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

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Abstract

Neurocognitive ability is a fundamental readout of brain function, and cognitive deficits are a critical component of neuropsychiatric disorders, yet neurocognition is poorly understood at the molecular level. In the present report, we present the largest genome-wide association studies (GWAS) of cognitive ability to date (N=107,207), and further enhance signal by combining results with a large-scale GWAS of educational attainment. We identified 70 independent genomic loci associated with cognitive ability, 34 of which were novel. A total of 350 genes were implicated, and this list showed significant enrichment for genes associated with Mendelian disorders with an intellectual disability phenotype. Competitive pathway analysis of gene results implicated the biological process of neurogenesis, 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 analysis revealed that the implicated genes were strongly expressed in neurons, but not astrocytes or oligodendrocytes, and were more strongly associated with fetal brain expression than adult brain expression. Several tissue-specific gene expression relationships to cognitive ability were observed (for example, *DAG1* levels in the hippocampus). Finally, we report novel genetic correlations between cognitive ability and disparate phenotypes such as maternal age at first birth and number of children, as well as several autoimmune disorders.

Introduction

Genome-wide association studies (GWAS) have been highly successful at uncovering hundreds of genetic loci associated with heritable quantitative traits such as height[1] and weight[2] (body mass index). However, identifying genetic loci underlying cognitive ability has been much more challenging, despite comparably high levels of heritability as determined by both classical twin studies[3] and molecular genetic studies[4]. 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[5-8] and genetically[9-11] correlated with cognition, as well as numerous non-psychiatric health-relevant phenotypes[12] that also are significantly genetically correlated with cognitive function.

In part, the difficulty with cognitive GWAS may be caused by the relative degree of 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[13]. Using this approach, several cognitive GWAS with fewer than 20,000 subjects yielded no genome-wide significant (GWS) effects[4,9,14], while a few GWS loci were identified in large GWAS of 35,298[15] subjects and 53,949[16] subjects, respectively. Notably, these efforts involved meta-analysis across cohorts using different sets of cognitive tests to derive the principal component score, which may have reduced power. By contrast, two independent GWAS of height with sample sizes of approximately 30,000 subjects each yielded 20-30 GWS hits[17,18]; allelic effect sizes were ~2-5 times larger than the largest obtained in cognitive GWAS[19].

Given the small effect sizes observed in cognitive GWAS, it has become evident that greatly increased sample sizes will be required to ascend the GWAS yield curve. Very recently, a cognitive GWAS[20] was able to leverage a very brief (two-minute) 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 more traditional cognitive GWAS.

Yet another approach to enhancing power in cognitive GWAS has focused on educational attainment as a proxy phenotype[21]. It is acknowledged that this phenotype is 'noisy,' as it is influenced by non-cognitive genetic[22] (e.g., personality) and environmental[23] (e.g., socio-economic) factors; consequently, observed allelic effect sizes have been even smaller than those obtained for GWAS of *g*[24]. 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[25]. Notably, the genetic correlation between educational attainment and psychometric *g* is very high, consistently reported in the range of .70-.75[15,16,20,25,26].

Thus, cognitive GWAS can be further enhanced by combining information from these large studies of educational attainment with studies of test-based cognitive performance. A new technique called multi-trait analysis of GWAS (MTAG)[27] 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. Notably, the developers of MTAG demonstrated its accuracy and utility in a study of traits that also demonstrate genetic correlations in the range of ~.70-.75 (depression, neuroticism, and subjective well-being). 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 GWAS[15] of psychometrically defined *g* with the recently reported GWAS[20] relying primarily on the brief measure, resulting in a combined cohort of N=107,207 non-overlapping samples. Next, we utilized MTAG to combine these results with the large-scale GWAS of educational attainment, resulting in 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

