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Large-scale Cognitive GWAS Meta-Analysis Reveals Tissue-Specific Neural Expression and Potential Nootropic Drug Targets

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Summary

Here, we present a large (N=107,207) genome-wide association study (GWAS) of general cognitive ability (*g*), further enhanced by combining results with a large-scale GWAS of educational attainment. We identified 70 independent genomic loci associated with GCA. Results showed significant enrichment for genes causing Mendelian disorders with an intellectual disability phenotype. Competitive pathway analysis implicated the biological processes of neurogenesis and synaptic regulation, as well as the gene targets of two pharmacologic agents: cinnarizine, a T-type calcium channel blocker; and LY97241, a potassium channel inhibitor. Transcriptome-wide and epigenome-wide analysis revealed that the implicated loci were enriched for genes expressed across all brain regions (most strongly in the cerebellum); enrichment was exclusive to genes expressed in neurons, but not oligodendrocytes or astrocytes. Finally, we report genetic correlations between cognitive ability and disparate phenotypes including psychiatric disorders, several autoimmune disorders, longevity, and maternal age at first birth.

Graphical abstract

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Author Contributions

T.L. designed the study and supervised the data analyses. M.L. performed the primary data analyses, and J.T.W., J.Y., and E.K. provided additional statistical input. A.K.M., D.C.G., I.J.D., K.E.B., and G.D. provided the initial conceptual framework for the COGENT consortium. M.L. and T.L. drafted the manuscript. All other authors were involved in ascertainment, assessment, and analysis of individual cohorts, provided conceptual input to study design, and critically reviewed the manuscript.

Web Resources

EasyQC <http://www.uni-regensburg.de/medizin/epidemiologie-praeventivmedizin/genetische-epidemiologie/software/>

METAL http://genome.sph.umich.edu/wiki/METAL_Documentation

MTAG <https://github.com/omeed-maghzian/mtag>

LD-HUB <http://ldsc.broadinstitute.org/>

LDSC <https://github.com/bulik/ldsc>

METAXCAN <https://github.com/hakymilab/MetaXcan>

FUMA <http://fuma.ctglab.nl/>

PRISice <http://prsisice.info/>

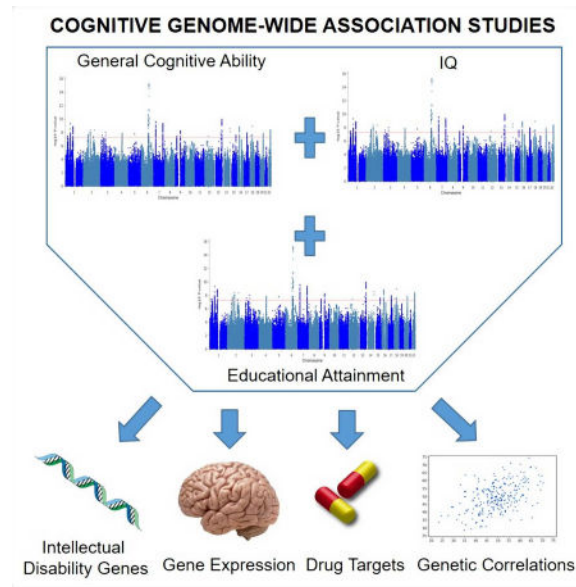
BRAINEAC <http://www.braineac.org/>

CommonMind <https://www.synapse.org/#!/Synapse:syn2759792/wiki/69613>

MAGMA <https://ctg.cncr.nl/software/magma>

Conflict of Interest

The authors declare no conflict of interest.



Keywords

GWAS; general cognitive ability; nootropics; gene expression; neurodevelopment; synapse; calcium channel; potassium channel; cerebellum

Introduction

Genome-wide association studies (GWAS) have been highly successful at uncovering hundreds of genetic loci associated with heritable quantitative traits such as height (Wood et al., 2014) and weight/body mass index (Locke et al., 2015). However, identifying genetic loci underlying cognitive ability has been much more challenging, despite heritability of 0.5 or greater, as determined by both classical twin studies (Deary et al., 2009) and molecular genetic studies (Davies et al., 2011a). In part, the difficulty with cognitive GWAS may be caused by the relative heterogeneity in the measurement of the cognitive phenotype. Traditionally, general cognitive ability (g) has been defined as a latent trait underlying shared variance across multiple subdomains of cognitive performance, psychometrically obtained as the first principal component of several distinct neuropsychological test scores (Johnson et al., 2008). Using this approach, several cognitive GWAS with fewer than 20,000 subjects yielded no genome-wide significant (GWS) effects (Benyamin et al., 2013; Davies et al., 2011b; Lencz et al., 2014), while a few GWS loci were identified in larger GWAS of 35,298 (Trampush et al., 2017) and 53,949 (Davies et al., 2015) subjects, respectively. By contrast, two independent GWAS of height with sample sizes of approximately 30,000 subjects each yielded 20–30 GWS hits (Gudbjartsson et al., 2008; Weedon et al., 2008); allelic effect sizes were ~2–5 times larger than the largest obtained in cognitive GWAS (Trampush et al., 2015).

Very recently, a cognitive GWAS (Sniekers et al., 2017) was able to leverage a very brief measure of fluid intelligence, highly correlated with psychometrically defined g , obtained in

over 50,000 subjects. In combination with several traditional cognitive GWAS cohorts, total sample size was 78,308. This sample size permitted discovery of 18 independent GWS allelic loci, as well as numerous additional loci from gene-based analysis. This report was critical in demonstrating that signal could be enhanced by combining data from cohorts with brief measures of intelligence with data from more traditional cognitive GWAS.

A further approach to enhancing power in cognitive GWAS has focused on educational attainment as a proxy phenotype (Rietveld et al., 2014). It is acknowledged that this phenotype is ‘noisy’, as it is influenced by non-cognitive genetic (Belsky et al., 2016) (e.g., personality) and environmental (Johnson et al., 2010) (e.g., socio-economic) factors; consequently, observed allelic effect sizes have been even smaller than those obtained for GWAS of *g* (Rietveld et al., 2013). However, by utilizing a single-item measure (years of education completed), obtained incidentally in large studies of other phenotypes, this approach has allowed investigators to obtain extremely large sample sizes. A recent study of educational attainment in nearly 300,000 individuals identified 74 independent GWS loci (Okbay et al., 2016). Moreover, a new technique called multi-trait analysis of GWAS (MTAG) (Turley et al., 2017) has been developed which permits integration of GWAS data across related traits, accounting for the possibility of overlapping samples across studies, and requiring only summary statistics. The developers of MTAG demonstrated its accuracy and utility in a study of traits (depression, neuroticism, and subjective well-being) that demonstrate genetic correlations in the range of $\sim .70-.75$; importantly, the genetic correlation between cognitive performance and educational attainment has been consistently reported to be in the same range (Davies et al. 2015, 2016; Okbay et al. 2016; Trampush et al. 2017; Snieder et al. 2017). MTAG is able to quantify the degree of “boost” to the signal of a single-trait GWAS, providing an estimate of observed sample size, and providing summary statistics (allelic weights) that can then be utilized in all downstream annotation pipelines available for GWAS output.

In the present study, we first utilized GWAS meta-analysis to combine our prior COGENT consortium GWAS (Trampush et al., 2017) of psychometrically defined *g* with the recently reported GWAS (Snieder et al., 2017) relying primarily on the brief measure, resulting in a combined cohort of $N=107,207$ non-overlapping samples measured for cognitive performance. Next, we utilized MTAG to combine these results with the large-scale GWAS of educational attainment, resulting in further enhanced power. At each step, we performed both allelic and gene-based tests. We then performed downstream analyses on the resulting MTAG summary statistics, including: 1) competitive gene set analyses to identify key biological processes and potential drug targets implicated; 2) stratified linkage disequilibrium score regression (LDSC) to identify differential cell type expression; 3) transcriptome-wide association study (TWAS) methods, to identify specific effects of altered gene expression in the brain on cognition; and 4) LDSC to identify genetic correlations with other anthropometric and biomedical phenotypes.

Results

Meta-Analysis: Cognitive Performance GWAS

Meta-analysis of all non-overlapping cohorts from the two GWAS of cognitive performance (total $N = 107,207$) identified 28 independent genomic loci reaching genome-wide significance (GWS, $P < 5E-08$), using default clumping parameters from the Functional Mapping and Annotation (FUMA) pipeline (Watanabe et al., 2017) pipeline (Figure 1a); this represents a 55.6% increase in loci compared to the previous GWAS (Snieder et al., 2017) of cognitive performance. Two of these loci each contained two uncorrelated variants with independent effects, resulting in 30 independent lead SNPs. Evidence for spurious inflation of statistical tests was quite limited for a large study of a highly polygenic trait ($\lambda = 1.23$; $\lambda_{1000} = 1.001$; LD score intercept = 1.03; see also PP plot in Supplementary Figure 1), and overall SNP heritability was .168. Of the 28 GWS loci, 12 were not previously reported as GWS in published studies of cognitive or educational phenotypes (Supplementary Table 1). The majority of the 5,610 markers reaching a nominal significance threshold were intronic SNPs followed by those in the intergenic regions (Supplementary Table 2). As shown in Supplementary Table 3, several of the GWS loci overlap with loci related to schizophrenia, bipolar disorder, and other neuropsychiatric phenotypes, as well as obesity/body mass index and other traits.

