlations between executive function and other cognitive phenotypes after controlling for overlap with cognitive performance and processing speed

	Common Factor	Inhibition = Shifting	Working Memory
Educational Attainment	**-0.3043 (0.0583)**	**-0.2961 (0.0576)**	*-0.1448 (0.0526)*
ADHD	0.0333 (0.0819)	-0.0010 (0.0803)	0.1389 (0.0851)

Autism	*-0.2831* *(0.1102)*	*-0.2339* *(0.1057)*	0.0357 (0.1034)
Schizophrenia	**-0.3265** **(0.0584)**	**-0.2704** **(0.0652)**	**0.4440** **(0.0788)**
Bipolar Disorder	**-0.3952** **(0.0692)**	*-0.2309* *(0.0790)*	**0.2711** **(0.0840)**
Anxiety	*-0.4174* *(0.1473)*	*-0.3740* *(0.1814)*	0.3093 (0.1644)
Anorexia Nervosa	**0.4671** **(0.0979)**	**0.3260** **(0.1026)**	*-0.1996* *(0.1014)*
Major Depressive Disorder	**-0.2473** **(0.0661)**	*-0.1595* *(0.0725)*	0.1312 (0.0733)
Obsessive-Compulsive Disorder	*-0.3803* *(0.1456)*	*-0.3480* *(0.1688)*	0.2860 (0.1761)
Tourette Syndrome	-0.0635 (0.1120)	*-0.2554* *(0.1301)*	0.2111 (0.1383)

Bolded results are statistically significant after adjusting for multiple testing (Bonferroni's corrected $p < 0.00167$). Italicized results are nominally significant at $p < 0.05$. Standard deviations in parentheses.

Discussion:

The purpose of this study was to perform a confirmatory factor analysis on currently available summary statistics from GWAS of executive function, in order to determine if these studies have been measuring the same construct and allowing us to perform more powerful GWAS on the basis of these shared latent factors. Our analysis produced a correlated factor model largely in line with previous research, with three factors identifiable with inhibitory control, working memory, and set-shifting. Furthermore, our acceptance of a more parsimonious model merging inhibition and shifting is consistent with other studies of adults over 50 years of age, which suggest a more unitary EF (Hull et al., 2008; Hedden & Yoon, 2006) including similar mergers of inhibition and shifting (De Frias et al., 2009; Gustavson et al., 2018). Given that both the UK Biobank and CHARGE consortium's cohorts skew older, that we would find similar results for factors loading only terms from these cohorts is not surprising. That these results could be obtained on the basis of genetic correlations between tests performed largely on unrelated individuals suggests that the unity-diversity model of EF likely captures real biological processes that are reflected in performance on EF tests.

However, our results are unusual with respect to the Stop-Signal test (Arnatkevicuite et al, 2023) which we found had no genetic relationship to any other EF test except for the CHARGE consortium's DSST. It is difficult to imagine why, if Stop-Signal is properly understood as a measure of inhibitory control, those results would so consistently fail to correlate genetically with other EF test results. One possible explanation lies in the different form of structural equation modelling used. Whereas classic SEM uses covariance from any source, Genomic SEM only takes genetic covariance into account, meaning any relationship between terms which is due to the environment will be absent from our model. If the previous correlation between Stop-Signal and other measures of inhibitory control have been primarily driven by the environment, there could be a very different genetic relationship being masked. Friedman et al.'s (2016) results in particular are consistent with this interpretation of our findings, as they found reduced loading for the Stop-Signal task onto inhibition at age 23, along with a loss of any statistically significant role for genetics in predicting its variance. However, it should be noted that the consortium sample used for the Stop-Signal GWAS skewed towards adolescents, in contrast to that of the UK Biobank and CHARGE, suggesting that

genetic variance in performance of this task may not be stable across age. As it is possible that Stop-Signal is not the only EF test for which covariance due to genetics and environment are divergent, future research will need to be mindful of the genetic relationship implied by twin studies in order to ensure the EF measures selected for GWAS indeed capture common genetic variance.