Fixed Effect Meta-Analysis: Cognitive Performance GWAS

Fixed effect 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 FUMA[28] pipeline (Figure 1a); this represents a 55.6% increase in loci compared to the previous GWAS[20] of cognitive performance. Two of these loci each contained two uncorrelated variants with independent effects, resulting in 30 independent lead SNPs. As demonstrated in the QQ plot (Supplementary Figure 1), statistical inflation was quite modest for a large study of a highly polygenic trait (λ=1.23; λ_{1000}=1.001; LD score intercept=1.03), and overall SNP heritability was .168. Of the 28 GWS loci, 12 are novel and not previously reported as GWS in published studies of cognitive or educational phenotypes (Supplementary Table 2). The majority of the 5,610 markers reaching a nominal significance threshold were intronic SNPs followed by those in the intergenic regions (Supplementary Table 3 and Supplementary Figure 2). As shown in Supplementary Table 4, 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 5), about half of which were in three large regions (Supplementary Figure 3), including two well-characterized regions: the distal 16p11.2 region, in which deletions have been associated with schizophrenia and other neuropsychiatric phenotypes[29], and the 17q21 region, in which inversions have been associated with neuropsychiatric disorders[30,31]. Using MAGMA[32] gene-based tests, 73 genes were genome-wide significant (Supplementary Figure 4; Supplementary Table 6), of which 39 were overlapping with the 88 genes noted above, resulting in a total of 122 genes with GWS 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 education attainment GWAS previously reported[25], 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 (Table 1). 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 QQ plot (Supplementary Figure 5), demonstrated polygenicity without substantial statistical inflation (λ=1.28; λ_{1000}=1.001; LD score intercept=0.91), and overall SNP heritability was 0.336. Of the 70 GWS loci, 34 are novel and not previously reported as GWS in published studies of cognitive or educational phenotypes (Figure 2; Supplementary Table 7). The majority of the 13,549 SNPs reaching a nominal significance threshold were intergenic or intronic (Supplementary Table 8; Supplementary Figures 6 & 7). As is typically the case in GWAS, few significant SNPs were exonic; GWS variants causing protein-coding changes rated as damaging by either Polyphen or SIFT are listed in Supplementary Table 9. Variants in only four genes demonstrated converging evidence for being damaging to protein structure: three at chromosome 17q21.31 (*KANSL1*, *MAPT*, and *SPPL2C*), as well as one at chromosome 3p21.31 (*MST1*). GWAS catalog annotations are listed in Supplementary Table 10.

Within the GWS loci, 267 protein coding genes were identified (Supplementary Table 11). Additionally, 257 genes were significant in MAGMA gene-based tests (Supplementary Figure 8; Supplementary Table 12); of these, 83 genes were non-overlapping with the 267 genes with SNP GWS loci, resulting in a total of 350 genes receiving GWS support from the MTAG results. We compared this list of 350 genes with a list of 621 genes known to cause autosomal dominant or autosomal recessive Mendelian disorders featuring intellectual disability[33,34]. As shown in Table 2, a total of 23 genes identified by MTAG appeared on this list, representing a 2-fold enrichment over chance (p=0.001).

As a formal validation that the MTAG methodology successfully predicts phenotype variance for cognitive performance, MTAG was re-analyzed, excluding the ASPIS and GCAP datasets from the COGENT cohorts; these 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 (Supplementary Figures 9 and 10), 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.

Gene Expression 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 3). 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 process of neurogenesis (Table 3a). Competitive pathway analysis for drug pathways[35] revealed that two drugs were significantly associated with the MTAG results (Table 3b): 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.

Stratified LD score regression[36] also demonstrated an enrichment of cell type expression for neuronal tissues only. Notably, genes found in the neuronal expression list of Cahoy[37] 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 13 for further details). No enrichment was observed in any non-neuronal tissue.