The significant loci harbored 88 known protein coding genes (Supplementary Table 4), about half of which were in three large regions (Supplementary Figure 2), including two well-characterized regions: the distal 16p11.2 region, in which deletions have been associated with schizophrenia and other neuropsychiatric phenotypes (Guha et al., 2013), and the 17q21 region, in which inversions have been associated with neuropsychiatric disorders (Cooper et al., 2011). Using MAGMA (Multi-marker Analysis of GenoMic Annotation; de Leeuw et al., 2015) gene-based tests, 73 genes were genome-wide significant (Supplementary Table 5), of which 39 were overlapping with the 88 genes noted above, resulting in a total of 122 candidate genes with statistical evidence of association to cognitive performance.

MTAG: Combining Cognitive Performance and Educational Attainment GWAS

MTAG analysis combining the cognitive performance results obtained above with the large educational attainment GWAS previously reported (Okbay et al., 2016), resulted in a 75% enrichment of statistical power, effectively boosting the original sample size of $N = 107,207$ to a GWAS equivalent of $N = 187,812$. Default clumping procedures revealed that 70 independent genomic loci reached genome-wide significance, with 82 independent SNPs (Figure 1b). Similar to the GWAS results above, the PP plot (Supplementary Figure 3) demonstrated polygenicity without evidence for artifactual inflation of statistical tests ($\lambda = 1.28$; $\lambda_{1000} = 1.001$; LD score intercept = 0.91), and overall SNP heritability was 0.336. Of the 70 GWS loci, 34 were not previously reported as GWS in published studies of cognitive or educational phenotypes (Figure 2; Supplementary Table 1). All but two of the 30 loci identified in the meta-analysis remained genome-wide significant in the MTAG results; even these two loci showed the same direction of allelic effects between cognitive meta-analytic GWAS and the educational GWAS. The majority of the 13,549 SNPs reaching a nominal

significance threshold in the MTAG analysis were intergenic or intronic (Supplementary Table 2; Supplementary Figure 4). GWAS catalog annotations are listed in Supplementary Table 3. Within the GWS loci, 265 protein coding genes were identified (Supplementary Table 4). Additionally, 256 genes were significant in MAGMA gene-based tests (Supplementary Table 6); of these, 85 genes were non-overlapping with the 265 genes within SNP GWS loci, resulting in a total of 350 genes receiving GWS support from the MTAG results.

As a formal validation that the MTAG methodology successfully predicts phenotype variance for cognitive performance, MTAG was re-analyzed, excluding the COGENT cohorts (i.e., the IQ GWAS of Sniekers et al. 2017 was combined with the educational GWAS of Okbay et al. 2016). The ASPIS and GCAP datasets were held out as target cohorts used for calculation of polygenic risk score modelling for “g”. Despite the relatively small size of these hold-out cohorts, results show strongly significant polygenic prediction of “g” using MTAG-derived allele weights (Figure 3a and 3c), accounting for more than 4% of the variance in the GCAP cohort. For both cohorts, polygenic prediction began to drop at P_T thresholds above 0.05, suggesting that there may be some degree of saturation of signal beyond the nominal 0.05 significance level at these sample sizes. Additional comparisons were made with IQ-only predictions (weights derived from Sniekers et al. 2017) and education-only predictions (weights derived from Okbay et al. 2016) for the same hold-out cohorts (Figure 3b and 3d), and we found that the MTAG-derived weights showed a 3.5-times and 3-times improvement in R^2 variance explained in the ASPIS cohort, for IQ and Education respectively. For the GCAP cohort, there was a 5.1-times to 96-times improvement in R^2 variance relative to IQ or education alone.

Overlap with Intellectual Disability Genes

We compared the list of 350 genes emerging from MTAG with a list of 621 genes known to cause autosomal dominant or autosomal recessive Mendelian disorders featuring intellectual disability (Harripaul et al., 2017; Vissers et al., 2016). As shown in Table 1, a total of 23 genes identified by MTAG appeared on this list, representing a 2-fold enrichment over chance (hypergeometric probability $p=0.001$). Examining autosomal dominant and recessive Mendelian genes demonstrated a somewhat stronger enrichment for autosomal dominant genes ($p=.0017$) than autosomal recessive genes ($p=.054$).

Tissue Expression Enrichment and Competitive Pathway Analysis

Downstream MAGMA expression profiles and competitive pathway analysis were conducted as part of the FUMA pipeline. MAGMA tissue expression profile analysis revealed that genes emerging from the MTAG analysis were significantly enriched for expression in nearly all central nervous system tissues (except for substantia nigra and spinal cord), and that this enrichment was exclusive to neural tissues (Figure 4a). Notably, the strongest enrichment was observed for genes expressed in the cerebellum, followed by cortex, and slightly weaker (but still strongly significant) enrichment in subcortical and limbic structures. Competitive pathway analysis (based on gene ontology categories) for GWS MAGMA genes identified by MTAG revealed significant enrichment of neuronal and synaptic cellular components, as well as the biological processes of neurogenesis and

regulation of synapse organization (Table 2, upper panel). Because three MTAG loci (at chromosome 3q21.31, 16p11.2, and 17q21.31) were unusually large, each containing 15 or more genes which may have disproportionately impacted enrichment results, we re-ran the above tissue expression and pathway analyses excluding these three regions. Results were substantively unchanged; all of the same neural tissues remained significantly enriched, in the same order of significance as shown in Figure 4a, and all of the same pathways remained significant (Bonferroni-corrected $p < .05$) as shown in Table 2, except for the cellular compartment “dendrite” (Bonferroni-corrected $p = .089$).

Competitive pathway analysis for drug pathways (Gaspar and Breen, 2017) revealed that the gene targets of two drugs were significantly enriched in the MTAG results (Table 2, lower panel): Cinnarizine, a T-type calcium channel blocker and LY97241, a potassium channel inhibitor. L-type calcium channel blockers and anti-inflammatories also showed suggestive evidence of enrichment. In a related analysis of drug classes, significant enrichment was observed for voltage-gated calcium channel subunits ($p = 9.28E-06$, Bonferroni-corrected $P = 5.38E-04$).

Stratified LD score regression (Finucane et al., 2017) also demonstrated an enrichment of cell type expression for neuronal tissues only. Notably, genes found in the neuronal expression list of Cahoy (Cahoy et al., 2008) were significantly enriched ($p = .0129$; Bonferroni-corrected $p = .0386$), whereas negative results were obtained for genes expressed in oligodendrocytes ($p = .4997$) and astrocytes ($p = .9057$). Additionally, using Roadmap annotations, epigenetic enrichment was strongest in fetal brain tissue DNase sites and H3K4me1 primed enhancers; followed by adult cortical H3K27ac active enhancer sites (see Supplementary Table 7 for further details). No enrichment was observed for any non-neuronal tissue. Again, results were not substantively changed when the three large loci were removed from these analyses.

Gene Expression Analyses

In order to derive specific biological insights from the broad association loci implicated by MTAG, we performed a series of analysis designed to identify individual gene expression changes associated with cognition. First, we performed transcriptome wide analysis (TWAS), using MetaXcan (Barbeira et al., 2016), on MTAG SNP results in order to identify transcripts for which up-regulation or down-regulation in specific neural compartments was associated with cognition. [Note that TWAS follows a similar logic to imputation, in that an external reference (in this case, publicly available GTEx eQTL data for 10 brain regions) is utilized to link SNP-based summary statistics to tissue-based expression levels]. As shown in Figure 4b (and detailed in Supplementary Table 8), most of the significant TWAS results are expressed across all neural tissues, involving genes such as *AMIGO3*, *RNF123*, and *RBM6*. Moreover, no individual tissue compartment was much more strongly enriched for associations compared to the others. However, a few strong transcriptomic associations were specific to individual brain regions. For example, the strongest result in hippocampus was with *DAG1*; TWAS demonstrated that greater expression of this gene in hippocampus was associated with higher cognitive scores. However, this gene was not expressed in other neural tissue types in the GTEx database. Similarly, lower levels of *ACTR1A* were

significantly associated with better cognition, but this transcript was observed only in frontal cortex.

