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Multivariate genetic analysis of personality and cognitive traits reveals abundant pleiotropy

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Author Contributions

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Code availability

Code for MOSTest, cFDR, PRSice, MTAG, and PRS-CS are publicly available at https://github.com/precimed/mostest/tree/mental, https://github.com/precimed/pleiofdr, https://github.com/choishingwan/PRSice, https://github.com/JonJala/mtag and https://github.com/getian107/PRScs, respectively. Functional annotation using FUMA can be accessed at https://fuma.ctglab.nl/.

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Abstract

Personality and cognitive function are heritable mental traits whose genetic foundations may be distributed across interconnected brain functions. Previous studies have typically treated these complex mental traits as distinct constructs. We applied the “pleiotropy-informed” multivariate omnibus statistical test to genome-wide association studies (GWAS) of 35 measures of neuroticism and cognitive function from the UK Biobank (n=336,993). We identified 431 significantly associated genetic loci with evidence of abundant shared genetic associations, or pleiotropy, across personality and cognitive function domains. Functional characterisation implicated genes with significant tissue-specific expression in all tested brain tissues and brain-specific gene-sets. We conditioned independent GWASs of the Big 5 personality traits and cognitive function on our multivariate findings, boosting genetic discovery in other personality traits and improving polygenic prediction. These findings advance our understanding of the polygenic architecture of these complex mental traits, indicating a prominence of pleiotropic genetic effects across higher-order domains of mental function such as personality and cognitive function.

Keywords

Cognitive function; personality; Big 5 personality; neuroticism; GWAS; multivariate GWAS; MOSTest; pleiotropy

Introduction

The brain is responsible for a diverse set of interconnected and overlapping functions. Among these, personality and cognitive functions both represent heritable, higher-order domains of mental functioning that (i) remain relatively stable between late adolescence and older age[1–3], (ii) form central components of an individual’s identity, and (iii) are related to

multiple physical and mental health outcomes[4,5]. They are also interrelated, with evidence of complex patterns of association between personality structure, cognitive functioning[6] and academic performance[7]. A comprehensive investigation of their genetic foundations can provide insights into the neurobiological mechanisms influencing these fundamental human traits[8].

Accelerated by the population-based cohort the UK Biobank (UKB; n=~500,000), genome-wide association studies (GWAS) have revealed evidence of genetic overlap between personality and cognitive traits. Multiple overlapping genetic loci have been discovered across large-scale GWAS of neuroticism[9,10], one of the "Big 5" personality traits defined broadly as the propensity to experience negative emotions[11], and general cognitive function[12–15], representing the shared variance across diverse cognitive functions. Neuroticism and general intelligence also exhibit weak but significant negative genetic correlation[9] and higher polygenic scores (PGS) for neuroticism predict lower intelligence[15,16], reflecting weak negative phenotypic correlations between neuroticism scores and IQ[17,18].

However, previous genetic studies have typically treated personality traits and cognitive ability as discrete constructs, reducing each complex mental trait into a single measure[9,12]. The limitations of this approach are underscored by a study which constructed a bifactor model of the neuroticism scale, showing that whilst a general factor of neuroticism showed a negative genetic correlation with cognitive function, two additional factors termed, anxiety/tension and worry/vulnerability, showed positive genetic correlations with the same cognitive function variable[16]. In addition, an item level analysis showed divergent patterns of genetic correlation between one of the neuroticism items and cognitive function and educational attainment and another with bipolar disorder[19]. In contrast, multivariate approaches simultaneously model the matrix of correlations between phenotypes, thus more accurately representing the interconnected nature of the brain and its functions.

Multivariate analysis can also increase statistical power in mental traits[19]. For example, multivariate analytical frameworks such as multi-trait analysis of GWAS (MTAG) and genomic structural equation modelling (GenomicSEM) have been applied to cognitive traits[15,20–22] and for the neuroticism sum-score in combination with other traits, such as depressive symptoms and subjective well-being[23] to improve genetic discovery. A multivariate approach to investigate pleiotropy across the two domains of cognitive function and neuroticism has not yet been conducted. Nevertheless, due to computational limitations it would be infeasible to apply MTAG to large numbers of phenotypes such as personality questionnaire item- and cognitive task-level data. Furthermore, neither MTAG nor GenomicSEM capture mixed effect directions, i.e. the presence of shared genetic variants with a mixture of concordant and discordant effects on two phenotypes resulting in minimal genetic correlation despite extensive overlapping genetic effects[24]. In contrast, a boost in genetic discovery has been demonstrated by the "pleiotropy-informed" multivariate omnibus statistical test (MOSTest), which is ambivalent to effect direction. Applying MOSTest to brain imaging phenotypes has shown that alterations in brain morphology and functional connectivity are associated with hundreds of genetic loci with "pleiotropic" genetic effects across the brain, even despite weak genetic correlation[25–28]. We hypothesised

that the genetic architecture of interconnected higher-order mental traits, such as cognitive function and personality traits are driven by similar pleiotropic effects.

Additionally, our understanding of the genetics of personality traits beyond neuroticism is limited[29–31], in part because UKB did not collect data on the four remaining personality traits within the "Big 5" taxonomy. As such, only eight loci have been reported across all five measures in the largest GWAS to date (n=76,600–122,886)[32]. However, it is possible to boost statistical power for genetic discovery, identify shared genetic loci, and improve prediction in underpowered GWAS by leveraging genetic overlap with a second, more powerful GWAS using the conditional false discovery rate framework (cFDR)[33–35]. This approach has recently been applied to MOSTest analyses of brain structural[36] and functional measures[28] to improve discovery and prediction of mental disorders.

Given evidence of genetic overlap between neuroticism and cognitive function, we sought to boost the statistical power for genetic discovery by exploiting pleiotropic genetic effects across questionnaire item and cognitive task-level measures of neuroticism and cognition. By applying "pleiotropy-informed" MOSTest, which incorporates scenarios of mixed effect directions, we found a substantial boost in discovery driven by shared genetic effects across domains. The widespread effects were supported by functional analysis, which identified underlying neurobiological processes distributed across brain regions. We additionally leveraged our multivariate analysis to boost genetic discovery across the remaining Big Five personality traits and improve polygenic prediction. A conceptual illustration of the study is provided in Figure 1.

Results

Sample description

The UKB is a population-based cohort comprising over 500,000 participants between the ages of 39–72[37]. At enrolment, all participants were invited to complete a touchscreen questionnaire, including 12 dichotomous items derived from the neuroticism subscale of the Eysenck Personality Questionnaire-Revised Short Form[38]. They additionally completed 25 diverse cognitive tasks, including 13 components of a measure of "fluid intelligence", either at enrolment or during follow-up visits. These included measures of fluid intelligence, reaction time, executive function, and memory[39,40] (table 1, supplementary table 1). After also calculating sum-scores for neuroticism and fluid intelligence, we included all 39 measures to maximise statistical power for genetic discovery. After removing participants of non-White British ancestry and related individuals, the mean sample size across all measures was 201,820, ranging from 3,627 to 336,993 (table 1, supplementary figure 1). Sample sizes were more variable among cognitive tasks than neuroticism items. Mean age was 56.9 years (s.d.=8.0) at enrolment and 53.7% of included participants were female.

Item-level heritability and genetic correlations

To provide an overview of the heritability of questionnaire item- and cognitive task-level measures, we first calculated linkage-disequilibrium score regression (LDSR) SNP-heritabilities (h^2_{SNP}) for all included measures. Since the inclusion of non-heritable

phenotypes may reduce statistical power[25], four measures were removed from the analysis, leaving 35 measures (supplementary figure 1, supplementary table 2). We next computed pair-wise LDSR genetic correlations followed by hierarchical clustering to explore directional genetic relationships (figure 2, supplementary results)[41]. Neuroticism and cognitive measures shared weak negative correlations (mean r_g=−0.15, s.d.=0.12) compared to moderate to strong positive correlations within each domain (neuroticism mean r_g=0.64, s.d.=0.14; cognitive mean rg=0.56, s.d.=0.23). Consequently, neuroticism and cognitive measures clustered separately. Neuroticism items further clustered into two sub-clusters: anxiety features ("worry") and depressive features ("depressed affect"), reproducing previous findings[19]. Cognitive measures were more heterogenous, with "reaction time" distinct from two clusters relating to fluid intelligence, prospective memory, and numeric memory ("fluid intelligence/memory"), and executive function and visuospatial memory ("executive function"). A similar pattern was observed for phenotypic correlations (figure 2, supplementary results).