Transcriptomic Wide Analysis and Brain Expression Lookups

We performed transcriptome-wide analysis (TWAS, using MetaXcan[38] with GTEx reference data) on MTAG-derived SNP summary statistics in order to determine whether up- or down-regulation of specific

transcripts in specific neural compartments were associated with cognition. (TWAS follows a similar logic to imputation, in that an external reference (in this case, GTEx) is utilized to link available SNP data to tissue-based, gene expression levels.) Several strong transcriptomic associations were specific to individual brain regions such as hippocampus, cortex, or cerebellum. 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 significantly associated in analyses of other neural tissue types. Similarly, lower levels of *ACTR1A* are associated with cognition, but only in frontal cortex. However, as shown in Supplementary Table 14, most of the strongest TWAS results are tissue non-specific, involving genes such as *AMIGO3, RNF123,* and *RBM6* (Supplementary Figure 11); and a QQ plot revealed that no individual tissue compartment was much more strongly enriched than the others (Supplementary Figure 12). Lookups of GWS SNPs from the MTAG analysis in two brain eQTL databases (BrainEAC[39] and CommonMind[40]) revealed several additional SNP-eQTL relationships that can explain variance in the cognitive phenotype (Supplementary Tables 15 and 16); 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* (Bonferroni-corrected p= 3.78E-31 averaged across all neural tissues for expression probe 3779863). 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.

Genetic Correlations with Other Phenotypes

LD-score regression was carried out across 98 traits in 15 broad phenotypic categories in LD-hub[41]: 1) aging, 2) anthropometric, 3) autoimmune, 4) brain volume, 5) cardiometabolic, 6) education, 7) gycemic, 8) lipids, 9) lung function, 10) neurological, 11) personality, 12) psychiatric, 13) reproductive behavior, 14) sleeping, and 15) smoking behavior. Cognition appeared to be strongly associated with aging, education, personality, neuropsychiatric disorders, reproductive behavior, and smoking behavior. Strong association with parental age at death was observed for both the GWAS 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). While many of these correlations have been reported previously[12,15,20,25], two novel results were observed in the present study. First, we report a strong positive genetic correlation between cognitive variables 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 = -0.2159; 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 age at first birth=0.7207, p=2.24E-244; r_g for number of children= -0.2623, p=3.34E-18). 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 results, there were notable divergences in correlations with psychiatric phenotypes, especially schizophrenia and bipolar disorder.

Discussion

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 novel approach to allow further 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, nearly half of which were novel, and ultimately implicated 350 genes underlying cognitive ability. In total, we found that common SNPs were able to account for nearly half of the overall heritability of the phenotype as determined by prior family studies[42].

Downstream analysis confirmed an important role for neurodevelopmental processes in cognitive ability, consistent with implications from the GWAS of educational attainment[25]. 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[43], but is also necessary for adult formation of hippocampal glutamatergic synapses[44]. Similarly, *SEMA3F* is a negative regulator of dendritic spine development in adult hippocampus[45], but embryonically serves as an endogenous chemorepellent, guiding septohippocampal fibers away from non-limbic regions of developing cortex[46].

To our knowledge, this is the first study of cognition to employ TWAS methodology, which was developed with the hope of isolating expression effects of specific genes within broad GWAS loci. In the present study, a few such genes were isolated, such as *ACTR1A*. This gene, which lies near the GWAS peak at chromosome 10q24, encodes a microtubular dynactin protein involved in retrograde axon transport[47]; 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[48,49]. 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 novel data demonstrating SNPs with smaller regulatory effects on the same phenotype (cognition), can be considered an "allelic series"[50] – 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[50,51]. 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 the drug set enrichment analysis pointed to 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 a novel 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[52]. 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. The present study provides supportive evidence for this approach.

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, 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 (~2%-4%) of the total variance in hold-out samples (Supplementary Figures 9 and 10). Thus, results of the present study do not hold the potential for individual prediction or classification. Nevertheless, results enhance our understanding of molecular mechanisms underlying cognitive ability, illuminating relationships to other health-relevant traits, and pointing towards specific transcriptomic effects and biological pathways that may form the basis of future cognitive enhancement approaches.

