Supporting Information

Hart et al. 10.1073/pnas.1318810111

SI Materials and Methods

Enrichment Datasets. ***GAIN Schizophrenia.*** This GWAS (1) included 1,351 European-American cases with schizophrenia and 1,378 European-American controls. Subjects were genotyped on the Affymetrix 6.0 array. After quality control, 729,454 SNPs were available for analysis. Precomputed association results were obtained from dbGaP (phs000021.v3.p2). This sample is a subset of the PGC1 schizophrenia sample (below).

PGC1 Schizophrenia. This mega-analysis (2) included 9,394 European cases and 12,462 European controls. Imputation was performed with the HapMap3 reference panel (3). After quality control, 1,252,902 SNPs were available for analysis. Publicly available association results were obtained from https://pgc.unc.edu/Sharing.php.

PGC1 ADHD. This meta-analysis (4) included four separate ADHD studies, with the final dataset comprised of 2,064 trios, 896 cases, and 2,455 controls of European ancestry. Imputation was performed with the HapMap3 reference panel (3). After quality control, 1,206,462 SNPs were available for analysis. Publicly available association results were obtained from https://pgc.unc.edu/Sharing.php.

PGC1 Bipolar Disorder. This GWAS (5) included 7,481 European cases and 9,250 European controls. Imputation was performed with the HapMap2 reference panel (6). After quality control, 2,541,952 SNPs were available for analysis. Publicly available association results were obtained from https://pgc.unc.edu/Sharing.php.

Negative control phenotype: Genetic Investigation of Anthropometric Traits Height. This meta-analysis (7) included 133,653 European individuals. Imputation was performed with the HapMap2 reference panel (6). After quality control, 2,469,636 SNPs were available for analysis. Publicly available association results were obtained from www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files.

Negative control phenotype: International Inflammatory Bowel Disease Genetics Consortium Inflammatory Bowel Disease. This GWAS (8) included 12,882 European inflammatory bowel disease (Crohn disease and ulcerative colitis) cases and 21,770 European controls. Imputation was performed with the HapMap3 reference panel (3). After quality control, 1,252,901 SNPs were available for analysis. Publicly available association results were obtained from www.ibdgenetics.org/downloads.html. Available results were restricted to $P \leq 0.01$; thus, we could not examine enrichment at the $P \leq 0.05$ threshold.

Negative control phenotype: Parkinson Disease GWAS Consortium Parkinson Disease. Study details are provided in the work by Pankratz et al. (9). The meta-analysis consisted of 4,238 European Parkinson disease cases and 4,239 European controls. Imputation was performed with the HapMap2 reference panel (6). After quality control, 2,525,705 SNPs were available for analysis. Full association results were obtained from ref. 9.

Replication Datasets. ***Swedish Schizophrenia Study.*** This GWAS (10) included 5,001 schizophrenia cases and 6,243 controls from a population-based sampling frame in Sweden ($n = 11,244$). Samples were genotyped in six batches using Affymetrix 5.0 (3.9%), Affymetrix 6.0 (38.6%), and Illumina OmniExpress (57.4%) chips. After quality control and imputation with the 1000 Genomes Project Phase 1 reference panel, we analyzed association result from allelic dosages for 9,871,789 high-quality polymorphic SNPs.

PGC2 ADHD. This meta-analysis included data from a total of nine cohorts [Cardiff: 641 cases and 1,752 controls; Chinese: 1,012 cases and 930 controls; Germany: 494 cases and 1,297 controls; International Multicenter ADHD Genetics project phase 2 (IMAGE2): 787 cases and 7,082 controls; Spain: 591 cases and 432 controls; Children's Hospital of Philadelphia (CHOP): 358 trios; Canada: 170 trios; International Multicenter ADHD Genetics project phase 1 (IMAGE1): 866 trios; Pfizer-funded study from the University of California, Los Angeles, Washington University, and the Massachusetts General Hospital (PUWMA): 702 trios]. The IMAGE1, IMAGE2, PUWMA, and CHOP trios constituted the PGC1 set described in the work by Neale et al. (4). The Cardiff, Chinese, Germany, Spain, and Canada cohorts constituted the independent replication sample. Imputation was performed with the HapMap3 reference panel (3). After quality control, 1,384,810 SNPs were available for analysis.