Multivariate GWAS identifies 431 genetic loci with pleiotropic genetic effects

On application of MOSTest to discover pleiotropic genetic effects, we identified 431 independent genetic loci significantly associated with the multivariate distribution of the 35 measures of neuroticism and cognition. This represented a 3.8x boost in locus discovery compared to mass univariate GWAS with correction for multiple testing ("min-P"), which identified 113 loci (figure 3a, supplementary figure 2, supplementary tables 3–4). Since MOSTest specifically leverages pleiotropy, this boost in discovery supports the hypothesis of pleiotropic genetic effects across mental traits. We also performed MOSTest analyses on neuroticism and cognitive measures separately to test the extent to which the boost in locus discovery was driven by cross-domain pleiotropy. Cognitive and neuroticism measures were associated with 221 and 199 loci, respectively. However, 153 loci discovered by the combined MOSTest analysis were not identified by either of the separate analyses, indicating that 35% of the discovered loci were driven by cross-domain pleiotropy. To test the effect of a) including participants with medical conditions which may affect cognition and b) the choice of covariates, we ran two sensitivity analyses of our MOSTest findings (supplementary results, supplementary figures 3–4). This showed a modest reduction in locus discovery, but evidence of substantial cross-domain pleiotropy remained. See supplementary results and supplementary figures 3–4 for further details. Given the importance of controlling for population stratification, we also performed an extended sensitivity analysis investigating the effect of including additional covariates on all analyses up and down-stream of our MOSTest analysis (supplementary results, supplementary figures 5–12, supplementary tables 5–6). This showed that our findings were robust to the inclusion of additional covariates.

To illustrate the distribution of genetic effects, we tested for cross-cluster genetic overlap among the 431 lead variants using univariate GWAS p-values (figure 3b, supplementary table 7). This showed an increase in the number of shared variants at decreasing significance thresholds ($p<5\times10^{-8}$, $p<1\times10^{-6}$, $p<1\times10^{-5}$), indicating that the pleiotropic genetic variants captured by MOSTest had predominantly sub-threshold associations. Comparing across clusters, the two neuroticism clusters "depressed affect" and "worry" shared the largest

number of lead variants at all thresholds (n=22–68). Nonetheless, there was a comparable number of shared variants between cognitive and neuroticism clusters (n=0–29) and within cognitive clusters (n=1–24). Although these findings are partly affected by differences in sample size, this provides further evidence of pleiotropic genetic effects across mental traits. We also describe the pattern of effect directions across shared variants and evidence of cross-cluster gene-level overlap in supplementary results and supplementary figure 13.

To further investigate the pattern of effect directions across mental traits, we performed hierarchical clustering of univariate z-scores from all 431 lead variants (supplementary figures 14–15). This revealed that most lead variants had discordant effect directions between neuroticism and cognitive measures (n=360), reflecting the weak negative phenotypic association[17,18]. However, a minority of variants had either concordant effects across all measures (n=23), or had mixed effects within cognitive and neuroticism clusters (n=48). This indicates the presence of mixed genetic effect directions but a predominance of discordant effects across domains.

We plotted univariate GWAS p-values from all 35 measures for the top 40 lead variants to illustrate item and task-level patterns of genetic association (supplementary figure 16). Plots for five of these variants are presented in figure 4, each exemplifying a distinct pattern of association. Whereas some variants were genome-wide significant in only neuroticism clusters (n=76) (figure 4c) or only cognitive clusters (n=85) (figure 4d–e), 10 variants were genome-wide significant in measures across both neuroticism and cognitive clusters (figure 4a). Nonetheless, most variants had sub-threshold effects (n=260), demonstrating the boost in power generated by multivariate analysis (figure 4b). We also present the effect directions at the individual variant level, showing that 4 of the 5 lead variants exhibit a discordant relationship between neuroticism and cognition, consistent with negative genetic correlations. Nonetheless, figure 4b exemplified mixed effect directions, with weak positive effects on both “depressed affect” items and cognitive clusters but negative effects on “worry”. We also present the distribution of z-scores across the five exemplar lead variants to further emphasise the pattern of effect directions in supplementary figure 17.

We provided further evidence of substantial genetic overlap with mixed effect directions using the bivariate causal mixture model (MiXeR) (supplementary methods). MiXeR estimates the total number of shared genetic variants between two phenotypes irrespective of effect directions. Applied to the most heritable phenotype within each phenotypic cluster (figure 2), there was extensive genetic overlap irrespective of the genetic correlation between each pair of traits (supplementary figure 18). This pattern is indicative of widespread shared genetic variants with mixed effect directions.

Replication in independent samples

In line with previous GWAS studies[42–44], we tested for nominal significance, Bonferroni-corrected significance, and consistency of effect direction for MOSTest-discovered lead variants in independent samples, including 23andMe neuroticism GWAS (n=59,225)[32] and CHARGE “general cognitive function” GWAS (n=113,981)[14] (supplementary table 8). Out of 140 lead variants which were present in all three samples and 286 LD-proxies (r^2>0.6) which had non-ambiguous alleles and were approximately independent from each

other (r^2<0.1), 65 were nominally significant in the 23andMe, Inc. neuroticism GWAS, 130 in the CHARGE general cognitive function GWAS, and 26 in both datasets. Using the exact binomial test to test the hypothesis that the number of variants were greater than that expected by chance, all three were highly significant (1.98E-15, p=5.80E-64, and 2.23E-27, respectively). After Bonferroni correction (p<0.05/426), 16 variants were significant in the CHARGE general cognitive function GWAS and 4 in the 23andMe neuroticism sample, none of which were significant in both. The exact binomial test showed this remained significant for cognition (p=5.24E-35) and neuroticism (p=2.39E-07) but not both phenotypes (p=1). We also tested for consistent genetic effects of lead variants across UKB and replication datasets[44,45]. Since they were the most comparable phenotypes within our analyses, we compared univariate GWAS effect directions for the neuroticism and fluid intelligence sum-scores with 23andMe neuroticism and CHARGE general cognitive function summary statistics, respectively. 304 had concordant effects in neuroticism (exact binomial p=2.57E-19) and 344 had concordant effects in cognition (p=1.54E-39). 244 variants were concordant in both neuroticism and cognition (p=2.22E-45), providing additional evidence of pleiotropic effects in independent samples.

Functional characterisation

Using FUMA (fuma.ctglab.nl)[46], we performed functional annotation to provide biological insights into the genetic associations captured by MOSTest. We first used multi-marker analysis of genomic annotation (MAGMA) which tests for the association between phenotypic variation and aggregated GWAS p-values for 18,952 human protein-coding genes irrespective of effect direction[47]. MAGMA identified 1062 multiple comparison-corrected significant genes associated with the 35 measures of neuroticism and cognition (supplementary table 9). Next, MAGMA-based tissue specific expression analysis demonstrated highly specific enrichment of mapped genes in brain tissues. At the general tissue level (n=30), the brain, pituitary, ovary and testis were significantly enriched (supplementary figure 19). At the detail tissue level (n=53), all of the 14 included brain tissues were significantly enriched, as well as testicular tissue (figure 4, supplementary figure 20). This was a modest increase compared to univariate measures alone, which identified the brain and pituitary at the general level and 13 brain tissues at the detail tissue level. However, none of the univariate analyses were associated with either ovary or testis at the general tissue level, nor the spinal cord and testis at the detailed tissue level (supplementary table 10). When applied to Gene Ontology and canonical pathways there was a clear predominance of brain-related gene-sets. Twenty-nine out of 43 gene-sets were directly implicated in the structure or function of the central nervous system, and eight out of the top 10 significantly enriched gene-sets were related to synaptic structure or function (figure 5). Outside of the top 10, other notable gene-sets included “observational learning”, “behavior” and “cognition”, in addition to several neurodevelopmental gene-sets and “gamma aminobutyric acid signalling pathway” (supplementary table 11). This also represented a significant boost in gene-set discovery compared to univariate analysis, which identified a total of 4 gene-sets across all 35 GWAS (supplementary table 11). We additionally explored the enrichment of different functional categories according to their pattern of association with the 35 included measures (supplementary material, supplementary figure 21).

Boosting discovery of genetic loci associated with Big 5 personality traits and cognitive function

We used the cFDR approach[34] to leverage the additional power generated by our multivariate analysis to boost discovery of novel genetic loci associated with the remaining big 5 personality traits: agreeableness, conscientiousness, extraversion and openness in an independent sample (n=59,225)[32]. cFDR applies a Bayesian model-free statistical framework to re-rank SNP associations with a primary trait given their strength of association with a conditional trait.

We identified novel loci associated agreeableness (n=11), conscientiousness (n=36), extraversion (n=89), and openness (n=24) (figure 6a, supplementary tables 12–15). The conditional analysis ensures that the boost in power from the MOSTest method is driven by overlapping genetic variants, and not non-specific effects. Functional annotation of cFDR results identified 47 positionally-mapped genes for agreeableness, 157 for conscientiousness, 531 for extraversion, and 114 for openness (supplementary tables 16–19). MAGMA cannot be applied to cFDR statistics because cFDR test statistics are not normally distributed under the null hypothesis and so violate the assumptions of the model. We therefore applied hypergeometric test-based gene-set and tissue enrichment analyses using positionally mapped genes to replicate the approach taken by MAGMA[46]. There were no gene-sets or tissues significantly enriched with mapped genes from any of the 4 traits.

