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Leveraging the Genetics of Psychiatric Disorders to Prioritize Potential Drug Targets and Compounds

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Summary

Background: Genetics has the potential to inform biologically relevant drug treatment and repurposing which may ultimately improve patient care. In this study, we combine methods which leverage the genetics of psychiatric disorders to prioritize potential drug targets and compounds.

Methods: We used the largest available genome-wide association studies, in European ancestry, of four psychiatric disorders [i.e., attention deficit hyperactivity disorder (ADHD), bipolar disorder, depression, and schizophrenia] along with genes encoding drug targets. With this data, we conducted drug enrichment analyses incorporating the novel and biologically specific GSA-MiXeR tool. We then conducted a series of molecular trait analyses using large-scale transcriptomic and proteomic datasets sampled from brain and blood tissue. This included the novel use of the UK Biobank proteomic data for a proteome-wide association study of psychiatric disorders. With the accumulated evidence, we prioritize potential drug targets and compounds for each disorder.

Findings: We reveal candidate drug targets shared across multiple disorders as well as disorder-specific targets. Drug prioritization indicated genetic support for several currently used psychotropic medications including the antipsychotic paliperidone as the top ranked drug for schizophrenia. We also observed genetic support for other commonly used psychotropics (e.g., clozapine, risperidone, duloxetine, lithium, and valproic acid). Opportunities for drug repurposing were revealed such as cholinergic drugs for ADHD, estrogens for depression, and gabapentin enacarbil for schizophrenia. Our findings also indicate the genetic liability to schizophrenia is associated with reduced brain and blood expression of *CYP2D6,* a gene encoding a metabolizer of drugs and neurotransmitters, suggesting a genetic risk for poor drug response and altered neurotransmission.

Interpretation: Here we present a series of complimentary and comprehensive analyses that highlight the utility of genetics for informing drug development and repurposing for psychiatric disorders. Our findings present novel opportunities for refining psychiatric treatment.

Introduction

Genetics can provide insights into the underlying mechanisms of a trait that can be leveraged to inform drug treatment. Drugs with supporting genetic evidence have a 2.6 times greater probability of success in development compared to drugs lacking genetic support.[1] Notably, drugs for psychiatric treatment tend to have targets with less supporting genetic evidence than drugs for respiratory, metabolic, and cardiovascular diseases.[1,2] This lack of genetically informed treatment may partly explain the poor therapeutic response, adverse drug effects, and poor treatment compliance observed in psychiatry.[1,3,4] Furthermore, complex traits, such as psychiatric disorders and other medical conditions, share associated genes to a varying degree, a concept known as pleiotropy.[5] This pleiotropy may facilitate the repurposing of drugs approved or previously investigated for different indications. Therefore, leveraging genetics to inform drug discover, target prioritization, and repurposing may help improve psychiatric treatment.

The genome-wide association study (GWAS) of various psychiatric disorders have previously been leveraged to prioritize drug targets and compounds. Some studies use GWAS to perform gene-set analyses testing for enrichment of genes encoding drug targets.[6–8] While this approach has provided genetic support for various drugs with psychiatric indications, standard tools may be biased towards drugs with many targets potentially providing less disorder specificity.[9] Moreover, disorder-associated genetic variants can modulate gene expression and protein abundance providing a link to molecular traits (i.e., genes and proteins) serving as potential drug targets.[10] Therefore, transcriptome or proteome wide association studies (i.e., TWAS or PWAS) have been used to prioritize molecular traits as potential drug targets for

several psychiatric disorders.[11,12] Moreover, Mendelian randomization (MR) is commonly used to identify causal relationships between molecular traits and psychiatric disorders.[13–16] Applying these analyses has revealed for example that calcium signalling is associated with multiple psychiatric disorders.[7,11,14] However, many studies tend to focus on one type of molecular trait or neglect bidirectional MR analyses. Also, while transcriptomic data provides greater coverage of the genome, drug targets are often proteins. Therefore, leveraging both types of molecular data is complementary and more comprehensive. Although studies leveraging multiple methodologies and types of molecular data to inform novel drug targets and indications exist,[17–21] few integrate enrichment and comprehensive molecular trait analyses with a focus on psychiatric disorders.

Here, we present an extensive genetic interrogation of potential drug targets and compounds for attention deficit hyperactivity disorder (ADHD), bipolar disorder (BIP), depression (DEP), schizophrenia (SCZ) and as a comparator diastolic blood pressure (DBP) (Figure 1). We conduct gene-set analysis incorporating the novel GSA-MiXeR tool which identifies enrichment for biologically specific and smaller gene-sets than common approaches.[9] We use large scale molecular trait data from brain and blood tissue to identify potential drug targets. Blood is more readily available than brain tissue, resulting in larger datasets, and provides complementary identification of potential drug targets. We apply a series of molecular trait analyses including the novel use of UK Biobank (UKB) data for PWAS of psychiatric disorders. Finally, we combine the results to prioritize potential drug targets and compounds.