Second, we applied a Bayesian fine-mapping approach (CAVIAR-BF, Chen et al. 2015) to identify putative causal SNPs within each associated locus, as defined in Supplementary Table 9. CAVIAR-BF revealed that there was strong evidence ($BF = 3.71e+2$) for at least 1 causal SNP within each of the 70 independent MTAG loci. There is also evidence that there is at least 2 causal SNPs in 65 of the loci ($BF = 3e+6$) and at least 3 causal SNPs in 47 of the loci ($BF = 2.86e+6$). In the extended region analysis, there was evidence for at least 1 causal SNP ($BF = 3.45e+2$) and 2 causal SNPs ($BF = 2.89e+6$) for 70 and 63 loci respectively. Model search revealed that there were 386 putative causal SNPs within the 70 independent loci (Supplementary Table 10). Lookups of these SNPs in two brain eQTL databases (BrainEAC (Ramasamy et al., 2014) and CommonMind (Hauberg et al., 2017)) revealed several additional SNP-eQTL relationships that can explain variance in the cognitive phenotype (Supplementary Tables 11 and 12); the most notable eQTL effect was observed for rs3809912 on chromosome 18. This SNP, which was GWS in the MTAG results ($p = 7.06E-09$), was a strong eQTL for *CEP192* ($p = 5.1e-38$, $FDR < 0.01$). This eQTL was confirmed in the CommonMind database ($FDR < .01$), which demonstrated that expression of 44 independent transcripts in frontal cortex were significantly associated with MTAG SNPs at the $FDR < .01$ level. Combining annotation information from the Mendelian gene analysis, MetaXcan TWAS, Braineac and CommonMind databases, we found supporting functional evidence for 112 of the 350 candidate genes nominated by MTAG (Supplementary Table 13). The remaining 238 genes without functional support had statistical evidence for association to cognition, but are considered to be ‘candidate genes’ requiring further functional or experimental support.

Genetic Correlations with Other Phenotypes

LD-score regression was carried out across 89 traits in 15 broad phenotypic categories in LD-hub (Zheng et al., 2017): 1) aging, 2) anthropometric, 3) autoimmune, 4) brain volume, 5) cardiometabolic, 6) education, 7) glycemic, 8) lipids, 9) lung function, 10) neurological, 11) personality, 12) psychiatric, 13) reproductive behavior, 14) sleep, and 15) smoking behavior (Figure 5; Supplementary Table 14). We performed LD-score regression separately for the results of our initial meta-analysis and for the MTAG results. For comparison, we also present LD-score regression results for the educational attainment GWAS of Okbay et al. (2016); it should be noted that only 14 phenotypes were examined for genetic correlation in that publication.

Cognition appeared to be strongly associated at the genetic level with aging, education, personality, neuropsychiatric disorders, reproductive behavior, and smoking behavior. Strong association with parental age at death was observed for both the GWAS meta-analysis and MTAG results. Meanwhile, moderate associations with anthropometric traits were observed, although associations with brain volumes were surprisingly modest, except for total intracranial volume (r_g for MTAG results = 0.31, $p = 7.37E-19$). While many of these correlations have been described previously (Hagenaars et al., 2016; Okbay et al., 2016; Snieder et al., 2017; Trampush et al., 2017), two results observed in the present study were

not reported in those prior publications. First, we report a strong positive genetic correlation between cognitive performance and maternal age at first birth (r_g for MTAG results = 0.63, $p=2.36E-163$) and inverse correlation with parental number of children ever born (r_g for MTAG results = -0.22; $p=6.91E-13$). It is possible that these effects are mediated by years of higher education, insofar as correlations were even stronger with educational attainment (r_g for parental age at first birth=0.72, $p=2.24E-244$; r_g for number of children= -0.26, $p=3.34E-18$). As with any other regression relationship, a role for unmeasured mediators, such as propensity for delayed gratification, cannot be ruled out. Second, we observed modest, yet nominally significant, inverse correlations between cognition and autoimmune diseases such as eczema and Crohn's disease, attaining Bonferroni significance for rheumatoid arthritis (r_g for MTAG results = -0.2086; $p=1.60E-08$); there was also a Bonferroni-significant positive genetic correlation with celiac disease (r_g for MTAG results = 0.1922; $p=0.0001$). While results of cross-trait analyses were largely consistent using either the GWAS results, the MTAG results, or the previously-published educational attainment datasets, there were notable divergences in correlations with psychiatric phenotypes, especially schizophrenia and bipolar disorder.

Discussion

Uncovering the molecular genetic basis of individual differences in cognitive performance can have a significant impact on our understanding of neuropsychiatric disorders, which are both phenotypically (Burdick et al., 2011; Ferreri et al., 2011; Keefe and Harvey, 2012; Snyder, 2013) and genetically (Lencz et al., 2014; Smeland et al., 2017; Stergiakouli et al., 2017) correlated with cognition, as well as numerous non-psychiatric health-relevant phenotypes (Hagenaars et al., 2016) which also demonstrate significant genetic correlations with cognitive function. Here, we have presented the largest GWAS of cognition to date, with 107,207 individuals phenotypically characterized for performance on standardized tests measuring general cognitive ability. Results were further enhanced by utilizing a relatively new approach to allow meta-analysis with a large-scale GWAS of educational attainment, which is highly (though not perfectly) correlated with cognitive ability at the genetic level. With this approach, we were able to identify 70 genomic loci significantly associated with cognition, implicating 350 candidate genes underlying cognitive ability. In total, we found that common SNPs were able to account for roughly half of the overall heritability of the phenotype as determined by prior family studies (Plomin and Deary, 2015).

Downstream analysis confirmed an important role for neurodevelopmental processes in cognitive ability, consistent with implications from the education GWAS (Okbay et al., 2016). Significant genes were more strongly enriched for expression in fetal brain tissue than adult tissue; results were also enriched for genes implicated in early neurodevelopmental disorders; and neurogenesis was the most strongly enriched GO biological process. At the same time, it is important to emphasize that adult neural tissues were also strongly represented in the results, and multiple synaptic components were significant in the pathway analysis. In this context, it is noteworthy that many cellular processes necessary for early neurodevelopment are also involved in adult synaptic plasticity. This duality is represented by several significant genes emerging from our analysis: *CELSR3* encodes an atypical cadherin plasma membrane protein involved in long-

range axon guidance in neurodevelopment through planar cell polarity signaling (Chai et al., 2015), but is also necessary for adult formation of hippocampal glutamatergic synapses (Thakar et al., 2017). Similarly *SEMA3F* is a negative regulator of dendritic spine development in adult hippocampus (Tran et al., 2009), but embryonically serves as an endogenous chemorepellent, guiding septohippocampal fibers away from non-limbic regions of developing cortex (Pascual et al., 2005).

While synaptic mechanisms were strongly implicated by our results, it is noteworthy that there was no statistical evidence for enrichment of genes expressed in oligodendrocytes or astrocytes. While developmental disorders primarily affecting oligodendrocytes, such as metachromatic leukodystrophy, are marked by cognitive impairment (Faust et al. 2010), it is possible that individual variation in cognitive ability within the normal range is less directly under genetic control via white matter mechanisms. By contrast, strong evidence was provided for the involvement of genes expressed in the cerebellum. Converging evidence from functional imaging studies, lesion studies, structural connectivity, and evolutionary considerations strongly implicate a role for cerebellum in higher cognitive functions (Buckner, 2013), possibly through the mechanism of prediction and error-based learning (Sokolov et al. 2017).

By utilizing TWAS methodology, we were able to isolate expression effects of specific genes within some of our broad GWAS loci. For example, *ACTR1A*, which lies near the GWAS peak at chromosome 10q24, encodes a microtubular dynactin protein involved in retrograde axon transport (Moughamian et al., 2013); other genes at this locus were not significant in the TWAS analysis (although a role in cognition cannot be ruled out, given the limited sample size in the reference brain expression datasets in GTEx). However, most of the genes implicated by TWAS were clustered in a few “hot” genomic loci, which may represent topologically associated domains (TADs) under the control of a shared 3-dimensional chromatin structure (Gonzalez-Sandoval and Gasser, 2016). Whether effects on cognition are driven by all differentially expressed genes within such loci, or if specific effects can be disentangled through experimental means, remains to be determined.

The overlap of 23 genes from our results with known genes for Mendelian disorders characterized by intellectual disability has several implications. First, this statistically significant enrichment provides partial validation of our MTAG results. Second, genes with known mutations of large effect, when combined with our data demonstrating SNPs with smaller regulatory effects on the same phenotype (cognition), can be considered an “allelic series” (Plenge et al., 2013) – a natural set of experiments powerfully demonstrating directional information (in the form of a dose-response curve) regarding gene function. Such information can be leveraged for the identification of novel drug targets. Third, converging evidence across the Mendelian and GWAS lists can aid interpretation of specific pathways and molecular processes that are necessary to normal neuronal function, and vice versa. For example, two genes on both the Mendelian and GWAS lists (*GMPPB* and *LARGE*) are associated with dystroglycanopathies with mental retardation. This information provides context for the observation that *DAG1*, which encodes dystroglycan 1, is the strongest TWAS result in the hippocampus. *DAG1* is necessary for GABAergic signaling in hippocampal interneurons (Früh et al., 2016). While dystroglycanopathies are most

prominently characterized by muscular dystrophy and retinal abnormalities, it is possible that all of these genes play a role in hippocampal synapse formation that is relevant to normal cognitive ability.