To test for pleiotropic effects in the remaining personality traits, we also performed conjunctional FDR (conjFDR), an extension of cFDR which identifies shared loci between two phenotypes. This revealed that 46–74% of loci associated with the Big 5 personality traits were also associated with our multivariate analysis of mental traits, indicating extensive pleiotropic effects beyond just neuroticism (supplementary tables 20–23).

We performed cFDR using independent neuroticism and general cognitive function GWAS, and compared these findings to the larger UKB-based GWAS to test the validity of cFDR in this context (supplementary tables 24–25). Of those present in both datasets, 50 out of 72 (69.4%) neuroticism and 92 out of 131 (70.2%) general cognitive function lead variants were nominally significant in the larger GWAS of neuroticism[9] and general intelligence[12], respectively.

Improving polygenic prediction of personality and cognitive function

We compared PGSs calculated based on the top 10–100,000 LD-independent SNPs using three setups: (i) original GWAS p-value ranking and original GWAS effect sizes (standard PGS), (ii) cFDR-based ranking and original GWAS effect sizes (pleioPGS)[35], and (iii) MTAG-based p-value ranking and corresponding MTAG-adjusted effect sizes (MTAG)[22]. In the pleioPGS approach we used SNP ranking based on cFDR analysis conditioning GWAS of the trait of interest (23andMe Big 5 personality traits and CHARGE cognitive function) on our multivariate GWAS of cognitive function and neuroticism. In the MTAG approach, our UKB-based GWAS of neuroticism summary score (N=274,056) was used to adjust p-values and effect sizes in 23andMe GWASs of five personality traits, and our UKB-based GWAS of fluid intelligence summary score (N=163,375) was used to adjust the

CHARGE cognitive function summary statistics. We also applied the PRS-CS method (iv), an approach which has been shown to outperform standard PGS models, which uses all SNPs in the model after adjusting effect sizes according to LD structure[45]. In all four setups the phenotypic variance explained by the PRS (r^2) was estimated using a linear regression model controlling for age, sex and first 20 genetic PCs. We hypothesised that the boost in power from our multivariate analysis leveraged by the pleioPGS approach will prioritize more informative variants than standard GWAS, MTAG or PRS-CS, resulting in improved PGS performance. When comparing the best performing model for pleioPGS and standard PGS, pleioPGS outperformed standard PGSs by 2.6 and 2.5 times for conscientiousness and cognitive function, respectively, as well as outperforming PRS-CS and MTAG-based rankings for conscientiousness (figure 6b). MTAG-based rankings outperformed pleioPGS for cognitive function, demonstrating that pleiotropy can be leveraged in other ways to boost polygenic prediction. None of the other PGS achieved statistically significant prediction compared to the null model after Bonferroni correction. This may indicate a lack of signal in the primary GWAS for successful prediction in the test sample.

Discussion

In this multivariate genome-wide association analysis of 35 heritable questionnaire items, cognitive tasks, and summary scores, we provide evidence of abundant pleiotropic genetic associations across personality and cognitive traits. Despite weak genetic and phenotypic correlations between neuroticism and cognitive domains, we discovered 431 genetic loci associated with the multivariate distribution of included traits, with evidence of pleiotropic associations across domains. Furthermore, we identified distinct patterns of relationships with evidence of cross-domain genetic association and mixed effect directions. This was confirmed by MiXeR analysis showing extensive genome-wide genetic overlap across all phenotypic clusters even in the presence of minimal genetic correlation. Nonetheless, most lead SNPs were not genome-wide significant in univariate GWAS, demonstrating the boost in power provided by our multivariate approach. Functional characterisation revealed that the genetic signal captured by MOSTest was associated with increased gene expression across all brain tissues, the testis and ovary, and implicated synaptic structure and neurodevelopmental processes. Moreover, we show that our multivariate analysis improves discovery of implicated gene-sets and tissues compared to univariate GWAS. We leveraged the extra power generated by our multivariate approach to boost discovery of genetic loci associated with the remaining Big 5 personality traits, identifying 160 loci for agreeableness (n=11), conscientiousness (n=36), extraversion (n=89), and openness (n=24). We further showed how the genetic loci shared across cognition and multiple personality traits improved polygenic prediction of conscientiousness and cognitive function in an independent sample. These findings have implications for how we conceptualise the neurobiology of personality and cognition, indicating that their genetic foundations are tightly interrelated. Dimensional, multivariate approaches which account for the complex set of interactions across domains are therefore better suited to fully elucidate the molecular mechanisms contributing to these fundamental human traits.

Firstly, the boost in power generated by our combined analysis of neuroticism and cognitive measures, alongside our findings of shared genetic associations across domains, is consistent

with the hypothesis that these two mental constructs are influenced by pleiotropic genetic variants. This builds on recent evidence that differences in brain structure and function are associated with a similar pattern of pleiotropic genetic effects[25,26,28]. As larger numbers of genetic loci associated with complex mental traits are discovered[48], it is becoming increasingly apparent that individual genetic variants impact multiple, diverse traits, with few phenotype-specific variants[24,49]. This represents a key conceptual advance which has several implications. Firstly, while large univariate GWAS have provided insights into the neurobiology of specific traits[9,12], future studies need to be aware of the lack of specificity of most variants associated with complex mental phenotypes. To fully characterise a given genetic variant, its effect should be evaluated beyond the specific phenotype of interest as it is likely to have pleiotropic effects across diverse domains[25,50]. Secondly, as statistical power increases, the relative effect size of a variant will likely be more informative with regards to specificity and relevance for a given phenotype than the presence or absence of a statistical association. In this respect, conventional GWAS may become less a tool for discovery and more focused on the precision of effect size estimates. Thirdly, as we have shown here, pleiotropic genetic effects can be leveraged to help boost the power for genetic discovery and polygenic prediction in related traits[15].

When comparing[489,1225,50] effect sizes of MOSTest discovered lead variants across included measures, there was also evidence of mixed effect directions between neuroticism and cognitive domains. This is consistent with the finding of minimal genetic correlation yet pleiotropic effects between these two domains. Genetic correlation is a genome-wide summary measure of the correlation of effect sizes between two phenotypes[41]. It is therefore possible for two phenotypes to share large numbers of genetic variants but possess minimal correlation if there is a balance of shared variants with the same and opposite effect directions on the two phenotypes[51–53]. Shared genetic variants with mixed effects reflect phenotypic findings that neuroticism does not significantly predict high school educational performance[7] or cognitive function in older adults[6]. Nonetheless, “executive function” and “reaction time” clusters shared variants with the “worry” cluster, and “fluid intelligence/memory” shared variants with the “depressed affect” cluster which were strongly discordant, despite weak negative genetic correlations. This suggests that MOSTest may prioritise variants which have more strongly aligned effect alleles in relation to the genome-wide average. Further, the recent findings of pleiotropic genetic effects on brain structure and function[26–28], as well as patterns of widespread gene expression across different brain regions[54] underscore the highly inter-related functions of brain regions and structures. Taken with our findings, this indicates that a complex interplay between heritable brain functions result in patterns of heritable, inter-related, higher-order mental traits which contribute to the core characteristics of an individual.

We used MAGMA to provide biological insights into the statistical associations captured by MOSTest. Firstly, tissue enrichment analysis showed significant enrichment in all included brain tissues[55], underscoring the distributed nature of the genetic variants discovered. There were also several relevant gene-sets identified, including “observational learning”, “behavior” and “cognition”, alongside several gene-sets related to synaptic structure and function. Since MAGMA tests for enrichment of positionally mapped genes and so is not biased by the selection of tissue-specific eQTL databases, this indicates that MOSTest is

capturing biologically plausible genes and is not driven by non-specific genetic overlap, helping to validate our findings. Furthermore, the diverse set of brain tissues identified, including cortical structures, sub-cortical structures, the midbrain and the hindbrain, supports the broader concept of pleiotropic effects across the brain both on a structural and functional level[26,28,56]. It is also interesting to note that both the testis and ovary were significantly enriched, although to a lesser degree than brain tissues. Sex hormones can act in the brain to regulate gene transcription and interact directly with neurotransmitter systems[57]. They are also known to impact cognition, particularly verbal and visuospatial abilities[58], and emotional regulation[59], a core feature of neuroticism[11]. Despite this, gonadal tissue was not significantly enriched in either the aforementioned general intelligence[12] or neuroticism GWAS[9]. This may be the result of the additional power achieved using MOSTest.