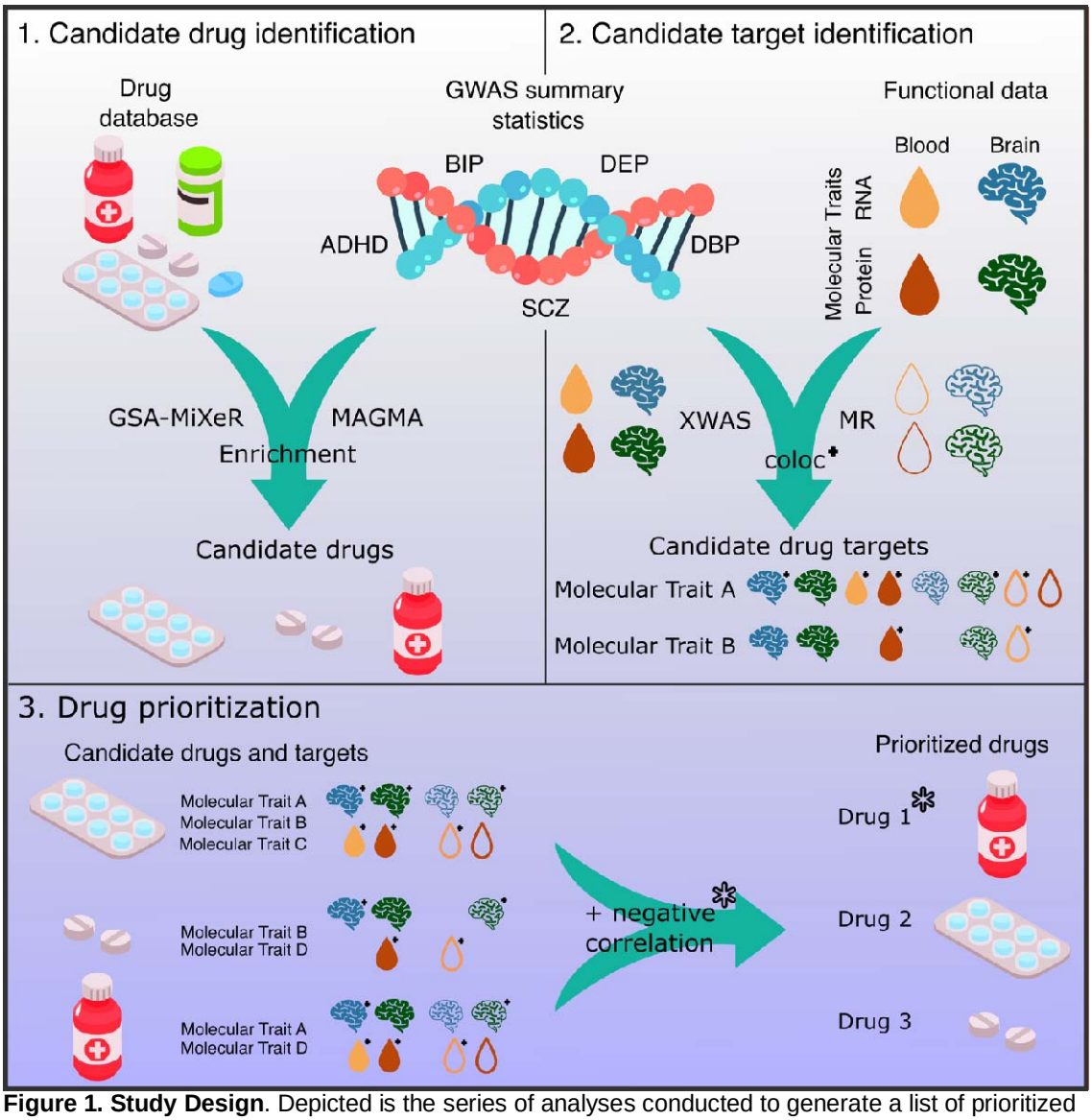

Figure 1. Study Design. Depicted is the series of analyses conducted to generate a list of prioritized drug targets and compounds. First pairings of genome-wide association study (GWAS) traits with drugs are generated using enrichment analyses. Next a series of molecular trait analyses are conducted to generate and rank list of potential drug targets for each GWAS trait. Finally, enrichment and molecular trait results are combined to generate a ranked list of prioritized drugs for each GWAS trait based on supporting genetic evidence. ADHD = Attention deficit hyperactivity disorder, BIP = Bipolar disorder, DEP = Depression, SCZ = Schizophrenia, DBP = Diastolic blood pressure, RNA = ribonucleic acid, XWAS = both transcriptome and proteome wide association studies, MR = Mendelian randomization, coloc = colocalization.

Methods

Genome Wide Association Study Summary Statistics

We used summary statistics from the largest publicly available GWAS of four major psychiatric disorders in European samples. For ADHD we used a GWAS containing a total of 38,691 cases and 186,843 controls.[22] For BIP we used a GWAS including 41,917 cases and 371,549 controls.[7] For DEP we used a GWAS by Als et al. (2022) that excluded the 23andMe sample (n_{cases}=294,322 $n_{controls}$=741,438).[23] For SCZ we used a GWAS including 76,755 cases and 243,649 controls.[24] As a comparator trait we used GWAS summary statistics for DBP containing a total of 1,076,093 individuals.[25] To avoid sample overlap in analyses with the UKB proteomic samples, we used summary statistics which excluded the UKB sample for BIP (n_{cases}=40,463, $n_{controls}$=313,436) and DEP (n_{cases}=166,773, $n_{controls}$=507,679), however, for DBP a GWAS conducted by the Million Veterans Program (n=220,387)[26] was used. We chose DBP as a comparator for several reasons: there are many blood pressure drugs and most target well-defined mechanisms, hypertension is associated with psychiatric disorders to a varying degree providing an interesting comparison for drug prioritization, and DBP is a continuous trait contrasting the dichotomous disorder GWAS and enriching the assessment of our approach.

Candidate Drug Identification

To obtain drug-target genes, we used data from the Drug Gene Interaction database (DGIdb; https://www.dgidb.org/)[27] which collates data from 28 different sources and is a common resource for drug enrichment analyses.[6,7,28,29] The Supplementary Methods contains data processing details.

As our primary method to test each GWAS trait (i.e., ADHD, BIP, DEP, SCZ, DBP) for drug gene-set enrichment, we used GSA-MiXeR (https://github.com/precimed/gsa-mixer).[9] Trait-drug pairs with a positive delta AIC value were considered enriched (Supplementary Methods). We additionally applied a gene-set analysis with MAGMA.[30] While MAGMA tends to identify enrichment among larger gene-sets than GSA-MiXeR,[9] observed enrichment with GSA-MiXeR validated at a nominal significance level ($p<0.05$) with MAGMA provides more robust and potentially clinically actionable associations.

A list of candidate drugs for each GWAS trait was determined based on enrichment using both GSA-MiXeR (AIC_{delta} >0) and MAGMA ($p<0.05$) and ranked using fold enrichment values from GSA-MiXeR (Supplementary Methods). To assess the degree of overlapping enriched drugs across GWAS traits, we used a hypergeometric test. Enriched drugs were assigned an anatomic therapeutic chemical (ATC) code using classifications released in June 2023 from BioPortal. To determine if Level 1 ATC codes were over-represented among the candidate drugs for each GWAS trait, we used hypergeometric tests.