Methods

GWAS Quality Control

Markers reported in the prior COGENT study[15] were updated to build 37 coordinates, but imputed against the HRC reference panel[53] via the Sanger imputation server. To ensure that markers, allele frequencies, and alleles are aligned to the 1000 genomes phase 3 reference panel[54], the COGENT summary statistics[15] were checked using the EasyQC pipeline[55] which allows summary statistics to be aligned and checked against a reference panel of choice. As both fluid intelligence[20] and education[25] summary statistics 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). Further quality control was provided as part of the Multi-trait Analysis for GWAS (MTAG[27]) pipeline. Alleles were aligned against the first dataset, and only SNPs present across datasets were included in the final analysis. The MTAG quality control pipeline is an adaptation of the '*munge_sumstats'* function found in LD score regression[39].

Fixed Effect Meta-Analysis

Fixed-effect meta-analysis was carried out via METAL[56]. First, fixed-effect meta-analysis was conducted for independent samples reported in the prior COGENT paper[15] that were not included in the GWAS of fluid intelligence[20]. These cohorts are reported in Supplementary Table 1. The initial meta-analysis resulted in total N = 28,799. Subsequently, further meta-analysis was conducted to combine independent samples from COGENT[15] and fluid intelligence[20] resulting in the combined sample size of N = 107,207 for the cognitive performance meta-analysis. Because the fluid intelligence GWAS 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 genetic regression and meta-analysis techniques across related traits: MTAG[27]. MTAG was applied to the GWAS results applied immediately above, combined with summary statistics from the recent, large-scale educational attainment GWAS[25]. MTAG analysis allows the boosting of genetic signals across related traits, and had been found to be effective in resolving unknown sample overlaps, and generates trait-specific effect estimates weighted by bivariate genetic correlation. The resulting effect estimates and p-values are interpreted in the same manner as single-trait GWAS, which allows standard downstream follow-up analysis on the summary statistics.

Functional Mapping and Annotation for GWAS

GWAS summary statistics from the METAL meta-analysis and MTAG analysis were entered to the Functional Mapping and Annotation (FUMA) pipeline[28]. The FUMA pipeline enables fast prioritization of

genomic variants, genes, and interactive visualization of genomic results with respective 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 structure[32]. Competitive gene set analysis using the Molecular Signature Database (MsigDB 5.2), and brain expression databases from GTEX and BrainEAC were also carried in MAGMA as part of the FUMA pipeline. The pipeline also generates aggregated statistics for independent loci, lead SNP, tagged genes, and supplementary plots – including SNP and Loci annotations. Default clumping parameters are GWAS p-value < 5E-08; r2 threshold to define LD structure of lead SNPs > 0.6; 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 locus < 250kb.

Follow-up queries were then made for top independent loci of the cognitive performance meta-analysis as well as the MTAG results and compared against summary statistics for the prior cognitive[20] and education[25] 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[33], supplemented by a subsequent large-scale study of consanguineous multiplex families[34].

FUMA was also utilized to perform competitive gene-set analyses for GO cell compartment and biological process categories. A separate competitive gene-set analysis was also conducted for the drug-based pathways previously described by Gaspar & Breen[35].

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 holding out these two cohorts. All polygenic score prediction was conducted using PRSice[57].

Stratified LD regression: Cell type Expression and Epigenomics

Functional characterization of GWAS summary statistics were carried out via stratified LD regression to investigate if cognitive heritability is enriched in specific tissue or cell types. Summary statistics were first subjected to baseline partitioned heritability and thereafter passed through cell type functional characterization pipeline [42]. Cell type characterization includes the DEPICT tissue expression, 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

Downstream transcriptomic wide analysis and brain expression lookups of top SNPs were carried out to examine if specific genomic regions were exclusive associated with specific or multiple brain regions. Transcriptomic wide analysis is carried out via MetaXcan [43], which allows for GTEX brain expression mechanisms to be integrated with GWAS summary statistics. Top SNPs obtained from the MTAG GWAS were also subjected to data lookup in the Brain eQTL Almanac (BrainEAC [44]), as well as CommonMind [45] brain expression datasets. GTEX brain tissue expression profiles include the Anterior Cingulate Cortex; Caudate – Basal Ganglia; Cerebellar Hemisphere; Cerebellum; Cortex; Frontal Cortex; Hippocampus; Hypothalamus; Nucleus Accumbens; and Putamen. BrainEAC top SNP lookups were available for the following tissue expression compartments: CRBL: cerebellum; FCTX: frontal cortex; HIPP: Hippocampus; MEDU: medulla; OCTX: occipital cortex; PUTM: putamen; SNIG: substantia nigra; TCTX: temporal cortex; THAL: thalamus; WHMT: white matter; and aveALL: All areas combined. Only one region (the prefrontal cortex) was available for the CommonMind consortium brain expression profile lookup.