Finally, we leveraged the boost in power from our multivariate analysis to improve discovery of genetic loci associated with agreeableness, conscientiousness, extraversion, and openness. This included, to the best of our knowledge, the first genetic loci reported for agreeableness. Nonetheless, these discoveries require replication in an independent sample to ensure their validity given they were discovered using cFDR and were not significant in the primary GWAS. Genetic overlap between schizophrenia and neuroticism and openness has previously been reported using cFDR[60]. Interestingly, five of the six loci shared between schizophrenia and openness were also identified in our openness cFDR analysis. Nonetheless, larger samples are required to validate these findings. By re-ranking genetic variants according to the MOSTest-informed cFDR values, we also improved polygenic prediction of conscientiousness and cognitive function. As has previously been shown for schizophrenia and bipolar disorder[36], the PGSs outperformed standard GWAS-based ranking despite using the same weightings, as well as PRS-CS, suggesting that this method prioritises more predictive variants. This approach is similar to other recent examples using multivariate GWAS to enhance discovery[28] and prediction[61,62]. Nonetheless, PGSs for agreeableness, extraversion, neuroticism, and openness failed to achieve statistically significant prediction in our independent test sample. This may have been due to a lack of statistical power, the use of different personality scales for the training[63] and test samples[64], or cultural differences between the American 23andMe sample[32] and the Norwegian, research-focussed TOP sample[65].

Among multivariate approaches, MOSTest was particularly well suited for the analysis of multiple personality and cognitive traits[25]. MOSTest is more flexible than canonical correlation analysis or MTAG since it can handle differences in sample size across included phenotypes and is more computationally efficient for high dimensional data[25]. By using permuted individual-level genotypes, MOSTest also robustly controls for type 1 error. It is also important to note that MOSTest differs fundamentally from genomicSEM[66], another widely used multivariate GWAS method. While genomicSEM is a statistical framework for applying the principles of structural equation modelling to GWAS summary statistics based on the flexible modelling of genetic covariance matrixes, MOSTest empirically models the multivariate distribution of included variables while being agnostic to effect direction. This means MOSTest can identify variants which are shared across phenotypes even if they have

mixed effect directions on each trait, which has been shown for many brain-related mental traits[52,67,68].

There were limitations to this study. Firstly, this analysis only included white European-ancestry participants due to differences in linkage disequilibrium between ancestral groups and a lack of large, deeply phenotyped non-white European samples. Whereas mixed models are increasingly used to account for ancestral diversity, they are currently not compatible with MOSTest due to MOSTest's use of randomly permutated genotypes. Larger samples and the application of novel permutation algorithms that respect ancestry and family structure will enable the inclusion of ancestrally diverse samples as well as related individuals in future work. Secondly, there were differences in sample size between measures. This means that the genetic associations captured by MOSTest are likely driven to a greater extent by measures with larger sample sizes and that z-score estimates for measures with smaller sample sizes may be less precise. Despite this, we showed statistically significant associations with measures from both domains, supporting our main finding of pleiotropic effects. There were also differences in the cognitive tasks and personality trait measures used in the UKB, CHARGE, 23andMe and TOP samples. This may have reduced the power in our replication and PGS analysis due to increased noise introduced by different measures. Thirdly, we combined cognitive measures taken at different timepoints during the study. While systematic differences in cognitive performance may subtly alter the results, it is unlikely to change the main findings of the study. Fourthly, MOSTest requires the use of individual level data. This limited our ability to include other personality traits in the main analysis which were not included in UKB. We mitigated this by using our multivariate analysis to boost discovery for the remaining four personality traits. Fifthly, we used MAGMA for gene-mapping, tissue enrichment and gene-set analyses, which does not incorporate eQTL or chromatin interaction gene-mapping. This increased the specificity of the gene-mapping approach and meant that the gene-set and tissue enrichment analyses were not biased by the selection of eQTL or chromatin interaction databases. However, this also reduced the sensitivity of our gene-mapping procedure. We considered this approach to be the most appropriate since discovery of individual causal genes is difficult due to a lack of experimental gene-mapping evidence. We demonstrate the value of the boosted power for locus discovery using MOSTest through gene-set and tissue enrichment analyses and improved PGS performance. Finally, we did not exclude individuals with acquired disorders which could affect cognitive functioning in the analysis and we only included 10 principal components as covariates in the initial GWAS step of the MOSTest analysis, which may not capture all the population stratification present in the UK Biobank sample. Nevertheless, our sensitivity analyses indicated that this was unlikely to affect our main finding of substantial pleiotropy across neuroticism and cognition.

In conclusion, by combining 35 item and task-level measures of mental functioning in a multivariate framework, we demonstrate that distinct cognitive and personality traits are influenced by hundreds of genetic variants with pleiotropic effects and mixed effect directions, despite minimal genetic and phenotypic correlations. This contributes to a growing body of evidence indicating that common genetic variants underlying complex mental traits are closely interrelated, suggesting that "the whole is more than the sum of its parts" for brain-related phenotypes.

Methods

Ethical considerations

All participants provided informed consent. UKB participants who withdrew consent were excluded from the study. UK Biobank data was accessed under accession number 27412. The 23andMe sample participated under a protocol approved by the external AAHRPP-accredited IRB, Ethical & Independent Review Services (E&I Review). Participants were included in the analysis on the basis of consent status as checked at the time data analyses were initiated. The use of summary statistics for cFDR analysis was evaluated by The Norwegian Institutional Review Board: Regional Committees for Medical and Health Research Ethics (REC) South-East Norway and found that no additional ethical approval was required because no individual data were used. TOP received ethical approval from Norwegian REC (ref. 2009/2485), Data Inspectorate (ref. 03/02051), and The Norwegian Directorate of Health (ref. 05/5821).

Samples and phenotyping

UK Biobank—Genotypes, demographic, and clinical data were obtained from the UK Biobank. We selected unrelated (included in UKB genetic principal components calculation), white British individuals (as derived from both self-declared ethnicity and principal component analysis) with no sex chromosome aneuploidies[37] and genotyping call rate greater than 0.9. Participants who had withdrawn their consent were removed. This resulted in 337,145 individuals with mean age of 56.9 (standard deviation = 8.0 years). 53.7% were female. For the association analysis we retained only variants on autosomes with minor allele frequency above 0.001 imputation info score > 0.8 and with Hardy-Weinberg Equilibrium p-value > 1E-10, leaving 12.9 million variants.

Table 1 and supplementary table 1 summarise the phenotypes included in our multivariate analysis. The UKB neuroticism items were derived from the Eysenck Personality Questionnaire-Revised Short Form[38]. The scale was completed by all participants during enrolment at the assessment centre as part of the touchscreen assessment. All items comprised binary yes/no response options. Cognitive measures were collected at three different timepoints – either as part of the touchscreen cognitive assessment at enrolment (2006–2010), online cognitive follow-up (2014–2015) or during a follow-up imaging visit (2016). Some items from the touchscreen assessment were repeated during the cognitive follow-up and so were merged to maximise sample size. Included measures spanned a variety of cognitive domains, including verbal/numeric reasoning, prospective memory, working memory, non-verbal reasoning, visual declarative memory, processing speed and executive function[40]. All cognitive measures were coded so that larger values indicated better performance (i.e. shorter reaction time, less matching errors, faster task completion etc.).

23andMe and CHARGE

For our replication and cFDR analyses, summary statistics for 23andMe Big 5 personality traits[32] and CHARGE general cognitive function[14] were accessed through collaborations. Sample make-up, genotyping procedures and phenotyping have been described in detail in

the original publications[14,32]. Briefly, the 23andMe samples comprised 59,225 individuals of European ancestry. Sum-scores for agreeableness, conscientiousness, extraversion, neuroticism, and openness were derived from the Big Five Inventory – 44-item edition[63]. 23andMe customers completed the questionnaire online. The CHARGE general cognitive function sample comprised a meta-analysis of 113,981 participants of European ancestry from 51 cohorts after excluding UK Biobank participants to eliminate overlap with the discovery sample as well as individuals enrolled in five additional cohorts that contributed data in the original publication (Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik), Atherosclerosis Risk in Communities (ARIC) Study, Cardiovascular Health Study (CHS), Framingham Heart Study (FHS), and Genetic Epidemiology Network of Arteriopathy (GENOA)). Cognitive function was assessed using a wide variety of different cognitive tests for fluid cognitive function. Each cohort included a minimum of three different cognitive tasks that tested different cognitive domains, For each cohort, principal component analysis was applied to the cognitive test scores. The score derived for the first unrotated principal component was used as a measure of represent the "general cognitive function" phenotype.

TOP Sample

The TOP sample comprised participants recruited as healthy controls for an observational study of severe mental illness. Participants were identified at random from the national population register.

Inclusion criteria included the absence of current or previous psychiatric disorder as identified by the Primary Care Evaluation of Mental Disorders (Prime-MD) delivered by a trained research assistant[69]. Exclusion criteria were substance use disorder, physical health condition, previous traumatic brain injury, neurological disorders, autism spectrum disorder, personal or family (1st degree relative) history of severe psychiatric disorder, and age outside of the range 13–72. Big 5 personality traits were assessed using the revised Neuroticism-Extraversion-Openness Five Factor Inventory (NEO-FFI)[70], Norwegian edition, a 60-item questionnaire comprising 5-point Likert scale responses. Cognitive function was measured using the Wechsler Abbreviated Scale of Intelligence second addition (WASI-II)[71]. Incomplete responses were dropped, leaving sample sizes of 587 for agreeableness, 600 for conscientiousness, 581 for extraversion, 598 for neuroticism, 578 for openness and 1066 for cognitive function.