GWAS

Our common factor GWAS showed a large number of significant associations, whereas the specified model returned null results. As expected, given its large contribution to the sample, gene mappings showed a great deal of unity with the UK Biobank GWAS, including a shared top gene, *EXOC4.* Nevertheless, although only a single SNP achieved genome-wide significance in any of the non-UK Biobank samples, there were still 18 genes newly associated with EF in this study. This demonstrates that the inclusion of these outside samples provided considerable new information, despite contributing only 49,547 additional participants to the GWAS. The top gene of the novel subset was *SLC6A4*, a serotonin transporter whose promoter region, 5-HTTLPR, has been a popular target for gene x environment interaction studies, although such results have largely failed to replicate (Border et al., 2019; Culverhouse et al., 2018). However, meta-analyses of other polymorphisms have suggested a possible role for *SLC6A4* in schizophrenia (Xu et al., 2018), bipolar disorder (Gatt et al., 2015), and obsessive-compulsive disorder (Sinopoli et al., 2017). In FUMA, the common factor also showed significant overlaps with gene-sets derived from GWAS of a number of cognitive phenotypes, most prominently brain morphology, autism, and schizophrenia. Four of the novel genes, including *SLC6A4,* have also been associated with some measure of cognitive performance, and two with educational attainment. Of the twelve remaining, 11 have been previously associated with brain morphology, suggesting an EF-specific relationship with these changes that may be more proximal than general cognitive ability.

LDSC

Our common factor model was at complete unity with the UK Biobank results in LDSC, showing that they measure the same phenotype. Consequentially, genetic associations are nearly identical to those reported by Hatoum et al (2022), with differences largely the result of the larger psychiatric genetics consortium studies that have since been made available. However, our inhibition = set-shifting factor correlated at only 0.42 with the UK Biobank common EF results, and had no significant association with cognitive performance. Despite this, it produced correlations with psychiatric diagnoses of similar effect size to the former, including significant associations with schizophrenia, bipolar disorder and anorexia nervosa. Regressing out overlap with processing speed and cognitive performance had only minor effects on these correlations, although the association with bipolar disorder did not survive correction for multiple testing. However, the factor gained a significant negative association with educational attainment which was not apparent before regression. Previous research has suggested a trade-off between common EF and shifting-specific variance, resulting in better shifting being associated with worse outcomes in behavioural domains (Friedman et al., 2011; Herd et al., 2014). Given that removing overlap with processing speed and cognitive performance likely also removed some of the overlap with common EF, it is likely that the negative association with educational attainment is driven by this same trade-off. The working memory factor contrasted with inhibition = set-shifting by showing no significant association with the UK Biobank EF but a weakly positive correlation with cognitive performance, consistent with previous findings suggesting that working memory is more strongly related to cognitive performance than other EF factors (Friedman et al., 2006). Its significant association with schizophrenia more than doubled in effect size after regressing out variance shared with processing speed and cognitive performance, and its association with bipolar disorder now survives correction for multiple testing.

However, the direction of the effect was notably opposite to that of the common and inhibition = set-shifting factor, a surprising and difficult-to-interpret finding given that working memory deficits in these disorders are well established (Johnson'Selfridge & Zalewski, 2001; Soraggi-Frez et al., 2017; Saldarini et al., 2022). Nevertheless, these results suggest that variance shared with EF plays an important role in the psychotic disorder cluster both via the common factor and through factor-specific variance.

Limitations and Future Directions

Given the potential complexity implied by competing theories of EF, our model contained relatively few terms, constrained by the availability of appropriate GWAS. Our analysis was incapable of separating working memory into updating and maintenance factors, as some EF models do (Engelhardt et al., 2015; Wongupparaj et al., 2015), nor could it examine any of the proposed subdivisions in inhibition (Friedman & Miyake, 2004; Stahl et al., 2014; Bender et al., 2016; Rey-Mermet et al., 2018). Furthermore, our interpretation of the inhibitory control – set-shifting merger must also be treated with caution. While previous work has established EF demands for the cognitive tests used to specify these factors, with the exception of Trail Making and Stroop they are not commonly used as such in the EF literature. Although they represent the best GWAS summary statistics currently available for measuring EF, it is nevertheless possible that the latent factors they tap may differ from those found in phenotypic literature. The loss of Stop-Signal from the model in particular limited our ability to specify an inhibition factor clearly in line with previous research; future GWAS of additional inhibition tasks such as Go/No-Go, Antisaccade, and Flanker may enable the identification of unique genetic variance. In considering these limitations and how they might be addressed in the future, we in fact highlight a major advantage of CFAs built in GenomicSEM over traditional CFAs. Because the covariance matrix is built on the basis of genetic covariance rather than within-person covariance, terms from future GWAS of EF can be introduced as they become available, collaboratively iterating upon these results and in doing so increasing conceptual clarity.