Linkage Disequilibrium Score Regression

LD score regression allows genetic correlations to be computed across traits[58] , 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 first conducted via the LD-hub pipeline, a centralized trait database[41]. Fifteen broad trait categories were investigated, including: 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, 14) Sleeping, and 15) Smoking behavior. Very recent results for ADHD[59] and intracranial volume[60] were included as additional phenotypes. The same procedures were also carried out for intelligence and education to investigate how the elucidated genetic architecture for the MTAG results differs from prior published works for education and intelligence. Additional LD score regression analysis was conducted between cognitive phenotypes, to examine the degree of genetic architecture overlap across related cognitive traits.

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Figure Captions

Figure 1. Manhattan plot depicting results of GWAS meta-analysis for cognitive performance (Figure 1a) and MTAG of cognitive performance with educational attainment. Dotted red line indicates threshold for genome-wide significance ($P<5x10^{-8}$).

Figure 2. Proportional 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.[20]; and the educational attainment GWAS of Okbay et al.[25].

Figure 3. 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.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Framingham Heart Study (FHS): phs000007.v23.p8 and phs000342.v11.p8

Multi-Site Collaborative Study for Genotype-Phenotype Associations in Alzheimer's Disease (GENADA): phs000219.v1.p1

Long Life Family Study (LLFS): phs000397.v1.p1

Genetics of Late Onset Alzheimer's Disease Study (LOAD): phs000168.v1.p1

Minnesota Center for Twin and Family Research (MCTFR): phs000620.v1.p1

Philadelphia Neurodevelopmental Cohort (PNC): phs000607.v1.p1

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Filippini N, Rao A, Wetten S, Gibson RA, Borrie M, Guzman D, Kertesz A, Loy-English I, Williams J, Nichols T, Whitcher B, Matthews PM. Anatomically-distinct genetic associations of APOE epsilon4 allele load with regional cortical atrophy in Alzheimer's disease. Neuroimage, Feb 1;44(3):724-8, 2009. (PMID: 19013250).

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Table 1

MTAG model output

Trait	N (max)	No. of SNPs	GWAS mean χ2	MTAG mean χ2	GWAS Equivalent N	MTAG Signal Boost
Cognition + Intelligence	107207	7333852	1.245	1.429	187812	75%
Education	328917	7333852	1.638	1.693	357156	8.6%

Table 2

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
ARFGEF2	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
KCNH1	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
					608840	AR	Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 6
MEF2C	5	88003975	1.74E-13	1.1304E-12	613443	AD	Mental retardation, stereotypic movements, epilepsy, and/or cerebral malformations
					613443	AD	Chromosome 5q14.3 deletion syndrome
NFIX	19	13096422	2.45E-06	5.3017E-09	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
					274300	AR	Thyroid hormone resistance, autosomal recessive
UBA7	3	49832640	2.11E-13	6.6613E-16	NA	AR	Nonsyndromal intellectual disability