As noted above, one of the most important aims of GWAS studies is the identification of novel drug targets, and it has been suggested that targets with supporting GWAS evidence may be twice as successful in clinical development compared to those without such evidence (Nelson et al. 2015). Our drug set enrichment analysis pointed to several potential nootropic mechanisms. Most notably, the strongest signal was for cinnarizine, a T-type calcium channel inhibitor typically prescribed for seasickness. In the present study, we discovered an association of cognition to *CACNA1I*, which encodes one component of the voltage-dependent T-Type Cav3.3 channel, and has been previously associated with schizophrenia (PGC2-SCZ, 2014). While cinnarizine has strong antihistamine activity and may be inappropriate for general cognitive enhancement, a novel agent targeting Cav3.3 has shown nootropic activity in preclinical models (Moriguchi et al., 2012). In addition to gene set results suggesting a potential role for calcium and potassium channel regulation, single-gene results also point towards a potential role for the metabotropic glutamate receptor encoded by *GRM3*. This gene is also implicated in schizophrenia (PGC-SCZ, 2014), and drugs targeting *GRM3* have been suggested as a potential treatment (Lencz & Malhotra, 2015) however, a large-scale trial of one such agent was unsuccessful in treating psychotic symptoms (Downing et al. 2014). Based on the present results, future studies may seek to examine a role for such compounds in cognitive remediation. It is also noteworthy that the present study identified genome-wide significant evidence implicating three phosphodiesterase genes: *PDE1C*, *PDE2A*, and *PDE4D*. In particular, there is growing interest in PDE2A inhibitors as potential agents for cognitive enhancement (Trabanco et al. 2016), and evidence suggests that these agents may enhance synaptic plasticity via presynaptic modulation of cAMP hydrolysis (Fernández-Fernández et al. 2015). PDE4D inhibition is also under investigation as a potential therapy for neurodegenerative disease (Ricciarelli et al. 2017).

It is important to emphasize that uncovering genetic variation underlying general cognitive ability in the healthy population does not have deterministic implications. As has been previously explicated in similar studies (e.g., Trampush et al. 2015), effect sizes for each allele are extremely small ($R^2 < 0.1\%$ for even the strongest effects), and the combined effects genome-wide predict only a small proportion of the total variance in hold-out samples (Figure 3). Thus, results of the present study do not hold the potential for individual prediction or classification. Nevertheless, the results may still have substantial impact on our understanding of molecular mechanisms underlying cognitive ability.

Experimental Procedures

Subject Details

The cohorts included in the current study were described in detail in two prior reports on cognitive performance (Sniekers et al., 2017; Trampush et al., 2017) and one prior report on educational attainment (Okbay et al., 2016). Sample sizes for these three studies were $N=78,308$, $N=35,298$, and $N = 328,917$, respectively. For the present study, two cohorts

reported in Trampush et al., 2017 were excluded, so that cohorts included will be independent from those reported in Sniekers et al., 2017: i) Minnesota Center for Twin and Family Research (MCTFR) and ii) Lothian Birth Cohort 1936 Study. As a result, sample sizes decreased from the originally reported $N = 35,298$ to $N = 28,899$. All phenotypes included were as reported originally in the respective publications. All subjects provided written, informed consent to procedures that were approved by local review boards for the institutions at which each cohort was collected. Further details are available in the supplementary materials to those three publications.

GWAS Quality Control

Markers reported in the prior COGENT study (Trampush et al., 2017) were updated to build 37 coordinates, but were originally imputed against the HRC reference panel (McCarthy et al., 2016) via the Sanger imputation server. To ensure that markers, allele frequencies, and alleles were aligned to the 1000 genomes phase 3 reference panel (The 1000 Genomes Project Consortium, 2015), the COGENT summary statistics (Trampush et al., 2017) were checked using the EasyQC pipeline (Winkler et al., 2014) which allows summary statistics to be aligned and checked against a reference panel of choice. We used the default 1000 genomes phase 3 reference panel (The 1000 Genomes Project Consortium, 2015), provided along with the EasyQC package. Markers were inspected for allele frequency outliers, presence of duplicated markers, and allele mismatches with the 1000 genomes reference panel. Quality control filters for $INFO < .6$ and $N < 10000$ were additionally implemented. After EasyQC quality control, 8,040,131 SNPs were available for analysis. Only 87 SNPs were excluded due to allele mismatches, 13,276 SNPs were excluded due to allele frequency mismatches from the 1000 genomes phase 3 reference panel, 283,163 were found to be duplicates and excluded, 104 SNPs were found on the HRC reference panel, but not on the 1000 genomes phase 3 reference panel, and 2,723,493 SNPs had sample sizes less 10000 individuals. None of the SNPs failed the $INFO < .6$ cutoff. The same set of SNPs was utilized for subsequent reduced sample meta-analysis without the overlapping LBC1936 and MCTFR cohorts in Trampush et al., 2017. As the other prior studies of cognitive performance (Sniekers et al., 2017) and education (Okbay et al., 2016) were imputed to the 1000 genomes phase 3 reference panel, summary statistics were used as provided (URL: https://ctg.cncr.nl/software/summary_statistics; <https://www.thessgac.org/data>).

GWAS Meta-Analysis

Fixed-effect meta-analysis was conducted between Sniekers et al., 2017 and independent cohorts reported in Trampush et al., 2017 using the METAL package (Willer et al., 2010). To ensure that results of the meta-analysis were contributed by both studies, markers present only in Sniekers et al., 2017 or Trampush et al., 2017 but not in both were excluded for further analysis. The number of available markers after QC filtering was 7,357,080. Because the GWAS of Sniekers et al. (2017) utilized the sample-size weighted method to perform meta-analysis across its own cohorts, and did not report variance terms, our meta-analysis was conducted using the sample-size weighted method.

Multi-Trait Analysis for GWAS (MTAG)

To further enrich genetic signals, we employed a newly developed methodology that integrates LD-score regression and meta-analysis techniques across related traits: MTAG (Turley et al., 2017). MTAG (v0.9.0) was applied to the METAL results described immediately above, combined with summary statistics from the recent, large-scale education GWAS (Okbay et al., 2016). MTAG analysis allows the boosting of genetic signals across related traits, and has been found to be effective in resolving unknown sample overlaps, generating trait-specific effect estimates weighted by bivariate genetic correlation. The MTAG QC pipeline aligned all alleles across both sets of summary statistics, and ensured that SNPs were present across all datasets. SNPs that were not present in either dataset were removed. The final SNP count for MTAG was 7,333,576. The MTAG methodology proceeds by i) estimating the variance-covariance matrix of the GWAS estimation error, by using a series of LD score regressions, of which, under the known properties of LD score regression captures relevant sources of estimation error, incorporating population stratification, unknown sample overlap and cryptic relatedness ii) estimating the variance-covariance of SNP effects using the maximum likelihood procedure reported in (Turley et al., 2017) and iii) computes the MTAG estimator for each SNP and each trait. Summary statistics consisting of SNP, CHR, BP, per SNP sample size, BETA and SE for each trait were entered to the MTAG python command line. The resulting effect estimates and p-values are interpreted in the same as single-trait GWAS, which allows standard downstream follow-up analysis on the summary statistics. The python code for MTAG is available at <https://github.com/omeed-maghzian/mtag>.

Functional Mapping and Annotation for GWAS

GWAS summary statistics from the METAL meta-analysis and MTAG analysis were separately entered into the Functional Mapping and Annotation (FUMA) pipeline (Watanabe et al., 2017). The FUMA pipeline enables fast prioritization of genomic variants and genes, and permits interactive visualization of genomic results with respect to state-of-art bioinformatics resources. Manhattan and QQ plots are produced, and MAGMA gene-based analysis is performed, accounting for gene size and LD structure³². FUMA was also utilized to perform competitive gene-set analyses for GO cell compartment and biological process categories using the Molecular Signature Database (MsigDB 5.2). A separate competitive gene-set analysis was also conducted for the drug-based pathways previously described by Gaspar & Breen (2017). The pipeline also generates aggregated statistics for independent loci, lead SNPs, tagged genes, and supplementary plots – including SNP and locus annotations. Default clumping parameters are GWAS p-value < 5E-08; r^2 threshold to define LD structure of independent SNPs > 0.1; maximum P-value cutoff < 0.05; population for clumping = EUR; minor allele frequency filter > 0.01; maximum distance between LD blocks to merge into a single locus: 250kb. Follow-up queries were then made for independent loci of the cognitive performance meta-analysis as well as the MTAG results and compared against summary statistics for the prior cognitive and education GWAS. For purposes of comparison, loci in which the lead SNPs were within 500kb of each other were considered overlapping.