Candidate Target Identification

Transcriptome- and Proteome-Wide Association Studies

To identify potential drug targets for each GWAS trait, we used the FUSION tool to conduct a TWAS and PWAS, which we jointly refer to as XWAS.[31] For TWAS using brain tissue, we used pre-computed single nucleotide polymorphism (SNP) weights for 14,751 genes from the PsychENCODE sample of 1321 individuals.[32] For TWAS

using blood tissue, we used pre-computed weights for 4,701 genes from the Young Finns Study (n=1,264).[31,33] For PWAS using brain tissue, we used pre-computed weights for 2,745 proteins in 720 participants from the Wingo et al. (2023) study.[34] For PWAS using blood tissue, we derived our own weights for 2841 proteins in 33,239 participants from the UKB (Supplementary Methods). We performed correction for multiple comparisons across all XWAS analyses using the Benjamini-Hochberg method.

Mendelian Randomization

To further interrogate potential drug targets, we applied MR analyses using the R package TwoSampleMR[35]. We assessed both forward causal relationships (i.e., from molecular trait to GWAS trait) and reverse causal relationships (i.e., from GWAS trait to molecular trait). The Supplementary Methods provides details on the handling of potentially pleiotropic and proxy SNPs. We used the Wald ratio or inverse variance weighted MR methods for analyses containing a single or multiple SNP(s), respectively.

For each trait, we performed analyses using local (cis) expression or protein quantitative trait loci (i.e., eQTL or pQTL), generally referred to as xQTLs. From brain tissue, we used eQTL data for 18,397 genes from the MetaBrain sample (n=6,518)[36] and pQTL data for 7,553 proteins from the Religious Orders Study (ROS)/Rush Memory and Aging Project (MAP) sample (n=376)[37]. From blood tissue, we used eQTL data for 19,250 genes from eQTLGen sample (n=31,684)[38] and pQTL data for 2938 proteins from the UK Biobank sample (n=34,090)[39]. To avoid sample overlap

between eQTLGen and DBP, we used GTEx v8 eQTL data. We performed correction for multiple comparisons across all MR analyses using the Benjamini-Hochberg method.

Colocalization

Colocalization analyses help determine if two phenotypes share causal SNPs. For all nominally significant ($p<0.05$) molecular trait associations, we conducted colocalization analyses with the associated GWAS trait using the R package COLOC.[40] We considered the molecular and GWAS trait colocalized when the posterior probability of colocalization was greater than 0.8 (Supplementary Methods).

Prioritization of Candidate Targets

To generate a ranked list of candidate drug targets for each GWAS trait, we combined evidence across the molecular trait analyses (i.e., XWAS, MR, and colocalization). We binarized (yes=1, no=0) and then summed the evidence supporting a particular molecular trait. Each molecular trait was then ranked based on their summed support score. For example, if ADHD was significantly associated with molecular trait A using blood TWAS (+1), blood and brain MR pQTL (+2) analyses, and colocalization with brain pQTLs (+1), the summed score would be 4. Note, this approach is biased towards proteins (or protein coding genes) as they have a larger scoring potential. For each GWAS trait, we performed a gene-ontology analysis of the candidate targets using the R package clusterProfiler.

Drug Prioritization

Negative Correlation Test

We extracted drug-induced gene expression data from Connectivity Map 2020 for all enriched drugs using the phase 2 release of the Library of Integrated Cellular Signatures (LINCS) with the cmapR package (v 4.3.1).[41,42] For each drug and GWAS trait pairing, a Spearman correlation between drug induced gene expression and variation in molecular trait associations was conducted. Negative correlations indicate the drug may reverse changes in molecular trait abundance associated with the GWAS trait. This “negative correlation test” was run separately for each molecular trait analysis and corrections for multiple comparisons, for XWAS and MR analyses, were conducted using the Benjamini Hochberg method.

Prioritization of Drugs

Our primary strategy to prioritize drugs for each GWAS trait first selected only the enriched drugs for each GWAS trait to increase biological specificity. Next, the support from the molecular trait analyses for drug-target genes and the negative correlation analyses, were binarized and summed. For example, say SCZ was enriched for drug A (+1). We then find drug A genes were implicated in SCZ analyses for TWAS in blood and brain (+2), MR pQTLs in blood (+1), and a negative correlation test with brain TWAS (+1). The resulting support score for drug A would be 5 for SCZ. Drugs were ranked for each GWAS trait using these scores. Our secondary strategy for ranking drugs was similar except there was no pre-filtering for

enriched drugs allowing all drugs with molecular trait support for a GWAS trait to be ranked.

Validation

Using the secondary approach to drug prioritization, we assessed genetic support for commonly used antidepressants, antipsychotics, mood stabilizers/anticonvulsants, and stimulants (Supplementary Methods).

Ethics

This study was approved by the Regional Committee for Medical Research Ethics including the use of individual and genetics data from the UKB (accession number 27412).

Results

Drug Enrichment Analyses

We used 7,235 drug gene-sets (Supplementary Table 1) to perform enrichment analyses. GWAS of ADHD, BIP, DEP, and SCZ were enriched for a total of 9, 52, 72, and 149 drugs using both GSA-MiXeR (Supplementary Table 2) and MAGMA (Supplementary Tables 3). We observed substantial overlap among the candidate drugs for BIP and SCZ (n=47, p=4.95e-21) but less among the other disorders (BIP-DEP: n=2, p=9.99e-1, DEP-SCZ: n=9, p=1.00), and none with ADHD (Figure 2). The

ATC code for nervous system drugs (Supplementary Table 4) was enriched, for BIP (n=6/25, p=4.77e-3) and SCZ (n=39/78, p=5.30e=25) but not ADHD (n=1/8, p=1.97e-1) or DEP (n=5/39, p=5.97e-1). Among the top 10 candidate drugs for BIP and SCZ were several drugs with antipsychotic properties (e.g., benperidol, mazapertine, and sarizotan). For DEP, the top 10 candidate drugs had antipsychotic and antidepressant properties (e.g., benperidol, nemonapride, cariprazine). For ADHD, candidate drugs were primarily acetylcholine receptor modulators.

The DBP GWAS was enriched for the most drugs (n=192; Supplementary Tables 2 and 3). No significant overlap between candidate drugs for DBP and the psychiatric disorders was observed (DBP-ADHD: n=1, p=9.91e-1, DBP-BIP: n=20, p=6.78e-1, DBP-DEP: n=6, p=1.00, DBP-SCZ: n=27, p=1.00; Supplementary Figure 1). There was no ATC code enrichment for nervous system drugs (n=3/112, p=1.00) but there was enrichment for cardiovascular system drugs (n=67/112, p<0.001).