1. Shi J, et al. (2009) Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature* 460(7256):753–757.
2. Ripke S, et al.; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium (2011) Genome-wide association study identifies five new schizophrenia loci. *Nat Genet* 43(10):969–976.
3. Altshuler DM, et al.; International HapMap 3 Consortium (2010) Integrating common and rare genetic variation in diverse human populations. *Nature* 467(7311):52–58.
4. Neale BM, et al.; IMAGE II Consortium Group (2010) Case-control genome-wide association study of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 49(9):906–920.
5. Sklar P, et al.; Psychiatric GWAS Consortium Bipolar Disorder Working Group (2011) Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet* 43(10):977–983.
6. Frazer KA, et al.; International HapMap Consortium (2007) A second generation human haplotype map of over 3.1 million SNPs. *Nature* 449(7164):851–861.
7. Lango Allen H, et al. (2010) Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* 467(7317):832–838.
8. Jostins L, et al.; International IBD Genetics Consortium (IIBDGC) (2012) Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 491(7422):119–124.
9. Pankratz N, et al.; PD GWAS Consortium (2012) Meta-analysis of Parkinson's disease: Identification of a novel locus, RIT2. *Ann Neurol* 71(3):370–384.
10. Franke A, et al. (2010) Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet* 42(12):1118–1125.

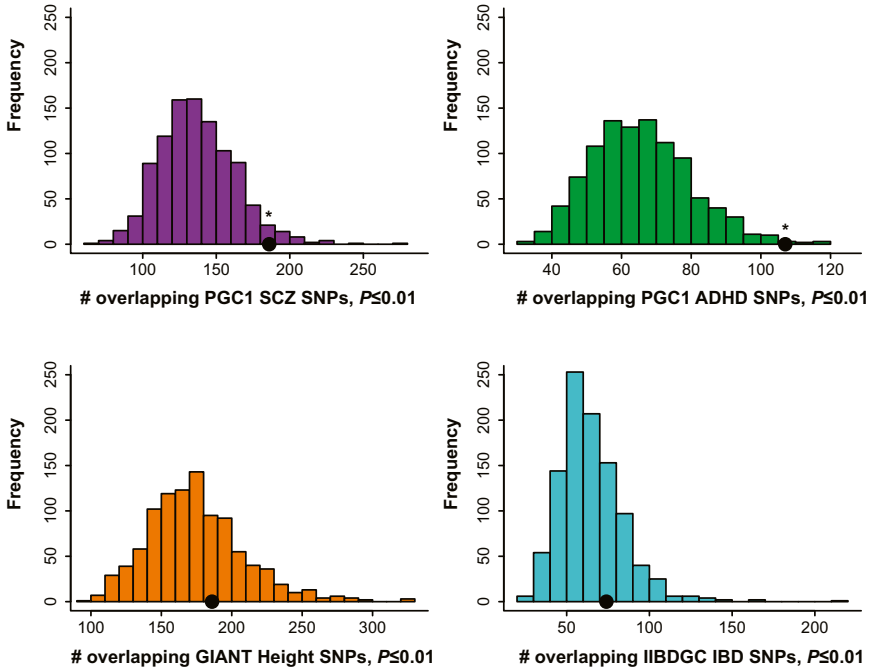

Fig. S1. Enrichment results for analyses limited to SNPs that were directly genotyped in the amphetamine response dataset. Significant enrichment is seen for schizophrenia- and attention deficit hyperactivity disorder (ADHD)-associated SNPs among amphetamine response associations computed with directly genotyped SNPs (nonimputed). The black dots represent the observed count of trait-associated SNPs among associations with *d*-amphetamine response. The histograms represent the number of SNPs that occurred among association results from 1,000 random permutations. GIANT, Genetic Investigation of Anthropometric Traits; IBD, inflammatory bowel disease; IIBDGC, International Inflammatory Bowel Disease Genetics Consortium; PGC1, Psychiatric Genomics Consortium phase 1; SCZ, schizophrenia. $*P < 0.05$.