Data analysis

Pre-processing of UKB variables—Prior to the association testing each item was manually pre-processed. Missing values were dropped from the analysis. Several continuous items with skewed and highly sparse distribution of answers were binarized. All continuous items were transformed using rank-based inverse normal transformation. Further details are provided in supplementary table 1.

LD score regression heritability, genetic correlation, phenotypic correlation and hierarchical clustering—Univariate h^2_{SNP} and pairwise genetic correlations (r_g) were estimated using LDSR[41,72]. Briefly, LDSR estimates univariate h^2_{SNP} from GWAS

summary statistics by modelling the relationship between variant-level effect size and extent of LD, building on the observation that the larger the region of LD the larger the effect size estimate. Genetic correlation is then computed as the co-variance of SNP effect size between two traits after controlling for LD. We performed hierarchical clustering on pair-wise genetic correlations using Agglomerative Clustering algorithm with distance function $1-|r_g|$, as implemented in sklearn Python package[73]. Phenotypic correlations were computed using Spearman rank correlation as implemented in the Python package SciPy[74].

MOSTest and min-P—Plink2[75] (v2.00a3LM AVX2 Intel (3 Jan 2021)) was applied to perform item-level genotype-phenotype association testing using linear regression for continuous items and logistic regression for binary items with sex, age, and first 10 genetic principal components as covariates. In total we performed GWAS of 13 neuroticism and 26 cognition measures. Corresponding summary statistics were processed with LD score regression[72] to estimate SNP-heritabilities (supplementary table 2, supplementary figure 1) and genetic correlations between items (figure 1). Since including non-heritable traits into MOSTest analysis may reduce statistical power[25], only items with h^2 p-value < 3.167E-5 were used for subsequent MOSTest and min-P analyses. This threshold is recommended by the developers of LDSR-based SNP-heritability[72] and has previously been used for large-scale heritability analyses of UKB genetic data[76]. In total 35 measures (13 neuroticism and 22 cognition cognitive) passed this h^2_{SNP} filter.

MOSTest analysis was performed using the following steps, as outlined in previous publications[25,26]: i) univariate GWAS was run for each individual phenotype using randomly permuted genotypes (in addition to univariate GWAS using original genotypes already performed); ii) covariance matrix of z scores was estimated from permuted genotypes; iii) MOSTest test statistics were estimated for permuted and original genotypes as the Mahalanobis norm of permuted and original z scores, respectively, using the regularized covariance matrix obtained in (ii), where the regularization parameter (r=3) was selected to maximize the yield of genome-wide significant loci as described previously[26]; iv) the distribution of the MOSTest test statistics was approximated under the null hypothesis (no genotype-phenotype association) from the observed distribution of the test statistics for permuted genotypes obtained in (iii), using the empirical distribution in the 99.99 percentile and a Gamma distribution in the upper tail, selecting the shape and scale parameters of the Gamma distribution to maximize the likelihood of the observed data; v) the cumulative distribution function from (iv) was used to calculate MOSTest p-values using test statistics obtained using original genotypes.[2626] We also performed MOSTest analyses for only neuroticism measures and only cognitive measures. Min-P was computed as the smallest p value for each variant across all univariate GWAS for each phenotype, followed by correction for the number of phenotypes tested, as described previously[77].

Genetic overlap between MOSTest across univariate GWAS analyses was determined at the lead-variant level. We extracted p-values for all MOSTest lead variants from each individual univariate GWAS for included measures. Genetic overlap was deemed present if the lead variant was significant in each pair of univariate GWAS at the specified significance threshold ($p<5\times10^{-8}$, $p<1\times10^{-6}$, $p<1\times10^{-5}$). The same procedure was used to quantify overlap across the three multivariate analyses.

We performed hierarchical clustering of univariate z-scores for each MOSTest-discovered lead variant. Hierarchical clustering was produced using AgglomerativeClustering algorithm with Euclidian distance, as implemented in sklearn Python package. Lead variants were split into 7 clusters. For each variable we then estimated the median z-score over all variants in the cluster.

Conditional/conjunctional false discovery rate—We applied cFDR to boost discovery of genetic variants associated with the Big 5 personality traits and general cognitive function. Firstly, conditional qq-plots were constructed by comparing enrichment of association in all variants in the primary trait (i.e Big 5 personality traits or general cognitive function) with 3 subsets of variants defined by their strength of association ($p<0.1$, $p<0.01$ and $p<0.001$) with the secondary trait (i.e. MOSTest summary statistics). Successive left-ward deflection, indicating greater enrichment of statistical associations, with increasing threshold of significance indicates cross-trait enrichment. Shift in enrichment conditional on the secondary trait can be directly interpreted according to the Bayesian definition of the true discovery rate (TDR = 1-FDR), whereby a larger shift is consistent with a smaller FDR. This means cFDR values can be computed for each variant by comparing enrichment of all variants with a subset of variants which are as strongly or more strongly associated with the secondary trait. The cFDR value can therefore be interpreted as the probability that a given SNP is not associated with the primary trait given that the SNP is more strongly or as strongly associated with both phenotypes than observed in the original GWAS. Look-up plots were constructed which provide cFDR values given the p-values in the primary and secondary traits. The conjunctional FDR statistic was computed by repeating the analysis having switched the primary and secondary trait. The maximum of the two cFDR statistics represents the probability that a given SNP is not associated with the primary or secondary trait given that the SNP is more strongly or as strongly associated with both phenotypes than observed in the original GWAS. We performed 100 iterations of each analysis after random pruning from independent LD blocks ($r^2>0.1$). Genomic inflation was corrected for by a conservative genomic control procedure utilizing intergenic variants which lack true associations relative to other functional regions[78]. The MHC region was excluded from the model-fitting procedure to prevent inflation of test statistics due to complex LD.

Locus definition

Genetic loci were defined based on association summary statistics produced with MOSTest, min-P and cFDR following the protocol implemented in FUMA with default parameters[46]. The protocol is summarised as follows:

1. Independent significant genetic variants were identified as variants with p-value<5E-8 or cFDR<0.05 and linkage disequilibrium (LD) r2<0.6 with each other.
2. A subset of these independent significant variants with LD r2<0.1 were selected as lead variants.
3. For each independent significant variant all candidate variants were identified as variants with LD r2≥0.6.

4. For a given lead variant the borders of the genomic locus were defined as min/max positional coordinates over all corresponding candidate variants.

5. Loci were merged if they were separated by less than 250kb.

Replication in independent samples

As applied in several recent GWAS[42–44], we tested for *en masse* sign concordance of genetic effects, nominal significance and Bonferroni corrected significance in MOSTest-discovered lead SNPs using UKB fluid intelligence sum-score and CHARGE general cognitive function summary statistics, and UKB neuroticism sum-score and 23andMe neuroticism summary statistics. We dropped all variants with ambivalent effect alleles and used LD proxies ($r^2 > 0.6$) if a lead SNP was not present in both replication cohorts. We first used an exact binomial test to test the null hypothesis that sign concordance, nominal significance, and Bonferroni corrected significance were randomly distributed (p=0.5, p=0.05, and p=0.05/n, respectively), given the total number of variants (n) and the number of variants with concordant effects in UKB and each independent dataset, and nominally significant and Bonferroni-corrected significant in the independent datasets, respectively (k). To test for evidence of pleiotropic effects, we used an exact binomial test to test the null hypothesis that sign concordance, nominal significance, and Bonferroni corrected significance in both neuroticism and cognitive function were randomly distributed (p=0.25, p=0.0025, and $p=(0.0025/n^2)$), given the total number of variants (n) and the number of variants which were concordant, nominally significant, and Bonferroni-corrected significant in both phenotypes simultaneously.

Mapped genes, tissue specificity and gene-set analyses

Gene-mapping of MOSTest GWAS summary statistics was performed using MAGMA as implemented in FUMA. The MHC region was excluded and all other settings were default. Gene analyses of individual items (supplementary results) were performed with MAGMA (version 1.09b)[47] applying a SNP-wide mean model to GWAS summary statistics excluding variants within MHC region (chr6:25000000–33000000) 1000 Genomes Phase 3 EUR were used as a reference panel and other settings being default. 18,952 genes were included in the analysis.