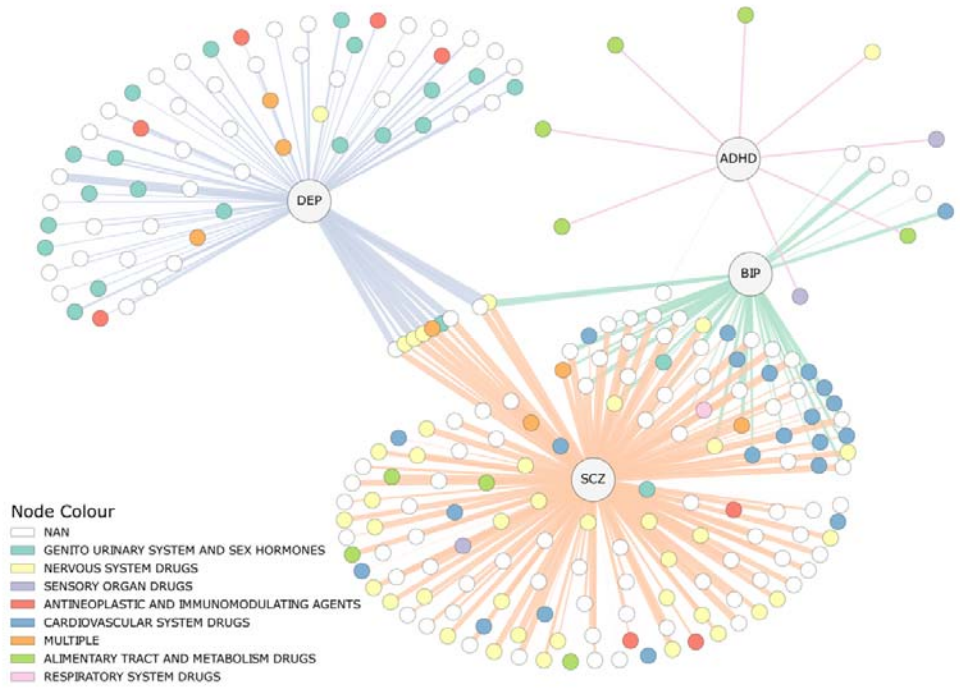

Figure 2. Overlap of Enriched Drugs for Psychiatric Disorders. A network plot depicting each of the enriched drugs (colored nodes) for each psychiatric disorder labelled central hubs. Each drug node is colored based on their level 1 anatomical therapeutic chemical classification. The thicker the edge (line connecting nodes to disorder), the larger the fold enrichment. ADHD = Attention deficit hyperactivity disorder, BIP = Bipolar disorder, DEP = Depression, SCZ = Schizophrenia, MULTIPLE = A drug with multiple classifications, NAN = No anatomical therapeutic chemical code.

Molecular Trait Analyses

XWAS analyses identified 440, 912, 940, and 1436 significant molecular trait associations for ADHD, BIP, DEP, SCZ, respectively (Figure 3, Supplementary Table 5). The molecular traits associated with enriched drugs are labelled in Figure 3 where several were supported by multiple XWAS analyses such as *ANKK1* with DEP. Colocalization analyses revealed 605 (16.23%) of the significant XWAS associations had colocalized genetic signal (Supplementary Tables 6) and 13 were enriched drug-target genes (Figure 3). Moreover, a significant negative correlation test was observed between estriol induced gene expression and DEP brain PWAS effects (Supplementary Table 7).

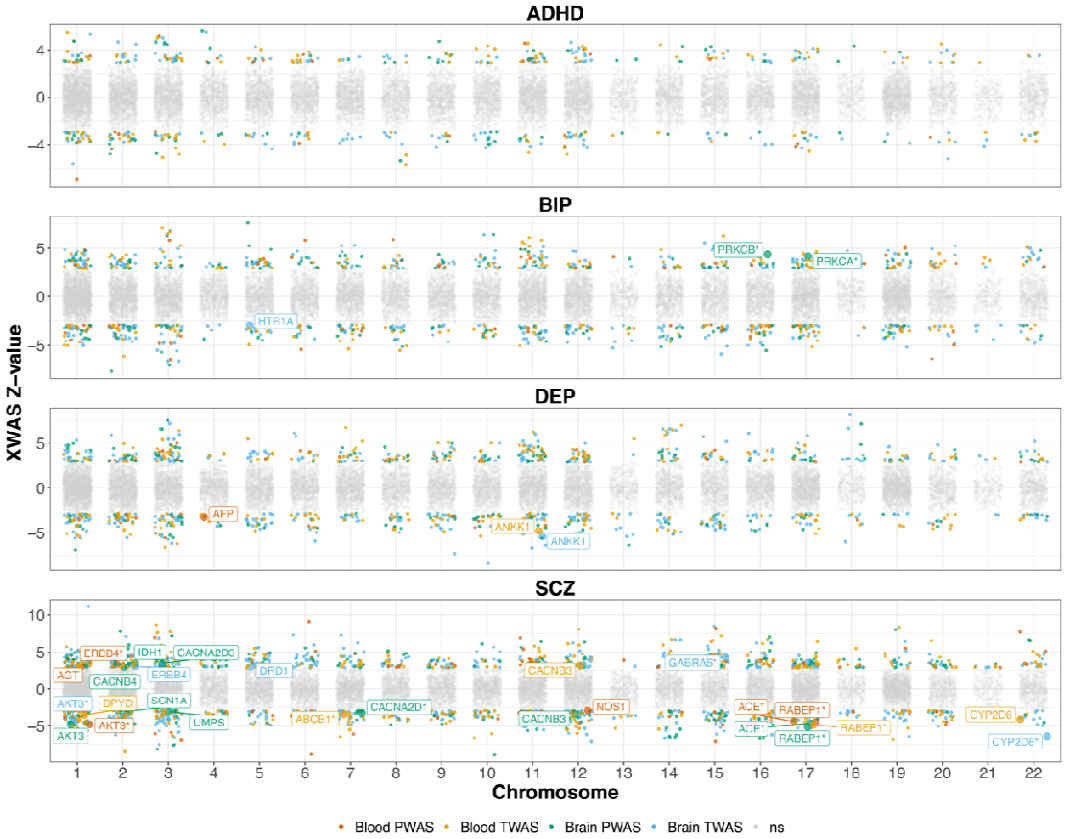

Figure 3. Transcriptome- and Proteome-Wide Association Study Results. For each psychiatric disorder the results of transcriptome- and proteome-wide association studies are presented. Significantly associated molecular traits that are also a part of gene sets for enriched drugs are labelled. Labelled molecular traits that were also colocalized are represented with an asterisk. ADHD: attention deficit hyperactivity disorder, BIP: bipolar disorder, DEP: Depression, SCZ: schizophrenia, TWAS = Transcriptome wide association study, PWAS = Proteome wide association study, ns= not significant.