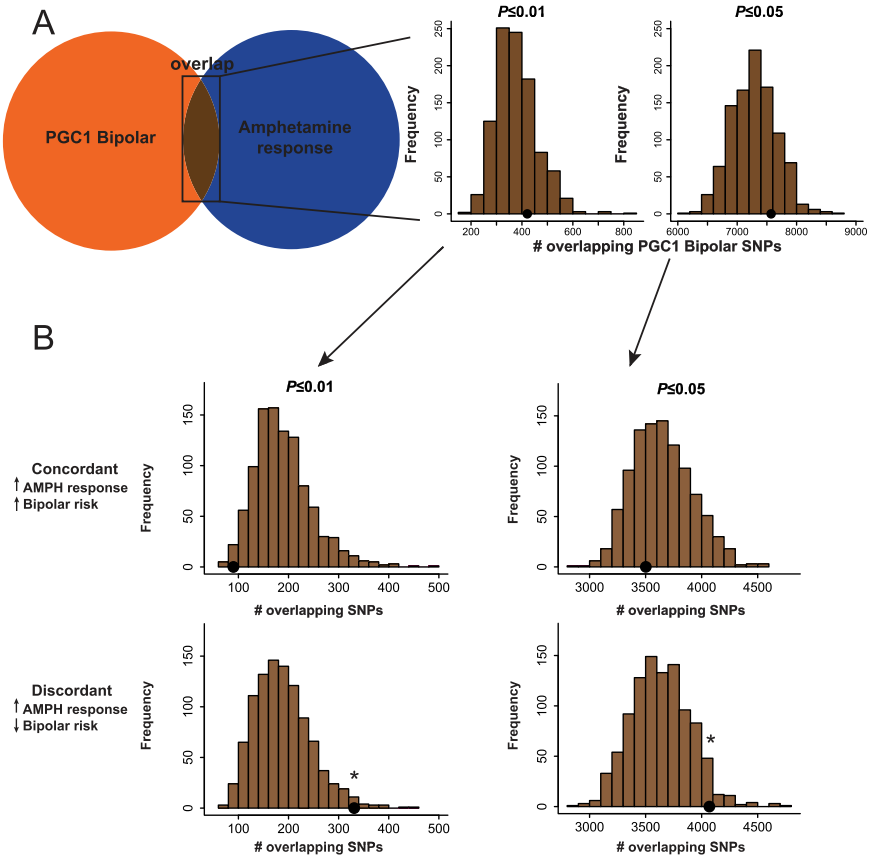

Fig. S2. SNPs associated with the euphoric response to *d*-amphetamine are enriched among SNPs associated with protection from bipolar disorder. *A* shows a schematic representation of the enrichment analysis. There was no significant enrichment of SNPs that were nominally associated with bipolar disorder from the PGC1 bipolar disorder sample among SNPs nominally associated with the euphoric response to *d*-amphetamine at either *P* value threshold. The black dots represent the observed number of overlapping SNPs. The histograms represent the null distribution of overlapping SNPs generated from 1,000 random permutations of the amphetamine data. *B* shows the same analysis as *A*, except that SNPs were only considered if they were concordant (*Upper*) or discordant (*Lower*) in direction. These results indicate an enrichment for discordant SNPs. AMPH, *d*-amphetamine; PGC1, Psychiatric Genomics Consortium phase 1. *$P < 0.05$.