Table 3

Table 3a

GO Category name	NGENES	BETA	BETA_STD	SE	P	Pbon
GO_cc:go_neuron_part	**1204**	**0.155**	**0.0385**	**0.0304**	**1.84E-07**	**0.002008**
GO_cc:go_neuron_projection	**898**	**0.179**	**0.0388**	**0.0352**	**1.84E-07**	**0.002009**
GO_bp:go_neurogenesis	**1355**	**0.148**	**0.0388**	**0.0291**	**1.92E-07**	**0.002092**
GO_cc:go_synapse	**718**	**0.198**	**0.0386**	**0.0393**	**2.25E-07**	**0.002455**
GO_cc:go_synapse_part	**580**	**0.21**	**0.0369**	**0.0436**	**7.37E-07**	**0.008026**
GO_cc:go_dendrite	**430**	**0.229**	**0.0348**	**0.0501**	**2.49E-06**	**0.027087**
GO_bp:go_regulation_of_synapse_organization	**106**	**0.447**	**0.034**	**0.0987**	**2.94E-06**	**0.031982**
GO_bp:go_regulation_of_synapse_structure_or_activity	223	0.291	0.032	0.0671	7.36E-06	0.080154
GO_bp:go_regulation_of_nervous_system_development	723	0.166	0.0325	0.0385	7.84E-06	0.085334
GO_bp:go_modulation_of_synaptic_transmission	291	0.253	0.0317	0.059	9.41E-06	0.102429
GO_bp:go_calcium_dependent_cell_cell_adhesion_via_plasma_membrane_cell_adhesion_molecules	26	1.06	0.0402	0.259	2.06E-05	0.224726
GO_cc:go_postsynapse	356	0.224	0.031	0.0553	2.64E-05	0.287583
GO_cc:go_neuron_spine	116	0.379	0.0302	0.0939	2.75E-05	0.299998
GO_cc:go_cell_projection	1710	0.103	0.0301	0.0258	3.36E-05	0.365381
GO_bp:go_regulation_of_cell_development	808	0.144	0.0297	0.0365	3.99E-05	0.434751

Table 3b

Drug name	NGENES	BETA	BETA_STD	SE	P	Pbon
CINNARIZINE	**9**	**1.62**	**0.036**	**0.355**	**2.61E-06**	**0.007071**
LY97241	**2**	**3.65**	**0.0382**	**0.842**	**7.59E-06**	**0.020535**
CELECOXIB	45	0.632	0.0314	0.159	3.49E-05	0.094545
ISRADIPINE	8	1.59	0.0334	0.404	4.18E-05	0.11317
NITRENDIPINE	12	1.19	0.0305	0.323	1.19E-04	0.323151
ABT-639;ML218;TTA-A2;Z944	3	2.31	0.0297	0.641	1.59E-04	0.429388
NEUREGULIN-1;NEUREGULIN-2	2	2.39	0.0251	0.669	1.75E-04	0.473469
FLUNARIZINE	6	1.58	0.0287	0.457	2.67E-04	0.723503
GLUCOCORTICOIDS	2	3.68	0.0386	1.08	3.22E-04	0.872117