Across the bidirectional MR analyses, 605, 1368, 1477, and 2460 molecular traits were significantly associated with ADHD, BIP, DEP, and SCZ, respectively (Figure 4, Supplementary Table 8). The molecular traits associated with enriched drugs are labelled in Figure 4 where several were supported by multiple MR analyses such as *ANKK1* with DEP and *CACNA1I* with SCZ. Colocalization analyses revealed 766 (12.96%) of the significant MR associations had colocalized genetic signal (Supplementary Tables 9) and 10 were enriched drug-target genes (Figure 4). There were no significant negative correlation tests (Supplementary Tables 10).

DBP had the largest number of significant molecular trait associations for XWAS (n=3547) and MR (n=3145) (Supplementary Tables 5 and 8) with many enriched drug-target genes implicated (Supplementary Figures 2 and 3). Colocalization was revealed for 503 (14.18%) and 312 (9.92%) of the significant XWAS and MR associations, respectively (Supplementary Tables 6 and 9). Meanwhile, a significant negative correlation was observed between Oxprenolol, a beta blocker, and DBP blood PWAS effects (Supplementary Tables 7).

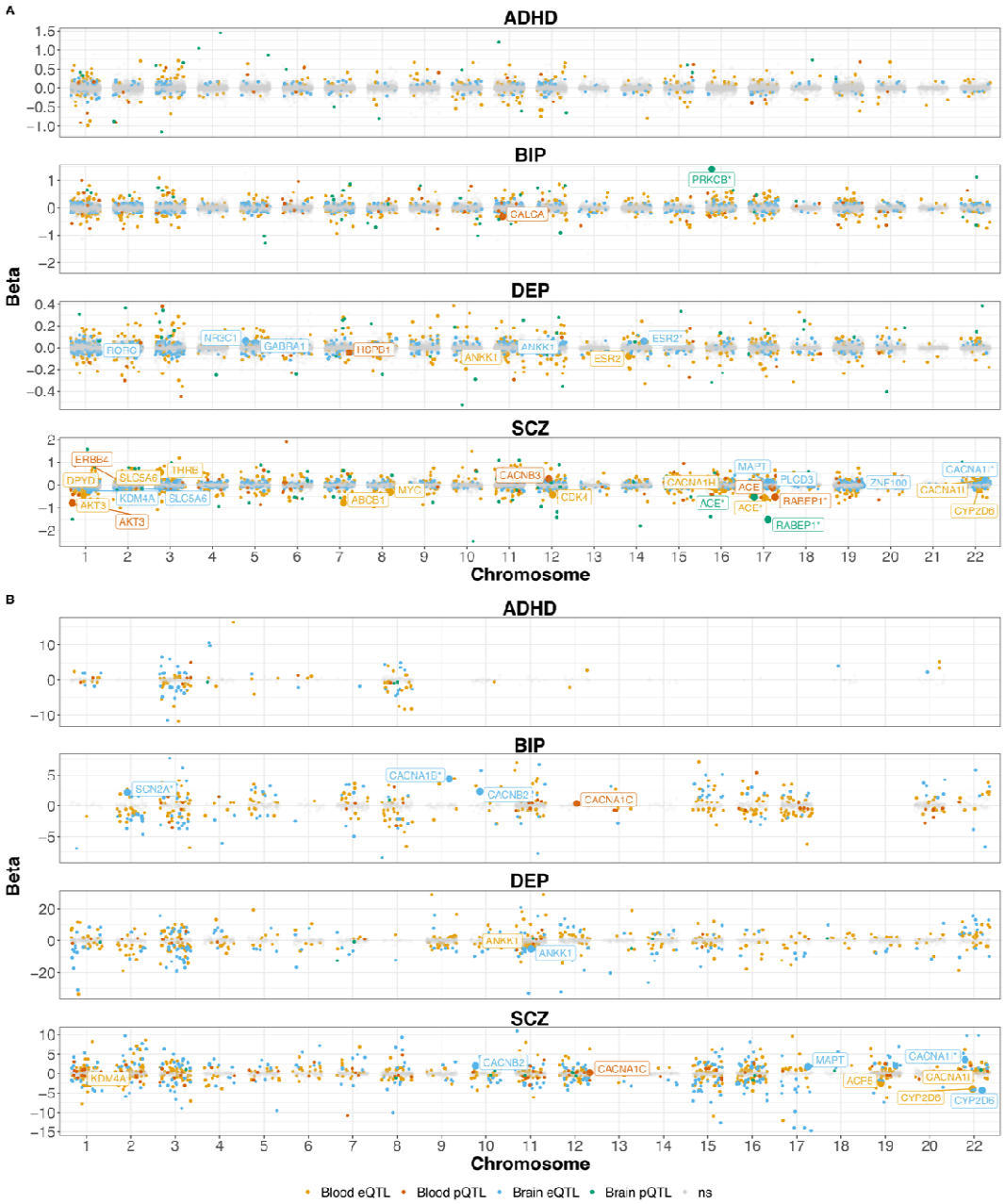

Figure 4. Mendelian Randomization Results. For each psychiatric disorder the results of the Mendelian Randomization (MR) analyses are presented. Panel A shows the MR results in the forward direction with the psychiatric disorders as the outcome traits. Panel B shows the MR results in the reverse direction with the psychiatric disorders as the exposure traits. Significantly associated molecular traits that are also a part of a drug gene set enriched for the disorder are labelled. Labelled molecular traits that were also colocalized are represented with an asterisk. ADHD: attention deficit hyperactivity disorder, BIP: bipolar disorder, DEP: Depression, SCZ: schizophrenia, eQTL = expression quantitative trait loci, pQTL = protein quantitative trait loci, ns= not significant.