We compared the list of genes resulting from the MTAG analysis (including all genes within GWS SNP loci, as well as GWS genes identified with MAGMA) with a list of 621 genes known to cause autosomal dominant or autosomal recessive Mendelian disorders featuring intellectual disability; this list is primarily derived from a recent comprehensive review (Vissers et al., 2016), supplemented by a subsequent large-scale study of consanguineous multiplex families (Harripaul et al., 2017). A total of 193 autosomal dominant genes were identified, and a total of 413 autosomal recessive genes were identified. Fifteen genes were annotated as causing both autosomal dominant and autosomal recessive disorders with intellectual disability. Statistical significance was determined by probabilities derived according to the hypergeometric distribution. For this purpose, the total pool of autosomal genes was set to 19,011 (per Gencode).

Polygenic Risk Prediction for Independent Datasets

To validate that the genetic architecture elucidated via the MTAG methodology, we attempted to predict the phenotypic variance of general cognitive function in two of the independent COGENT cohorts (ASPIS and GCAP). MTAG analysis was conducted as above, but removing the COGENT cohorts. Polygenic score prediction across multiple thresholds of P_T was conducted using PRSice (Euesden et al., 2015). To compare the effectiveness of MTAG, we also conducted polygenic risk prediction using IQ only and Education only summary statistics. Finally, R^2 across SNP thresholds are compared to obtain the degree of improvement in terms of the ratio of MTAG PRS R^2 values versus those of IQ or Education PRS R^2 .

Stratified LD regression: Cell type Expression and Epigenomics

Functional characterization of GWAS summary statistics was carried out via stratified LD regression to investigate if heritability of cognitive performance is enriched in specific tissue or cell types. Summary statistics were first subjected to baseline partitioned heritability and thereafter passed through a cell type-specific functional characterization pipeline (Finucane et al., 2017). Cell type characterization includes the DEPICT tissue expression database, GTEx tissue expression, IMMGEN immune cell types, CAHOY brain level cell types, and the ROADMAP cell epigenomic marks.

Transcriptome Wide Analysis and Brain Expression lookups

Transcriptome wide analysis was carried out via MetaXcan (Barbeira et al., 2016), which allows for GTEx brain expression data to be integrated with GWAS summary statistics. MetaXcan computes downstream phenotypic associations of genetic regulation of molecular traits, using elastic, adjustment for model uncertainty and colocalization of GWAS and eQTL signals (Barbeira et al., 2016). GTEx Version 6, brain tissue expression profiles/sample sizes include the Anterior Cingulate Cortex (N=72); Caudate – Basal Ganglia (N=100); Cerebellar Hemisphere (N=89); Cerebellum (N=103); Cortex (N=96); Frontal Cortex (N=92); Hippocampus (N=81); Hypothalamus (N=81); Nucleus Accumbens (N=93); and Putamen (N=82).

Bayesian Fine-mapping Analysis and functional annotations

To identify potential causal variants in each of the independent loci, CAVIAR-BF is implemented to a region ± 50 KB of a lead SNP identified in the MTAG analysis. We followed similar procedures setting prior effect distribution σ_a to 0.1 in the model, which was recommended for GWAS studies (Chen et al., 2015; <https://bitbucket.org/Wenan/caviarbf>). The prior probability of being causal for each SNP is set to $1/m$, where m is the number of SNPs. Bayes factor was calculated for three model sets for independent loci, which modelled for 1, 2, and up to 3 causal SNPs within each independent regions. After which a model search algorithm searches and identifies the putative causal SNPs. These SNPs were then annotated using the Ensembl Variant Effect Predictor (McLaren et al., 2016). The analysis was repeated for extended regions taking into account the length of the independent loci identified by earlier FUMA procedures modelling for either 1 or 2 causal SNPs. SNPs identified by the two stage CAVIARBF analysis were then examined for potential gene expression in the BrainEAC (Ramasamy et al., 2014) and CommonMind (Hauberg et al., 2017) databases. BrainEAC top SNP lookups were for the following tissue expression: aveALL: All area combined; CRBL: cerebellum; FCTX: frontal cortex; HIPP: Hippocampus; MEDU: medulla; OCTX: occipital cortex; PUTM: putamen; SNIG: substantia nigra; TCTX: temporal cortex; THAL: thalamus; and WHMT: white matter across $N=134$ individuals. Finally, the prefrontal cortex lookup was included as part of the CommonMind consortium brain expression profile in $n=467$ genetically-inferred Caucasian samples.

Linkage Disequilibrium Score Regression

LD score regression allows genetic correlations to be computed across traits (Bulik-Sullivan et al., 2015a, 2015b), which allows further insights to be drawn from understanding the degree to which genetic architecture are shared across traits. To further examine potential traits that overlap with the cognitive architecture from the cognition meta-analysis results and MTAG results, LD score regression was conducted via the LD-hub pipeline, a centralized trait database (Zheng et al. 2017). LD-score regression was carried out across 89 traits in 15 broad phenotypic categories: 1) aging, 2) anthropometric, 3) autoimmune, 4) brain volume, 5) cardiometabolic, 6) education, 7) glycemic, 8) lipids, 9) lung function, 10) neurological, 11) personality, 12) psychiatric, 13) reproductive behavior, 14) sleep, and 15) smoking behavior. Very recent reported GWAS summary statistics for attention deficit hyperactivity disorder (ADHD, Demontis et al., 2017) and intracranial volume (ICV, Adams et al., 2016) were included as additional phenotypes. For comparison, we also present LD-score regression results for the educational attainment GWAS of Okbay et al. (2016); it should be noted that only 14 phenotypes were examined for genetic correlation in that publication. It should be noted that the MHC region was redacted from all datasets prior to LD score regression analysis, as per standard protocol at LD-Hub.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1a

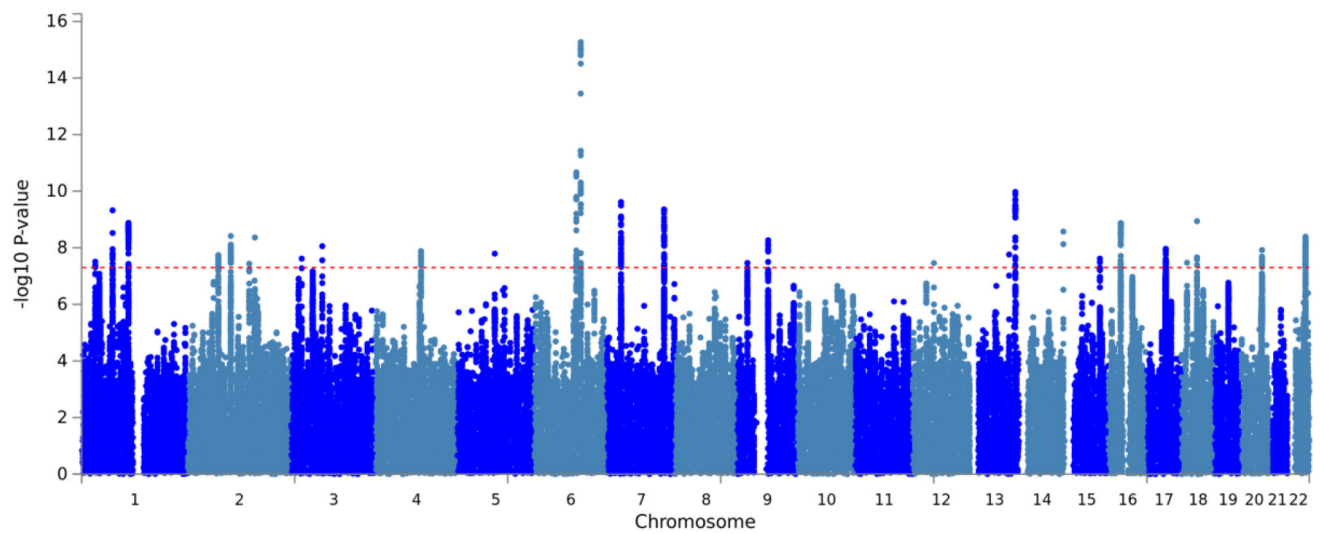
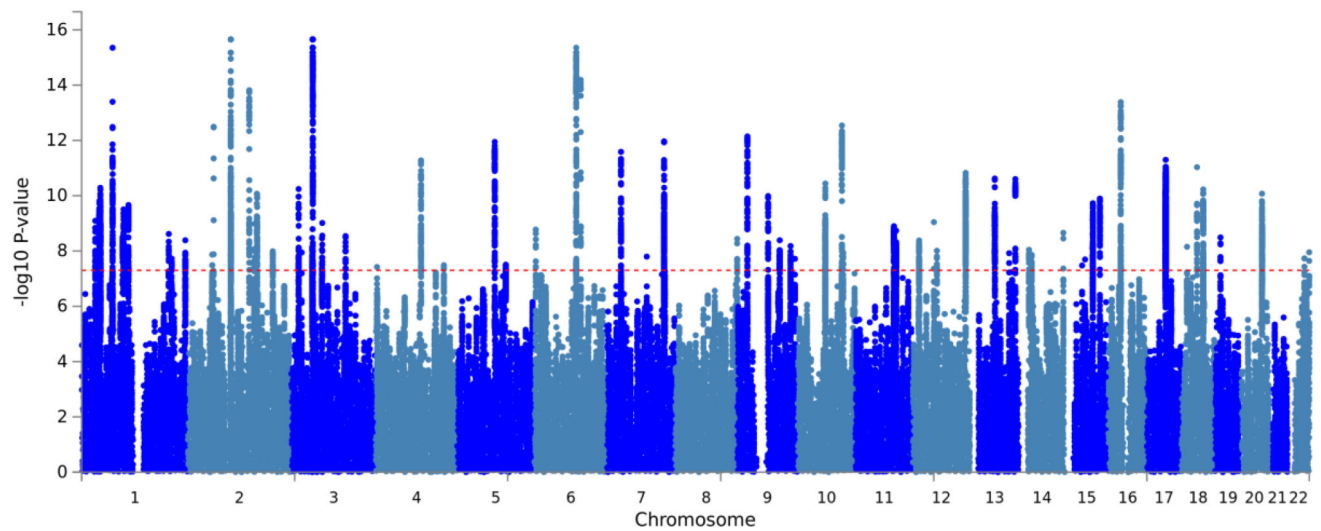