Tissue specificity and gene-set enrichment analysis of MOSTest summary statistics was performed using MAGMA as implemented in FUMA[47]. Tissue specificity was tested in GTEx version 7 eQTL database[55] across 53 “detail tissues” and 30 “general tissues”. Gene-set enrichment was tested in Gene Ontology[79] and curated gene-sets from MsigDB[80] (n=10,678). Bonferroni correction was applied to correct for multiple comparisons.

cFDR statistics are not applicable to MAGMA because the distribution of cFDR statistics under the null hypothesis does not fit the assumption that the association statistic is normally distributed. Genes were therefore mapped to candidate SNPs identified by cFDR using positional mapping, i.e. according to their physical proximity (<10kb) to each variant. We performed tissue specificity and gene-set analysis using the GENE2FUNC functionality in FUMA using default settings. Positionally mapped genes were used as input for all analyses. Over-representation of mapped genes within tissue-specific differentially expressed genes,

and Gene Ontology and curated gene-sets was tested using a hypergeometric test. Correction for multiple comparisons was performed using the Bonferroni method.

Polygenic score analysis

We calculated and compared PGS for the Big 5 personality traits and cognitive function in TOP sample using four different setups. The first three setups were based on the C+T (clumping + thresholding) approach[81] using different strategies for ranking SNPs and adjusting their effect sizes: (i) original GWAS p-value-based ranking with original GWAS effect sizes (standard PGS); (ii) cFDR-based ranking with original GWAS effect sizes[35], where cFDR analysis was performed conditioning GWAS of the trait of interest (23andMe Big 5 personality traits and CHARGE cognitive function) on our multivariate GWAS of cognitive function and neuroticism; (iii) multi-trait analysis of GWAS-based p-value ranking and corresponding adjusted effect sizes (MTAG)[23]. In the MTAG approach, our UKB-based GWAS of neuroticism summary score (N = 274,056) was used to adjust p-values and effect sizes in the 23andMe GWASs of Big 5 personality traits, and our UKB-based GWAS of fluid intelligence summary score (N = 163,375) was used to adjust summary statistics in the CHARGE GWAS of cognitive function. Default MTAG settings were applied as described in Turley et al.[23], besides the application of the "--no_overlap" parameter given the absence of sample overlap across the UKB, 23andMe and no-UKB CHARGE datasets[14,32]. For these three setups PGS were calculated across five sets of LD-independent SNPs (N = 10, 100, 10,00, 10,000, 100,000) using PRSice-2 (v2.3.3)[81] with no additional clumping (--no-clump option). Sets of LD-independent SNPs were obtained using plink v1.90b6.17 based on the setup-defined SNP ranking with --clump-kb 250, --clump-r2 0.1 parameters and in-sample LD estimates. In the fourth setup (iv) PRS-CS method was deployed, which uses Bayesian regression and continuous shrinkage to adjust weights for all available SNPs accounting for LD structure[82]. PRS-CS was applied with default settings using the 1000 Genomes Project phase 3 European LD reference panel as described in Ge et al.[82]. In all four setups, the phenotypic variance explained by the PRS (r^2) was estimated using linear regression model controlling for age, sex and first 20 genetic PCs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing interests

O.A.A. has received speaker's honorarium from Lundbeck and is a consultant for Healthlytix. A.M.D. is a founder of and holds equity interest in CorTechs Labs and serves on its scientific advisory board. He is also a member of the Scientific Advisory Board of Healthlytix and receives research funding from General Electric Healthcare (GEHC). The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies. I.J.D. is a participant in UK Biobank. S.S. has consulted for Biogen. Remaining authors have nothing to disclose.

Data availability

Individual-level UKB data is available through a publicly accessible application via UKB (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). The full GWAS summary statistics for the 23andMe discovery data set will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Please visit https://research.23andme.com/collaborate/#dataset-access/ for more information and to apply to access the data. CHARGE general cognitive function summary statistics are available on request to the chair of the NeuroChARGE Cognitive Working Group (Email: jan.bressler@uth.tmc.edu).

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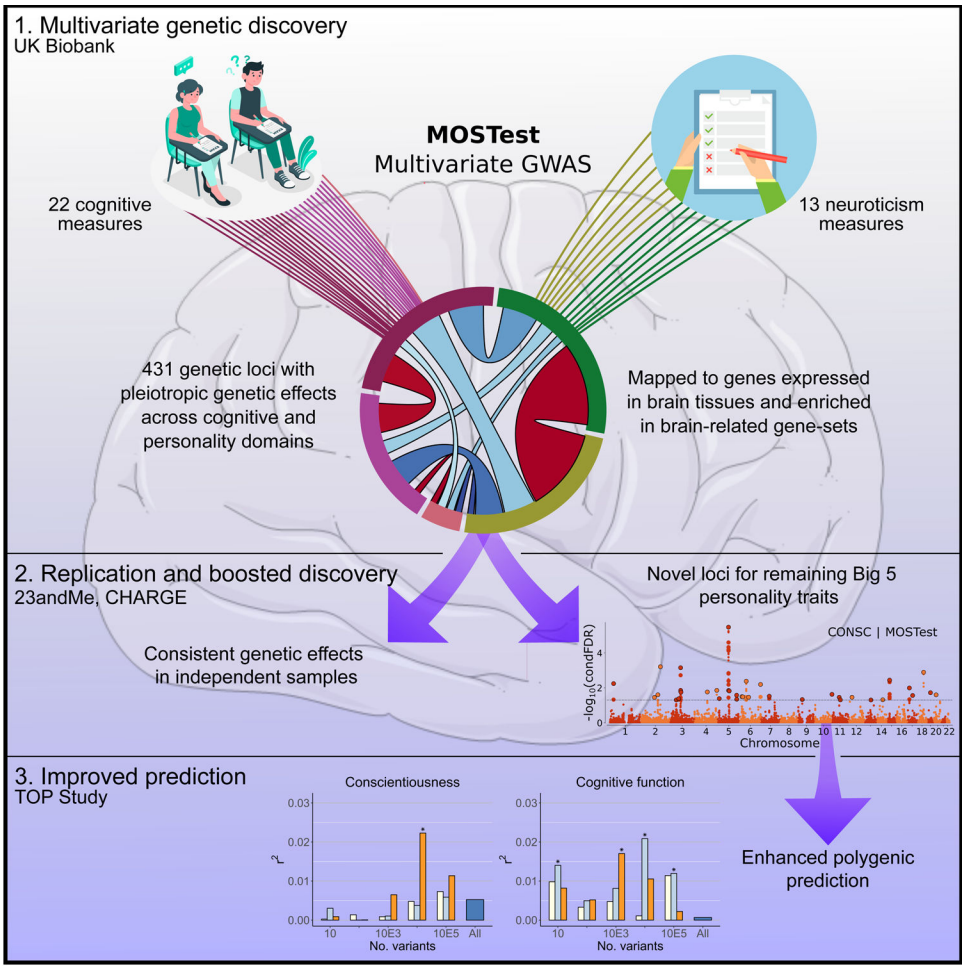

Figure 1: Conceptual overview of study design and main findings.

We performed a multivariate genome-wide association analysis of 35 measures of cognitive function and neuroticism in the UK Biobank. We show that discovered loci have distributed genetic effects across both neuroticism and cognitive domains, with differential expression of mapped genes across brain tissues. We replicate these findings in independent samples before leveraging the additional power generated by multivariate analysis to boost discovery of genetic loci associated with the remaining Big 5 personality traits and improve polygenic prediction of conscientiousness and cognitive function.

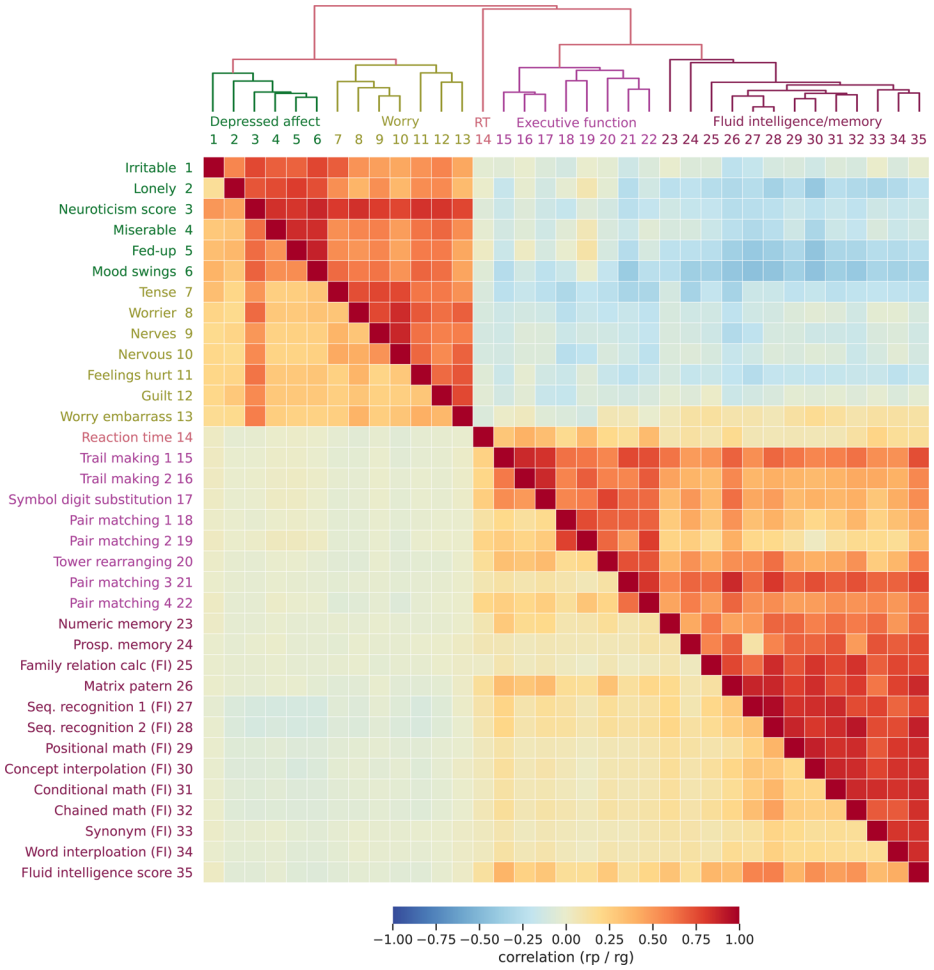

Figure 2: Heatmap of genetic and phenotypic correlations across mental traits.