Prioritization of Potential Drug Targets and Compounds

We identified 769, 1537, 1605, and 2454 candidate drug targets supported by at least one molecular trait analysis for ADHD, BIP, DEP, and SCZ, respectively (Supplementary Table 11). Among these candidate targets, there was significant overlap observed between BIP and SCZ (n=589, p=1.04e-7) as well as ADHD and DEP (n=206, p=9.74e-5). Figure 5 presents the top 10 candidate targets for each psychiatric disorder and their supporting evidence. Notably, FES, was among the top 10 candidates for ADHD, DEP, and SCZ (ranked 14th for BIP). The gene ontology term “glutamatergic synapse" was enriched among the candidate targets for BIP, DEP, and SCZ (Supplementary Table 12). DBP had the most candidate targets (n=4139; Supplementary Table 11) and these did not significantly overlap with psychiatric disorders. DBP and SCZ shared several enriched gene-sets related to protein dephosphorylation and cell division (Supplementary Table 12).

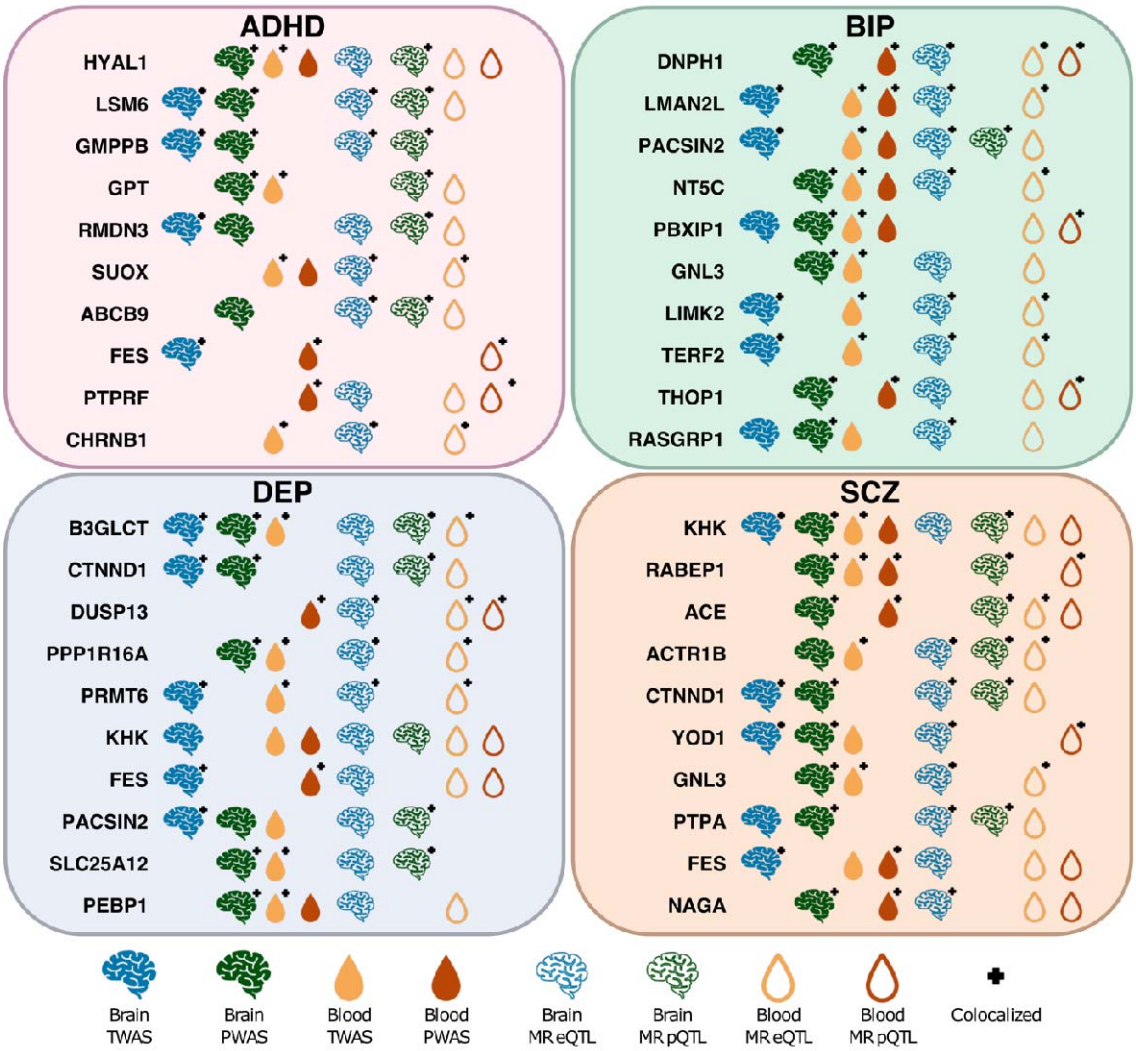

Figure 5. Prioritization of Candidate Drug Targets. The list of prioritized potential drug targets for each psychiatric disorder after combining results of molecular trait analyses from transcriptome and proteome wide association studies, Mendelian randomization, and colocalization. ADHD: attention deficit hyperactivity disorder, BIP: bipolar disorder, DEP: Depression, SCZ: schizophrenia, TWAS = Transcriptome wide association study, PWAS = Proteome wide association study, MR = Mendelian randomization, eQTL = expression quantitative trait loci, pQTL = protein quantitative trait loci, ns= not significant.

After combining molecular trait support with drug enrichment for each psychiatric disorder, 29 (55.77%), 39 (54.17%), and 82 (55.03%) were supported for BIP, DEP, and SCZ, respectively (Supplementary Table 14-17). The nine ADHD enriched drugs had no molecular trait support (Supplementary Table 13). Figure 6 presents the top 10 prioritized candidate drugs and their supporting evidence. For BIP, 5 compounds

have putative antipsychotic or antimanic properties (elepetrigine, mazapertine succinate, sarizotan, umespirone, mem-1003). For DEP, the top 10 drugs included predominantly estrogen related compounds except nemonapride, an antipsychotic. For SCZ, two antipsychotics were among the top 10 including the top ranked drug paliperidone. Several calcium channel blockers were highly ranked for both BIP and SCZ.

In our secondary approach (i.e., not restricting to enriched drugs), the top 10 drugs for ADHD, BIP, and DEP predominantly included known or investigational antineoplastic compounds. However, for SCZ, the top 10 drugs included 4 antipsychotics (clozapine, paliperidone, aripiprazole, and risperidone) but the size of the drug gene-sets ($mean_{genes}$=36, sd=20.90) were significantly larger than the top 10 enriched drugs ($mean_{genes}$=13.4, sd=11.97, $p_{difference}$=9.98e-3).