Figure 1b

**Figure 1.**

a) Manhattan plot depicting results of GWAS meta-analysis of cognitive performance. Dotted red line indicates threshold for genome-wide significance ($P < 5 \times 10^{-8}$). b) Manhattan plot depicting results of MTAG of cognitive performance with educational attainment. Dotted red line indicates threshold for genome-wide significance ($P < 5 \times 10^{-8}$).

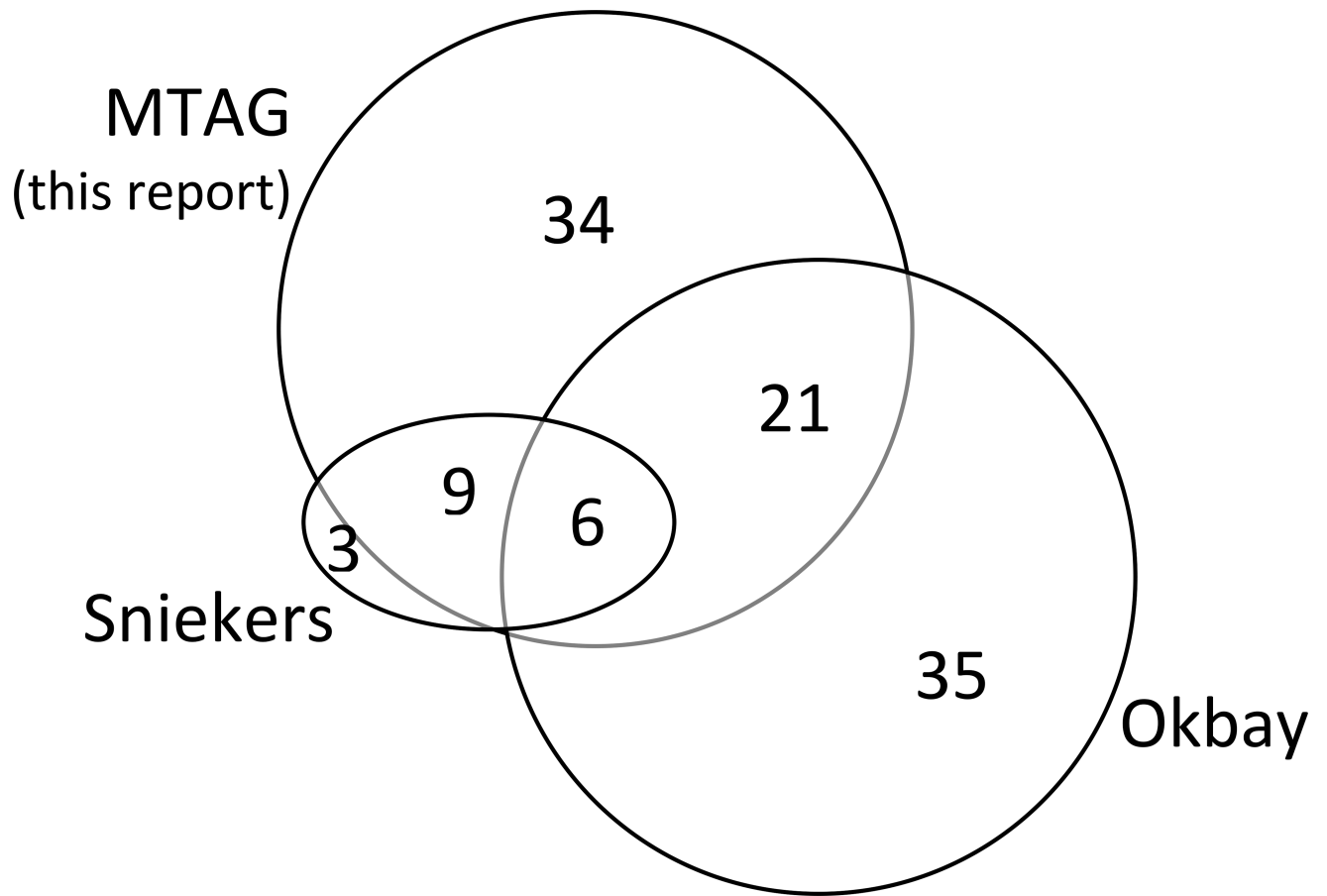


Figure 2.

Venn diagram depicting overlap and independence of genome-wide significant SNP loci observed in three studies: the MTAG analysis of the present report; the cognitive performance GWAS reported by Sniekers et al. (2017); and the educational attainment GWAS of Okbay et al. (2016).

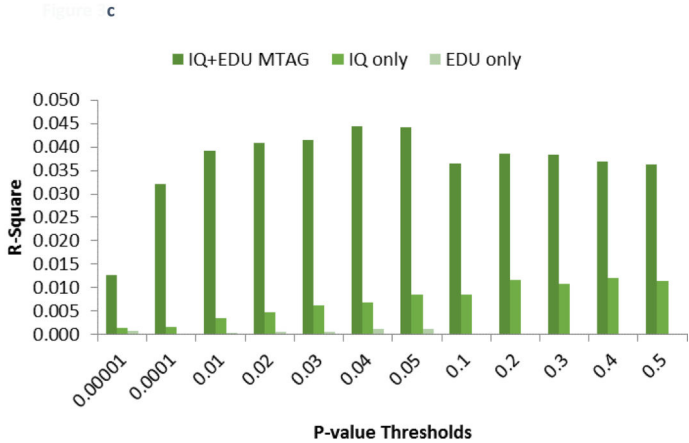
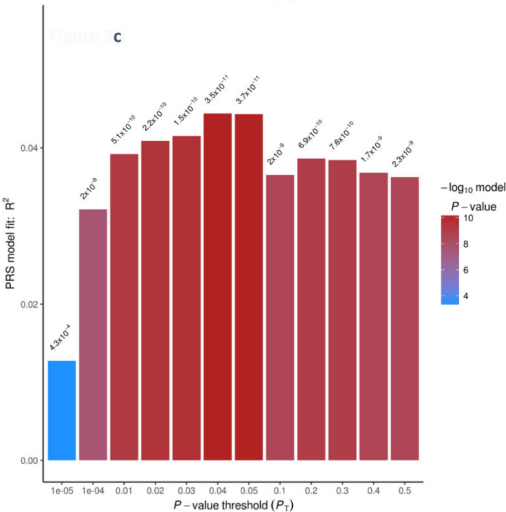
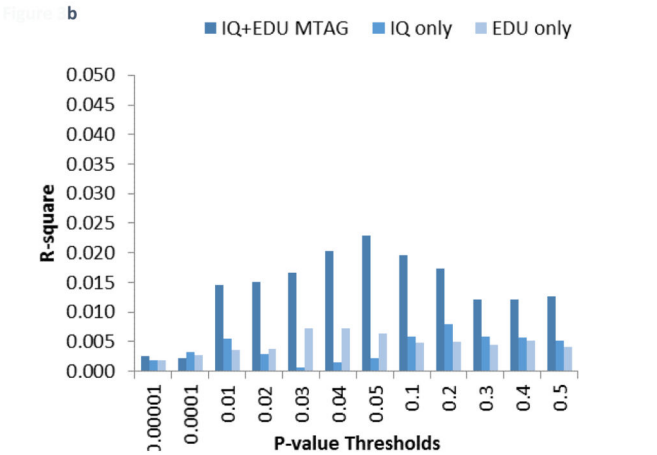
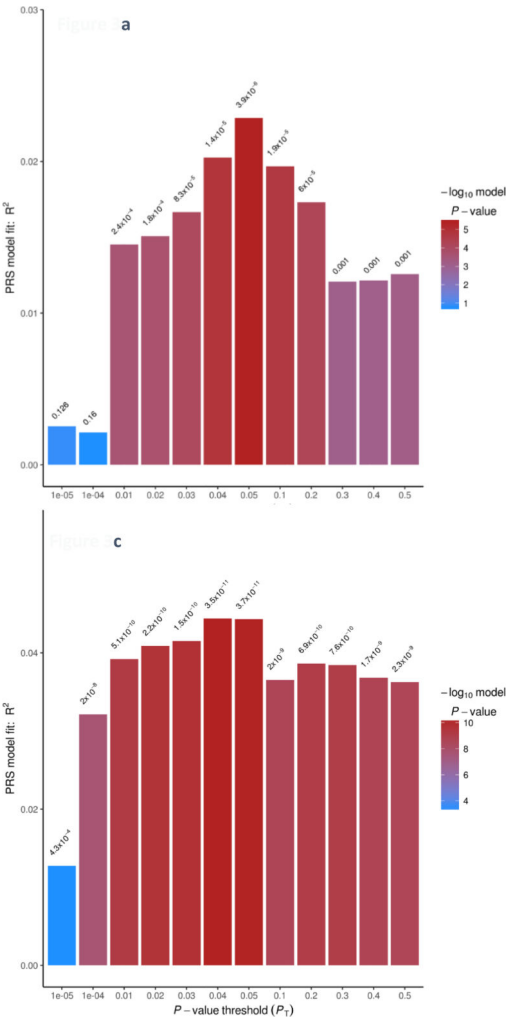