LDSR genetic correlations (rg, top right) and Spearman rank phenotypic correlations (rp, bottom left) reveal a pattern of moderate to strong positive genetic correlations within neuroticism and cognitive domains but weak negative genetic correlations across cognition and neuroticism measures. Phenotypically, there were also stronger positive correlations within domains but minimal correlation across domains. Measures were clustered on genetic correlation, revealing 2 neuroticism clusters reproducing previously reported clusters “depressed affect” and “worry”[19], and 3 cognition clusters, broadly mapping on to “reaction time”, “executive function” and “fluid intelligence/memory”.

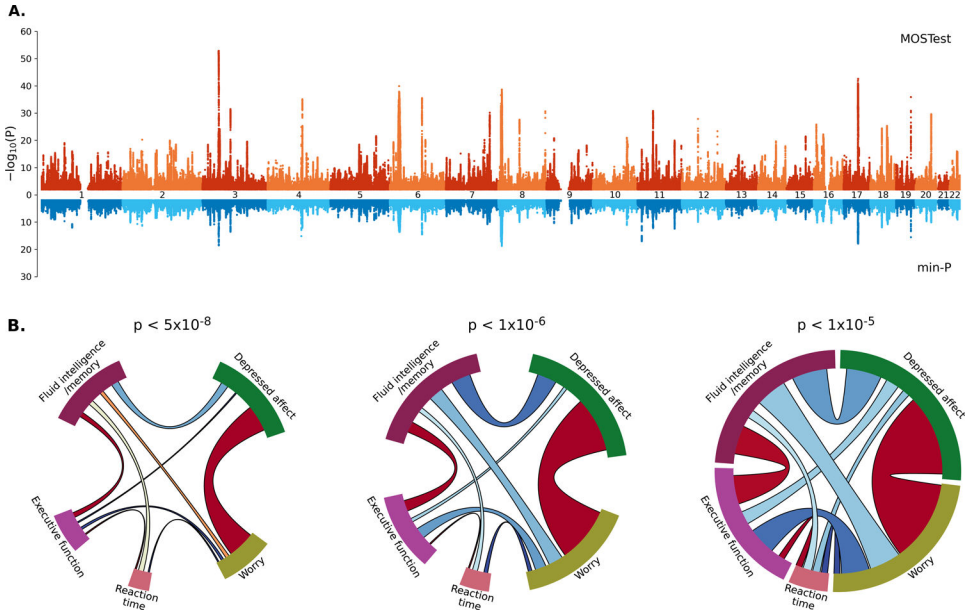

Figure 3: Boosting the signal of genetic association for 35 mental traits by leveraging pleiotropy.

A. Miami plot for MOSTest (orange) and min-P (blue), plotting each SNP's $-\log_{10}$(p-values) against chromosomal position. By applying a multivariate framework which leverages pleiotropic effects, there is a substantial boost in signal compared to a "mass univariate" approach such as min-P, evidenced by smaller p-values and a larger number of discovered loci (n=431 vs. 113). This indicates the presence of pleiotropic genetic effects across mental traits. **B.** Shared genetic associations of lead variants across 5 genetic correlation-based clusters (figure 1) at three significance thresholds. The number of lead variants within each cluster individually at each significance threshold is represented by the size of the coloured segments. The number of lead variants shared between each pair of clusters is represented by the width of the coloured ribbons. The proportion of variants with concordant effect directions on each cluster is represented by the colour of the ribbons from blue (0) to red (1).

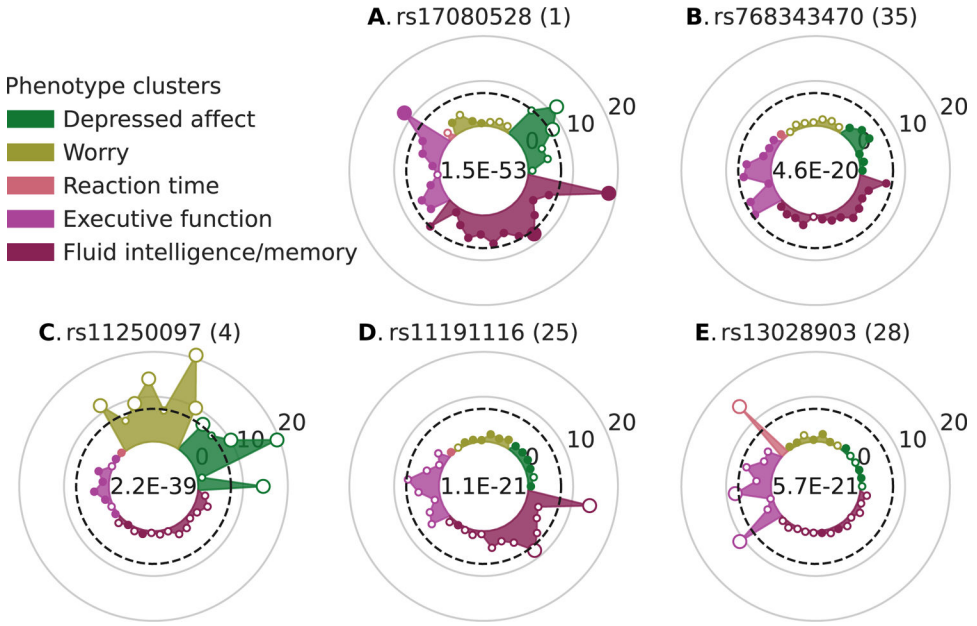

Figure 4. Patterns of pleiotropic genetic associations at the SNP-level.

P-values from univariate GWAS of 35 mental traits plotted for 5 lead variants, selected to illustrate five distinct patterns of association. The locus number, which corresponds to MOSTest significance rank, is provided in brackets. Univariate p-values are plotted on the logarithmic scale as the distance from the centre of each circular plot. Genome-wide significance ($p<5\times10^{-8}$) is represented by the dashed line. Positive effect direction is illustrated by a filled circle and negative effect direction by a clear circle. Phenotype clusters are derived from genetic correlation-based hierarchical clustering (figure 2) **A:** SNP which is genome-wide significant across neuroticism measures (with apparent specificity for the “depressed affect” cluster) and cognitive measures (both in “executive function” and fluid intelligence/memory” clusters), with predominantly positive effects on cognitive tasks and negative effects in neuroticism items. **B:** SNP which is non-significant across all measures, with indication of weak association with “depressed affect” cluster, “executive function” and “fluid intelligence/memory” clusters, and predominantly concordant effects in “cognitive tasks and depressed affect” items. **C:** SNP with genome-wide significance across neuroticism measures but minimal association with cognitive measures, and negative effects on neuroticism items and predominantly positive effects on “executive function”. **D:** SNP with genome-wide significance with “fluid intelligence/memory”, sub-threshold association with “executive function” and minimal association with neuroticism measures, and predominantly negative effects on cognitive tasks and positive effects on neuroticism items. **E:** SNP with genome-wide significance with “reaction time” and “executive function” but minimal association with “fluid intelligence/memory” and neuroticism measures, and negative effects in “fluid intelligence/memory” but weak, mixed effects in all other measures.