DBP enriched drugs had the most molecular trait support [n=169 (88.02%)] (Supplementary Table 17) and the top 10 candidate drugs included several modulators of blood pressure (e.g., amlodipine besylate, cilazapril, quinapril, and verapamil). Using the secondary approach, the top 10 drugs included many antineoplastic compounds.

Validation analyses revealed varying degrees of molecular trait support for commonly used antidepressants for DEP (e.g., duloxetine) and antipsychotics/mood stabilizers for BIP (e.g., haloperidol, lithium, and valproic acid) in addition to the above mentioned SCZ findings (Supplementary Table 18).

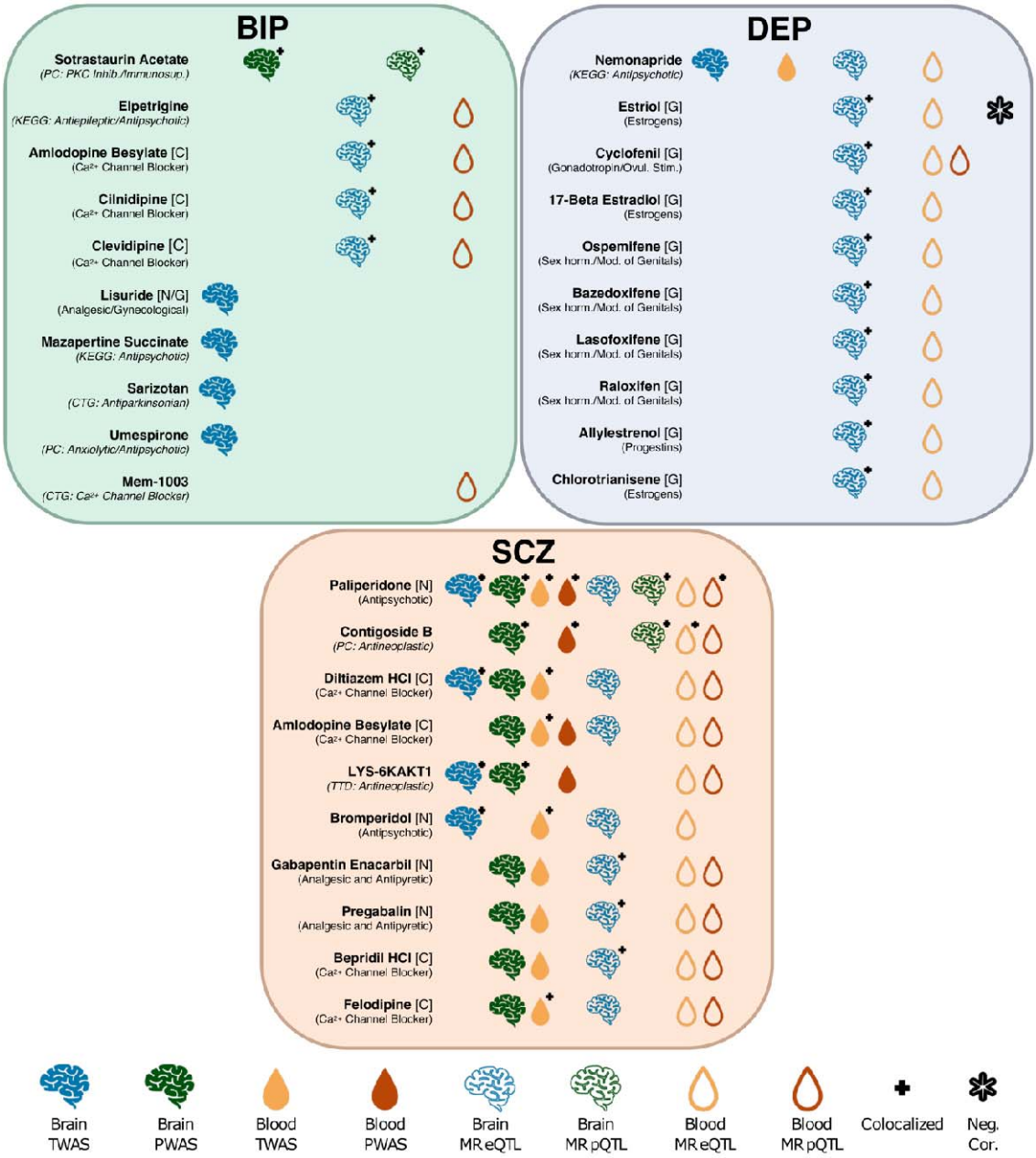

Figure 6. Prioritization of Drug Compounds. The prioritized list of drug compounds (in bold) for each psychiatric disorder with molecular trait support for enriched drugs. In brackets next to each drug compound is the level 1 anatomical therapeutic chemical (ATC) classification code. Below each drug compound is a brief description. In most cases the description is based on the level 3 ATC classification. Drugs without an ATC code use descriptions from various other sources including: ClinicalTrials.gov (CTG; https://clinicaltrials.gov/), PubChem (PC; https://pubchem.ncbi.nlm.nih.gov/), Kyoto encyclopedia of genes and genomes (KEGG; https://www.genome.jp/kegg/kegg2.html), Therapeutic target database (TTD; https://idrblab.net/ttd/). For drug compounds with the same support score, priority went to those with an ATC code (prioritizing nervous system classification) or to drugs previously associated with psychiatric disorders. [C] = Cardiovasculat system drug, [G] = Genito urinary system and sex hormones, [N] = Nervous system drug, PKC inhib/immunosup. = Protein kinase C inhibitor and immunosuppressant, Neg. Cor. = Drug with negative correlation support between proteome wide association study effect estimate and drug induced gene expression.

Discussion

We prioritized potential drug targets and compounds for psychiatric disorders using an extensive genetically informed investigation. Our approach employed novel tools such as GSA-MiXeR[9] for drug gene-set enrichment and the novel use of UKB proteomic data[39] for PWAS of psychiatric disorders. The series of molecular trait analyses revealed candidate drug targets with varying degrees of disorder specificity. The prioritization of potential drugs revealed known and investigational compounds with indications for psychiatric treatment as well as potential opportunities for repurposing. Altogether, this work highlights the potential utility of genetics for informing psychiatric treatment.