Modelling a more complex factor structure came at significant cost to power for the GWAS, meaning we were only able to achieve genome-wide significant results with the common factor model. This is perhaps unsurprising for the working memory factor, which had loadings from only two GWAS. However, this result is more disappointing for the inhibition = set-shifting factor, which represented only a modest decrease in sample size from the common factor model. This suggests that the increase in complexity in modelling multiple latent factors and regressing them all onto SNPs significantly detracts from power in GWAS performed through GenomicSEM, a trade-off researchers will need to consider when using the method to study EF in the future. The corresponding loss in statistical power must also be taken into account when interpreting the genetic correlations. As it was estimated with both a larger sample size and a simpler model, that the common factor was more correlated with terms of interest than inhibition = set-shifting or working memory may not represent real differences in their relationship, nor should it be assumed that null results will necessarily hold if better-powered samples can be assembled. In particular, several of the associations that were nominally significant before correcting for multiple testing, such as those between inhibition = set-shifting and autism and obsessive-compulsive disorder, appear theoretically sound and may reach full significance if the model were replicated with a larger sample size.

A final limitation worth noting is the inclusion of GWAS only of European populations in our analysis. This limitation is unfortunately built into GenomicSEM itself, which requires that only GWAS of ethnically homogeneous samples be used. Two of the studies, which contributed GWAS summary statistics to the present study, Ibrahim-Verbaas et al, 2016 and Arnatkeviciute et al, 2023, made a point to construct their GWAS with multi-racial samples. This should be commended, as

GWAS have historically and continue to overrepresent Caucasian populations in their sample (Popejoy & Fullerton, 2016; Rosenberg et al., 2010). However, because of the limitations of GenomicSEM, we were forced to use only the Caucasian subsample of these studies. Members of the GenomicSEM development team have indicated that GenomicSEM will in the future be improved to allow the inclusion of multiple LD files, making trans-ancestry GenomicSEM studies possible (*Multi-Ancestry LDSC in GenomicSEM*, n.d.). However, they have also indicated that progress on this development is limited by the paucity of multi-ancestry cohorts.

Conclusions:

This study demonstrates the viability of combining distinct EF tests from differing samples using a latent genetic factor. This will allow for larger meta-analytic GWAS of EF to be conducted in GenomicSEM without the need to unify EF measures across cohorts. However, while this study supports the existence of the unity-diversity structure of EF on the genetic level, the statistical power needed to fully model it for latent factor GWAS still poses a significant challenge at the current stage. Furthermore, our results suggest a need to reexamine the tests used to measure EF, particularly with respect to inhibition. The failure of the Stop-Signal to correlate genetically with other EF tests or load significantly onto latent EF factors limited the models that could be constructed, highlighting a need for greater theoretical clarity as to the relationship between EF tests and the latent construct. GWAS results suggest a potential relationship between various components of EF and psychiatric diagnoses. Furthermore, some results are suggestive of unique associations with specific EF domains, although additional research is needed to clarify these effects. In total, these results suggest that while single-test measures of EF may not be ideal in most circumstances, there is nonetheless value in conducting GWAS of such tests for their contribution to larger analyses of latent genetic factors.

Acknowledgements and Data Availability

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Summary statistics will be made available through GWAS Catalog upon publication. FUMA results for the common factor model will likewise be made publicly available on that platform. Code is available on Github : https://github.com/LCPerry/EFGSEM

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