Figure 3.
a) Polygenic risk score prediction for MTAG results against held-out ASPIS cohort. b) Comparison of MTAG, cognitive (IQ) GWAS (Sniekers et al. 2017), and educational attainment (EDU) GWAS (Okbay et al. 2016) as source of weights for polygenic risk score prediction against held-out ASPIS cohort. c) Polygenic risk score prediction for MTAG results against held-out GCAP cohort. d) Comparison of MTAG, cognitive (IQ) GWAS (Sniekers et al. 2017), and educational attainment (EDU) GWAS (Okbay et al. 2016) as source of weights for polygenic risk score prediction against held-out GCAP cohort.

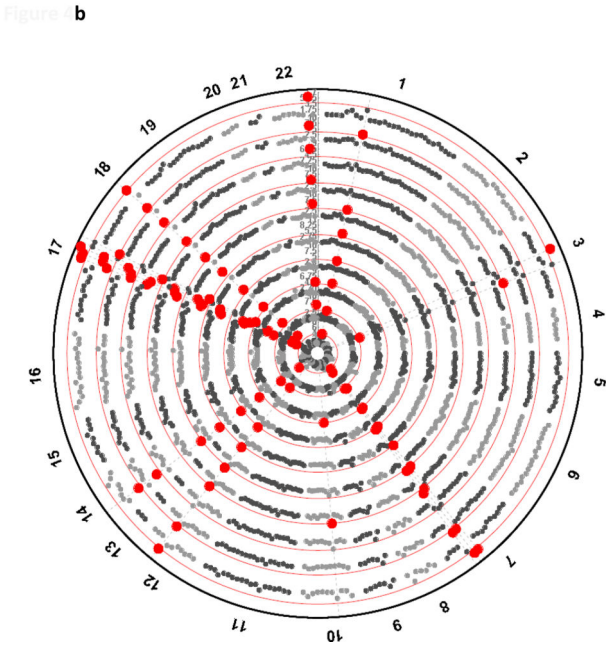
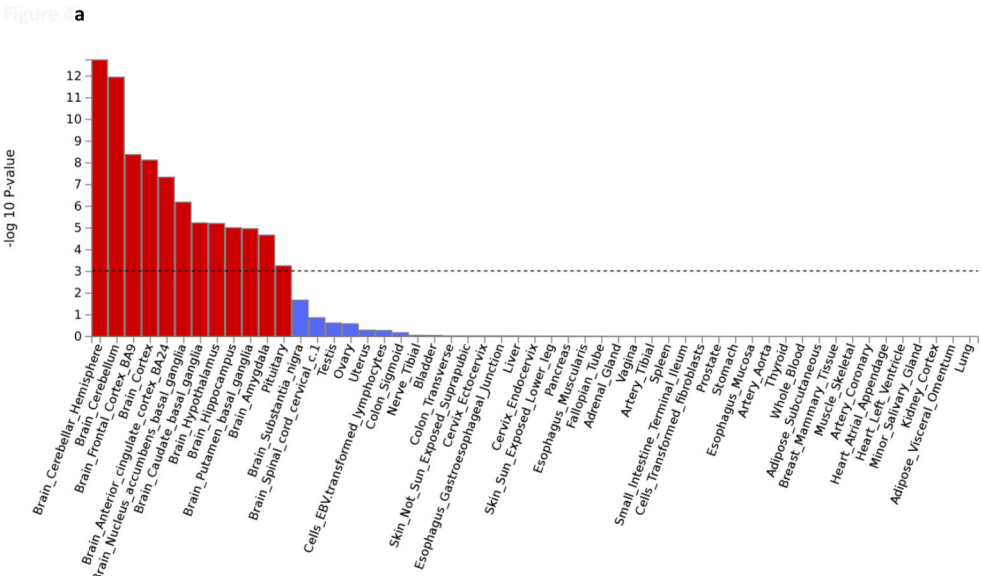


Figure 4.
a) Tissue expression profile analysis for genome-wide significant genes (as defined by MAGMA) emerging from the MTAG analysis. Gene results were significantly enriched for expression in nearly all central nervous system tissues (except for substantia nigra and spinal cord), but no tissues outside the CNS. b) Circular Manhattan Plot for MetaXcan results based on MTAG of cognitive performance with educational attainment. From inner circle out, GTEx tissue order is as follows: ACC: Anterior Cingulate Cortex; CDBG: Caudate – Basal Ganglia; CRBHM: Cerebellar Hemisphere; CRBLM: Cerebellum; CRTX: Cortex;

FCTX: Frontal Cortex; HIPP: Hippocampus; HYPO: Hypothalamus; NACMB: Nucleus Accumbens; PUTM: Putamen. GWAS threshold is set at Bonferroni-corrected $P < 0.05$.

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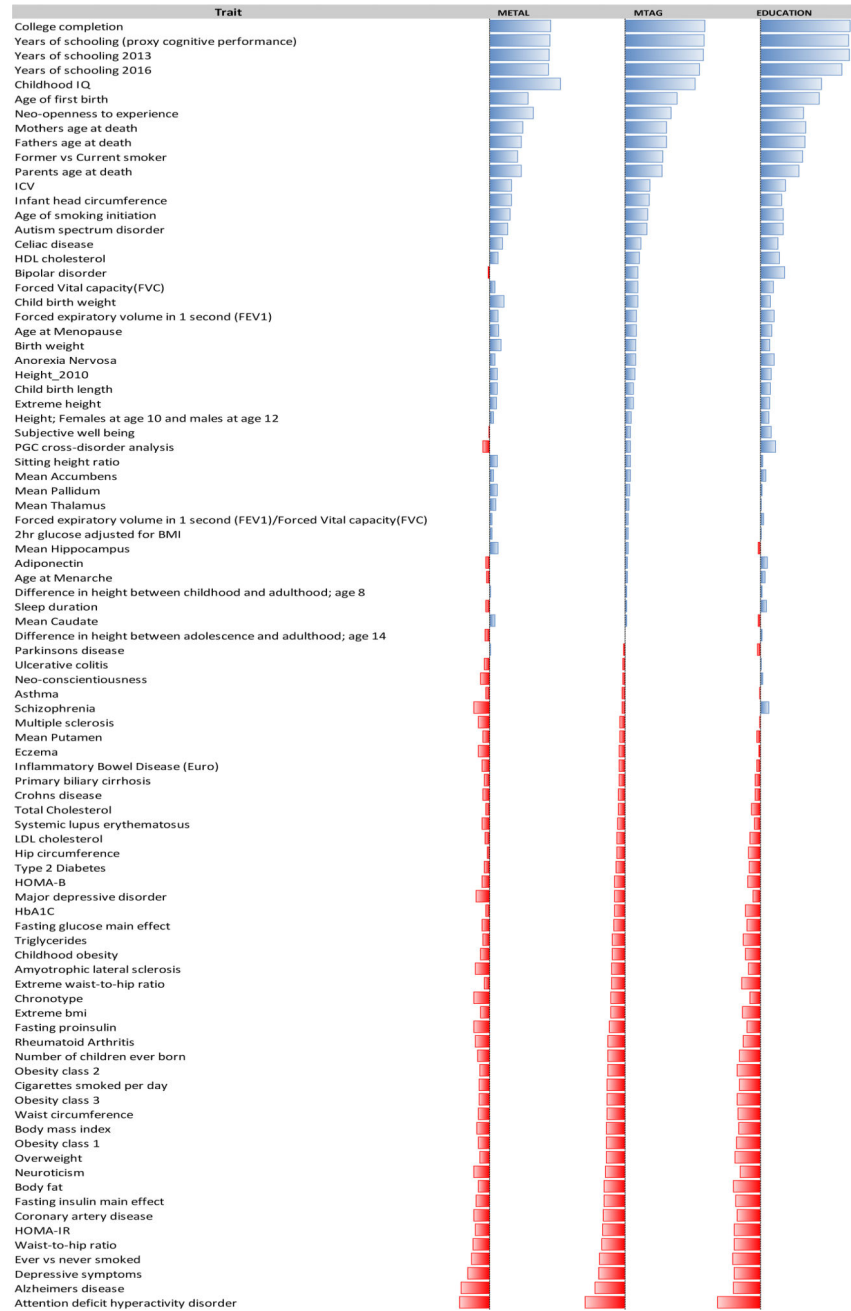