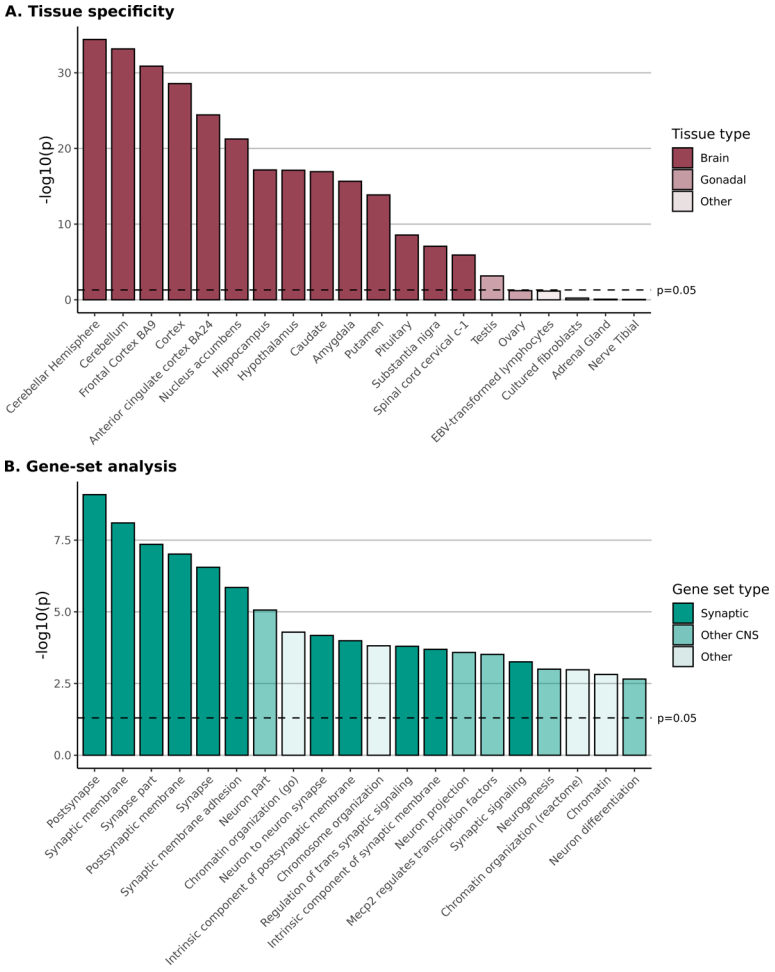

Figure 5. MAGMA tissue specific gene expression and gene-set enrichments.

A. MAGMA-based tissue specificity analysis of multivariate GWAS of 35 mental traits shows highly specific enrichment across all brain tissues and the testis. All tissues with corrected p<0.1 are presented. All tissues tested are shown in supplementary figures 11–12. Please note that the ovary was significant when tested at the “general tissues” level (supplementary figure 11**). B**. Top 20 gene-sets significantly enriched for gene-level associations with multivariate GWAS of 35 mental traits. All significant gene sets are presented in supplementary table 8. All p-values are corrected for multiple comparisons using Bonferroni correction.

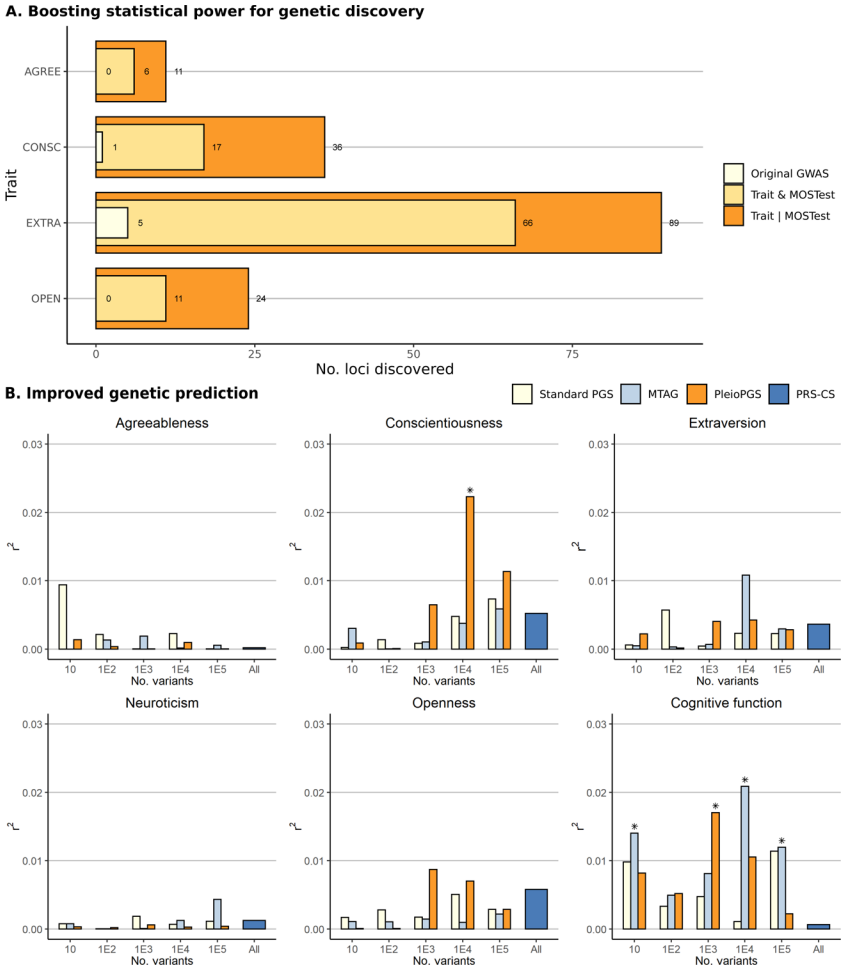

Figure 6: Leveraging multivariate analysis to boost discovery and polygenic prediction of personality and cognitive function.

A. The number of loci associated with agreeableness (AGREE), conscientiousness (CONSC), extraversion (EXTRA), and openness (OPEN) in the primary GWAS (pale orange) compared to the conditional false discovery rate conditioning on the multivariate analysis of 35 mental measures (cFDR, dark orange). We also provide the number of shared genetic loci between personality and the multivariate analysis of 35 mental measures (conjFDR, orange). The number of loci discovered increased substantially, including the first loci reported for AGREE. **B.** Explained variance of Big 5 personality and cognitive function polygenic scores (PGS) (r2, y-axis) for top 10, 100, 1000, 10,000 and 100,000 independent variants using primary GWAS p-value based ranking (light orange), multi-trait analysis of GWAS (MTAG, light blue) adjusted on UKB neuroticism (for personality traits) and fluid intelligence (for cognitive function), and pleiotropy informed (pleioPGS) ranking (dark orange), alongside PRS-CS using all SNPs (blue) from 23andMe and CHARGE GWAS summary statistics respectively. * Indicates statistical significance at $p<0.05$ after Bonferroni correction compared to a null model. PGSs were tested in healthy participants from the Thematically Organised Psychosis study.

Table 1:
Overview of neuroticism and cognitive measures from UK Biobank.

Clusters are derived from genetic correlation-based hierarchical clustering (figure 1). Further details are provided in supplementary table 1.

	Cluster	Measure	Abbreviation	Sample size
Neuroticism	Depressed affect	Neuroticism sum-score	NEUR sum-score	274,056
		Are you an irritable person?	Irritable	322,599
		Do you often feel lonely?	Lonely	332,193
		Do you often feel fed-up?	Fed-up	330,478
		Do you ever feel just miserable for no reason?	Miserable	331,782
		Does your mood often go up and down?	Mood swings	329,358
	Worry	Do you suffer from nerves?	Nerves	325,181
		Are you often troubled by feelings of guilt?	Guilt	328,700
		Would you call yourself tense or highly strung?	Tense	327,162
		Are your feelings easily hurt?	Feelings hurt	327,762
		Would you call yourself a nervous person?	Nervous	328,653
		Do you worry too long after an embarrassing experience?	Embarrass	323,698
		Are you a worrier?	Worrier	328,647
Cognition	Fluid intelligence/memory	Fluid intelligence sum-score:	FI sum-score	163,375
		Word interpolation	Word interp.	162,937
		Positional arithmetic	Pos. math	161,768
		Family relationship calculation	Fam. rel. calc.	158,977
		Conditional arithmetic	Cond. Math	144,648
		Synonym	Synonym	120,891
		Chained arithmetic	Chained math	109,731
		Concept interpolation	Concept interp.	50,331
		Arithmetic sequence recognition	Seq. recog. 2	34,286
		Square sequence recognition	Seq. recog. 1	11,679
		Numeric memory	Num. memory	104,319
		Prospective memory	Prosp. memory	111,079
		Matrix pattern completion.	Matrix pattern	22,335
	Executive function	Pair matching:		
		Full game.	Pair match. 1	336,993
		Time of full game.	Pair match. 2	330,143
		Basic game.	Pair match. 3	336,993
		Time of basic game.	Pair match. 4	330,777
		Symbol digit substitution	Symb. dig. Subs.	94,153
		Tower rearranging	Tower rearrang.	22,159
		Trail making:		
		Part A	Trail making 1	85,595
		Part B	Trail making 2	85,597
	Reaction time	Reaction time.	Reaction time	335,066

Cluster	Measure	Abbreviation	Sample size
	Fluid intelligence:		
	Numeric addition test	N/a	162,846
Non- heritable	Identify largest number	N/a	162,989
	Antonym	N/a	17,417
	Subset inclusion logic	N/a	3,627