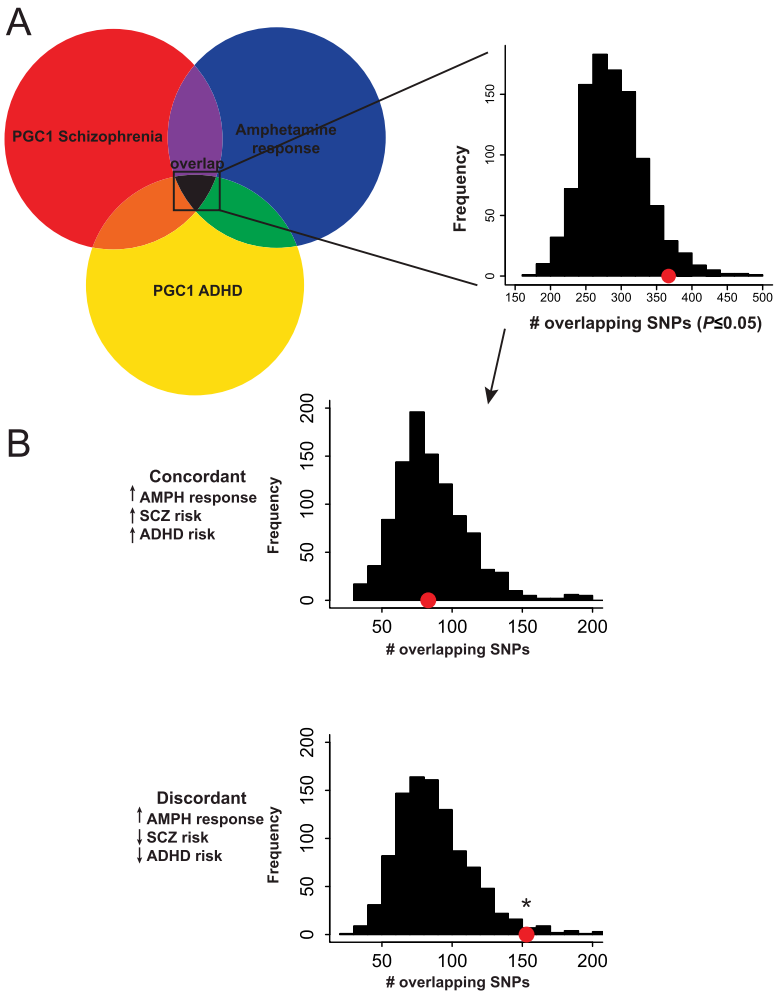

Fig. S3. SNPs associated with the euphoric response to amphetamine overlap with SNPs associated with decreased risk for schizophrenia and decreased risk for ADHD. We examined the SNPs that were overlapping between the three dopaminergic phenotypes: euphoric response to *d*-amphetamine, schizophrenia, and ADHD. *A* shows the results for the overall nominally significant enrichment for SNPs that overlap between the three phenotypes ($P = 0.062$). (*A* and *B*) The red dots represent the observed number of overlapping SNPs. The histograms represent the null distribution of overlapping SNPs generated from 1,000 random permutations of the amphetamine data. *B* shows the results for the concordant SNPs (SNPs associated with increased euphoria and increased schizophrenia and ADHD risk) and the discordant SNPs (SNPs associated with increased euphoria and decreased risk for schizophrenia and ADHD). We only observed enrichment for the discordant SNPs. AMPH, *d*-amphetamine; PGC1, Psychiatric Genomics Consortium phase 1; SCZ, schizophrenia. *$P < 0.05$.

Table S1. Description of enrichment samples

Sample	Ref.	Sample size	Other information
Genetics of Amphetamine	1	325	
Genetic Association Information Network Schizophrenia	2	1,351 cases; 1,378 controls	Subset of PGC1 Schizophrenia sample
PGC1 Schizophrenia	3	9,394 cases; 12,462 controls	
PGC1 ADHD	4	896 cases; 2,455 controls; 2,064 trios	
PGC1 Bipolar Disorder	5	7,481 cases; 9,250 controls	
Genetic Investigation of Anthropometric Traits Height	6	133,653	
IIBDGC Inflammatory Bowel Disease	7	12,882 cases; 21,770 controls	
Parkinson Disease GWAS Consortium Parkinson Disease	8	4,238 cases; 4,239 controls	
Swedish Schizophrenia	9	5,001 cases; 6,243 controls	Replication sample
PGC2 ADHD	—	2,738 cases; 4,411 controls; 170 trios	Replication sample

GWAS, genome-wide association study; IIBDGC, International Inflammatory Bowel Disease Genetics Consortium; PGC1, Psychiatric Genomics Consortium phase 1; PGC2, Psychiatric Genomics Consortium phase 2.

1. Hart AB, et al. (2012) Genome-wide association study of d-amphetamine response in healthy volunteers identifies putative associations, including cadherin 13 (CDH13). *PLoS ONE* 7(8):e42646.
2. Shi J, et al. (2009) Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature* 460(7256):753–757.
3. Ripke S, et al.; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium (2011) Genome-wide association study identifies five new schizophrenia loci. *Nat Genet* 43(10):969–976.
4. Neale BM, et al.; IMAGE II Consortium Group (2010) Case-control genome-wide association study of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 49(9): 906–920.
5. Sklar P, et al.; Psychiatric GWAS Consortium Bipolar Disorder Working Group (2011) Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet* 43(10):977–983.
6. Lango Allen H, et al. (2010) Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* 467(7317):832–838.
7. Jostins L, et al.; International IBD Genetics Consortium (IIBDGC) (2012) Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 491(7422):119–124.
8. Pankratz N, et al.; PD GWAS Consortium (2012) Meta-analysis of Parkinson's disease: Identification of a novel locus, RIT2. *Ann Neurol* 71(3):370–384.
9. Franke A, et al. (2010) Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet* 42(12):1118–1125.

Table S2. Numbers of SNPs available from each dataset for the enrichment analysis

	$P \leq 0.01$		$P \leq 0.05$	
Dataset	Total no. of SNPs	No. of SNPs available to overlap with GAP	Total no. of SNPs	No. of SNPs available to overlap with GAP
Genetic Association Information Network Schizophrenia	9,154	8,938	41,928	40,924
PGC1 Schizophrenia	29,687	26,824	101,642	92,673
Swedish Schizophrenia	20,704	18,431	82,614	74,890
PGC1 Schizophrenia + Swedish Schizophrenia meta-analysis	35,750	32,386	112,207	101,942
PGC1 ADHD	13,489	12,648	63,807	59,970
PGC2 ADHD	16,727	15,283	75,767	67,989
PGC1 ADHD + PGC2 ADHD meta-analysis	15,527	14,228	72,719	65,704
PGC1 Bipolar Disorder	43,729	40,415	168,699	155,924
Genetic Investigation of Anthropometric Traits Height	72,893	66,200	186,092	170,137
IIBDGC Inflammatory Bowel Disease	14,377	13,713	—	—
Parkinson Disease	27,200	23,939	128,484	115,096

Because of differences in which SNPs were genotyped and imputed between the amphetamine response dataset [Genetics of Amphetamine (GAP)] and the various datasets listed below, a slightly smaller number of SNPs was available for the enrichment analysis. IIBDGC, International Inflammatory Bowel Disease Genetics Consortium; PGC1, Psychiatric Genomics Consortium phase 1; PGC2, Psychiatric Genomics Consortium phase 2.