Figure 5. Genetic correlations (r_g) between cognitive phenotypes and other publicly available GWAS results, based on LD score regression. The first and second columns (labelled METAL and MTAG, respectively) refer to results of the cognitive meta-analyses in the present report. The third column displays correlations for the educational attainment GWAS of Okbay et al. (2016).

Table 1

GENE	CHR	START	MAGMA P	Min MTAG P	OMIM	Mode	Phenotype
AFF3	2	100152323	6.53E-12	6.8834E-15	NA	AR	Nonsyndromal intellectual disability
AMT	3	49444211	1.74E-09	8.5543E-09	605899	AR	Glycine encephalopathy
ARFGF2	20	47528427	7.28E-10	4.1558E-10	608097	AR	Periventricular heterotopia with microcephaly
BCL11A	2	60668302	8.5E-12	3.2174E-13	617101	AD	Intellectual developmental disorder with persistence of fetal hemoglobin
C12orf65	12	123707463	1.48E-10	1.8088E-11	613559	AR	Combined oxidative phosphorylation deficiency 7
					615035	AR	Spastic paraplegia 55
CLN3	16	28467983	2.31E-08	1.9502E-08	204200	AR	Ceroid lipofuscinosis, neuronal 3
DPYD	1	97533299	0.005108	4.4603E-08	274270	AR	Dihydropyrimidine dehydrogenase deficiency
					274270	AR	5-fluorouracil toxicity
ERCC8	5	60159658	2.96E-07	5.5002E-7	216400	AR	Cockayne syndrome, Type A
					614621	AR	UV-sensitive syndrome 2
FOXP1	3	70993844	6.32E-07	3.5007E-09	613670	AD	Mental retardation with language impairment and autistic features
GMPPB	3	49744277	1.75E-14	6.6613E-16	613530	AR	Muscular dystrophy-dystroglycanopathy (congenital w/ brain, eye anomalies), type A, 14
					615351	AR	Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 14
					615352	AR	Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 14
KANSL1	17	44097282	1.62E-08	5.0278E-12	610443	AD	Koolen-De Vries syndrome
KCNHI	1	210846555	1.04E-06	5.2513E-08	135500	AD	Zimmermann-Laband syndrome
KMT2D	12	49402758	1.69E-07	4.3422E-08	147920	AD	Kabuki syndrome, 1
LARGE	22	33548212	7.99E-07	5.4265E-07	613154	AR	Muscular dystrophy-dystroglycanopathy (congenital w/ brain, eye anomalies), type A, 6
MEF2C	5	88003975	1.74E-13	1.1304E-12	608840	AR	Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 6
					613443	AD	Mental retardation, stereotypic movements, epilepsy, and/or cerebral malformations
NFIX	19	13096422	2.45E-06	5.3017E-09	613443	AD	Chromosome 5q14.3 deletion syndrome
					602535	AD	Marshall-Smith syndrome
					614753	AD	Sotos syndrome
PDE4D	5	58254865	9.13E-08	3.6537E-07	614613	AD	Acrodysostosis 2 with or without hormone resistance
SHANK3	22	51102843	2.7E-10	8.0006E-08	606232	AD	Phelan-McDermid syndrome
ST3GAL3	1	44161495	3.58E-13	1.6388E-10	611090	AR	Mental retardation, autosomal recessive 12
SUOX	12	56380964	3.07E-05	4.1129E-08	272300	AR	Sulfite oxidase deficiency
TCF4	18	52879562	1.02E-06	3.5713E-05	610954	AD	Pitt-Hopkins syndrome
THRB	3	24148651	0.000682	4.6883E-06	188570	AD	Thyroid hormone resistance

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GENE	CHR	START	MAGMA P	Min MTAG P	OMIM	Mode	Phenotype
UBA7	3	49832640	2.11E-13	6.6613E-16	274300	AR	Thyroid hormone resistance, autosomal recessive
					NA	AR	Nonsyndromal intellectual disability

AD=Autosomal Dominant; AR=Autosomal Recessive

Table 2

GO Category name	NGENES	BETA	BETA_STD	SE	P	Phon
<i>GO_cc:go_neuron_part</i>	1204	0.155	0.0385	0.0304	1.84E-07	0.002008
<i>GO_cc:go_neuron_projection</i>	898	0.179	0.0388	0.0352	1.84E-07	0.002009
<i>GO_bp:go_neurogenesis</i>	1355	0.148	0.0388	0.0291	1.92E-07	0.002092
<i>GO_cc:go_synapse</i>	718	0.198	0.0386	0.0393	2.25E-07	0.002455
<i>GO_cc:go_synapse_part</i>	580	0.21	0.0369	0.0436	7.37E-07	0.008026
<i>GO_cc:go_dendrite</i>	430	0.229	0.0348	0.0501	2.49E-06	0.027087
<i>GO_bp:go_regulation_of_synapse_organization</i>	106	0.447	0.034	0.0987	2.94E-06	0.031982
<i>GO_bp:go_regulation_of_synapse_structure_or_activity</i>	223	0.291	0.032	0.0671	7.36E-06	0.080154
<i>GO_bp:go_regulation_of_nervous_system_development</i>	723	0.166	0.0325	0.0385	7.84E-06	0.085334
<i>GO_bp:go_modulation_of_synaptic_transmission</i>	291	0.253	0.0317	0.059	9.41E-06	0.102429
<i>GO_bp:go_calcium_dependent_cell_cell_adhesion_via_plasma_membrane_cell_adhesion_molecules</i>	26	1.06	0.0402	0.259	2.06E-05	0.224726
<i>GO_cc:go_postsynapse</i>	356	0.224	0.031	0.0553	2.64E-05	0.287583
<i>GO_cc:go_neuron_spine</i>	116	0.379	0.0302	0.0939	2.75E-05	0.299998
<i>GO_cc:go_cell_projection</i>	1710	0.103	0.0301	0.0258	3.36E-05	0.365381
<i>GO_bp:go_regulation_of_cell_development</i>	808	0.144	0.0297	0.0365	3.99E-05	0.434751
Drug name	NGENES	BETA	BETA_STD	SE	P	Phon
<i>CINNARIZINE</i>	9	1.62	0.036	0.355	2.61E-06	0.007071
<i>LY97241</i>	2	3.65	0.0382	0.842	7.59E-06	0.020535
<i>CELECOXIB</i>	45	0.632	0.0314	0.159	3.49E-05	0.094545
<i>ISRADIPINE</i>	8	1.59	0.0334	0.404	4.18E-05	0.11317
<i>NITRENDIPINE</i>	12	1.19	0.0305	0.323	1.19E-04	0.323151
<i>ABT-639;ML218;TTA-A2;Z944</i>	3	2.31	0.0297	0.641	1.59E-04	0.429388
<i>NEUREGULIN-1;NEUREGULIN-2</i>	2	2.39	0.0251	0.669	1.75E-04	0.473469
<i>FLUNARIZINE</i>	6	1.58	0.0287	0.457	2.67E-04	0.723503
<i>GLUCOCORTICOIDS</i>	2	3.68	0.0386	1.08	3.22E-04	0.872117