Figure 1a

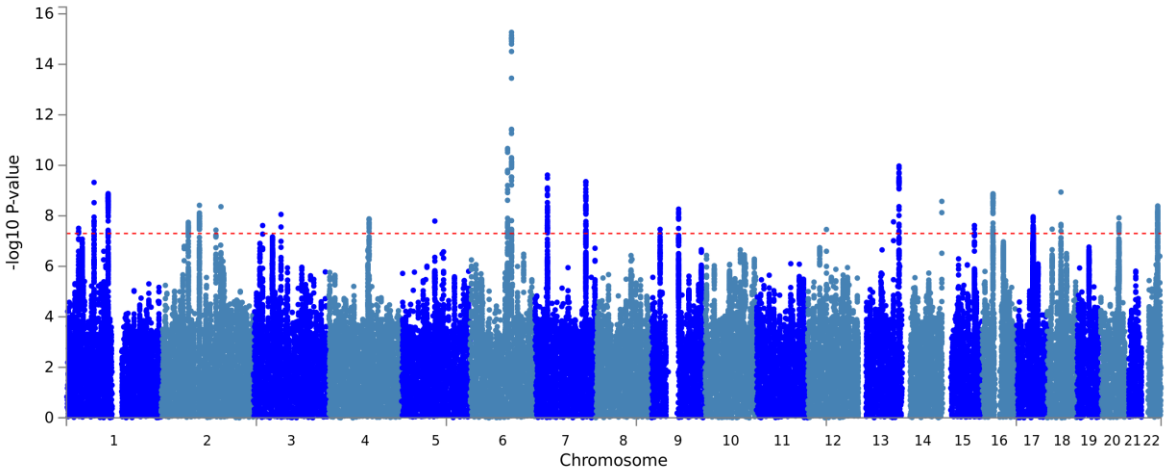

Figure 1b

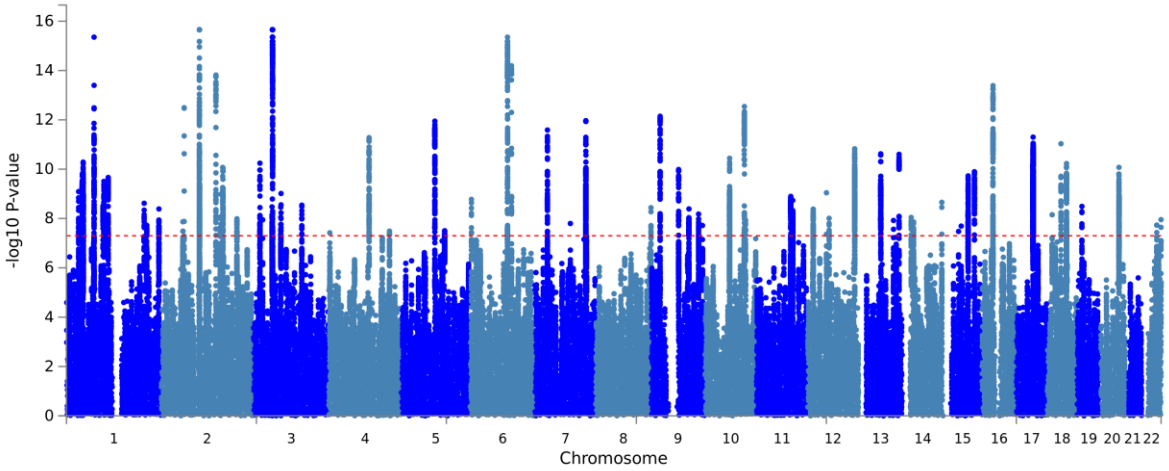

Figure 2

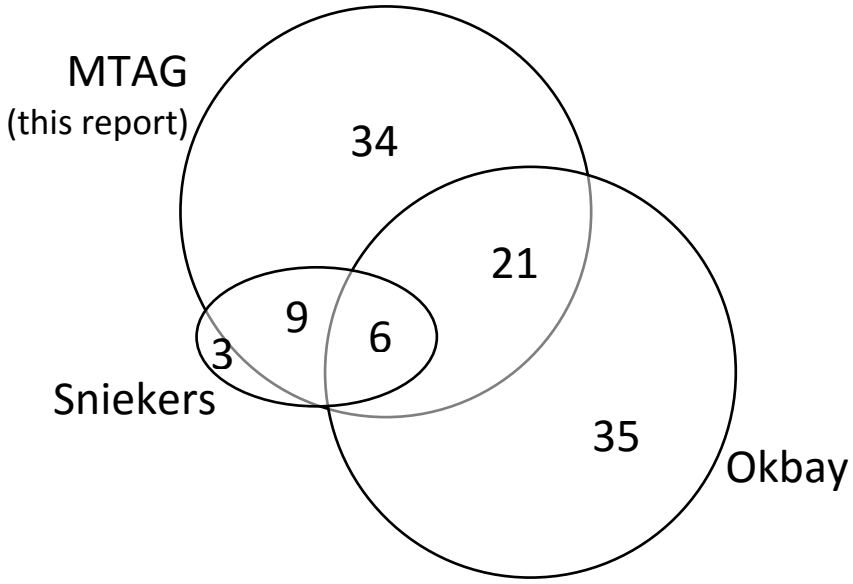

Figure 3