Top-ranked candidate targets exhibited varying degrees of pleiotropy. For example, FES was highly ranked for all GWAS traits (including DBP) and is a tyrosine kinase linked to semaphorin signalling which plays a role in development of the nervous and cardiovascular system, neurodegeneration, and cancer cell behaviour.[43,44] Therefore, FES may implicate cross-disorder similarities in pathophysiology. Similarly, sharing of candidate targets between BIP, DEP, and SCZ revealed enrichment for the gene ontology term “excitatory glutamatergic synapse” which is consistent with glutamate signalling as a therapeutic target for psychiatric disorders.[45] Meanwhile, we and others[12,46] have linked B3GLCT to DEP using multiple methods and since we found only BIP was also associated, B3GLCT may be mood disorder specific. In contrast, RABEP1, a mediator of vesicle transport and neurotransmission, was ranked second and was specific to SCZ.[47] Therefore, we prioritized candidate targets with varying degrees of specificity for psychiatric

disorders potentially informing development of drugs for cross-disorder or disorder-specific treatment.

Consistent with previous studies, our results provide genetic support for drugs with known or putative indications for psychiatric treatment.[6,7,11,29] The top 10 prioritized drugs for BIP included 5 putative antipsychotic/antimanic compounds and for SCZ, two common antipsychotics. By filtering for enriched drugs using GSA-MiXeR, our primary approach allowed for prioritization of drugs with fewer, more biologically specific targets which resulted in less non-specific prioritization of antineoplastic drugs. Our secondary approach, without filtering on enrichment, highly ranked several commonly used antipsychotics for SCZ (e.g., clozapine, aripiprazole, and risperidone) and revealed high candidate target support for other common psychotropics such as valproic acid and haloperidol for BIP. Therefore, genetic support for psychotropic drugs exist but whether our primary, biologically specific approach informs improved treatment for psychiatric patients remains to be seen.

Identified drugs additionally highlight opportunities for repurposing. Eight of the nine enriched drugs for ADHD modulate acetylcholine receptors and while none of those drugs had candidate target support, cholinergic drugs have been proposed for ADHD treatment.[48] Top ranked drugs for DEP included the antipsychotic nemonapride and many estrogen modulators which both have been linked to antidepressant activity.[49–51] Also, gabapentin enacarbil was highly ranked for SCZ and is occasionally used, off-label or as an adjunct, in psychiatric treatment.[52,53] Therefore, among our top 10 prioritized drugs alone there are several repurposing opportunities.

Combining enrichment with molecular trait analyses revealed important clinical implications for enriched drug targets. Across several analyses and consistent with previous reports, genetic liability to SCZ was associated with reduced expression of *CYP2D6*, an enriched drug target that plays a role in metabolism of neurotransmitters and drugs, including antipsychotics.[14,54–56] Therefore, lower levels of *CYP2D6* may contribute to SCZ pathophysiology and also disrupt treatment response which supports efforts for therapeutic monitoring of *CYP2D6* polymorphisms and evidence-based drug dosing.[14,57] ANKK1 was negatively associated with DEP in several analyses, includes a polymorphism linked to reductions in dopamine receptor abundance, and is a target for several psychotropic drugs, including the DEP enriched nemonapride.[58,59] Therefore, while many antipsychotics have high affinity for both dopamine and serotonin receptors,[60] ANKK1 may be an alternative link for response to antipsychotics in patients with DEP. Consistent with previous reports, BIP and SCZ were associated with candidate targets related to cellular calcium supporting the prioritization of calcium channel blockers and their continued investigation as therapeutic drugs in psychiatry.[7,14,61] Altogether, these currently druggable targets revealed important implications for psychiatric treatment.

This study has several strengths and limitations. Using DBP as a comparator revealed the specificity of our approach given candidate drug targets and enriched drug compounds for DBP did not significantly overlap with any psychiatric disorder. DBP results also showed the generalizability of our approach beyond psychiatric traits. Our approach prioritizes drugs irrespective of effect direction. Therefore, we identify drugs with genetic evidence for beneficial or detrimental effects for a trait.

While this is useful, our findings require careful interpretation and further investigation. We also use transcriptomic and proteomic data from both brain and blood tissue. The molecular traits and tissue sources are complimentary but not completely correlated, however, their integration improves the power to identify modifiable drug targets.[62,63] Our findings may lack generalizability beyond individuals of European ancestry due in part to the reliance of tools on European references and a lack of well powered non-European GWASs and sources of molecular trait data. Additionally, the power of the included GWASs varies which likely contributes to greater molecular support for enriched drugs of high powered GWAS traits (i.e., SCZ and DBP).

In conclusion, our extensive analytical approach leveraged psychiatric GWAS combined with novel tools and molecular trait data to prioritize potential drug targets and compounds. The candidate targets can be used for future development of either cross-disorder or more disorder-specific drugs. Meanwhile, the prioritized drugs can be used for future repurposing efforts. This study provides clinically relevant evidence for how psychiatric genetics can inform treatment. Overall, our findings provide a basis for future drug development, repurposing, and treatment decision making in psychiatry.

Contributions

NP and OBS conceived of the study and EK, AAS, GFLH, SS, PJ, KSO, and OAA were involved in study design. NP, EK, AAS, TSW, and APW were involved in data acquisition and processing. NP, EK, AAS, and JF were involved in data analysis. NP

had access to all data and drafted the initial manuscript. All authors contributed to data interpretation and editing of the manuscript and accepted responsibility to submit the manuscript for publication.

Declarations

OAA has received speaker fees from Lundbeck, Janssen, Otsuka, and Sunovion and is a consultant to Cortechs.ai. and Precision Health. AMD is Founding Director, holds equity in CorTechs Labs, Inc. (DBA Cortechs.ai), and serves on its Board of Directors and the Scientific Advisory Board. He is an unpaid consultant for Oslo University Hospital. The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict-of-interest policies. OF is a consultant to Precision Health. TSW is a co-founder of revXon, which is disclosed and approved to University of California, Davis per its conflict-of-interest policy.

Data Sharing

All GWAS summary statistics and molecular trait data included in this study are publicly available. We generated PWAS weights using proteomic data from the UK Biobank and have shared those weights on figshare [link to be added]. The GWAS summary statistics from the Million Veteran Program were downloaded from the dbGaP web site, under accession phs001672.

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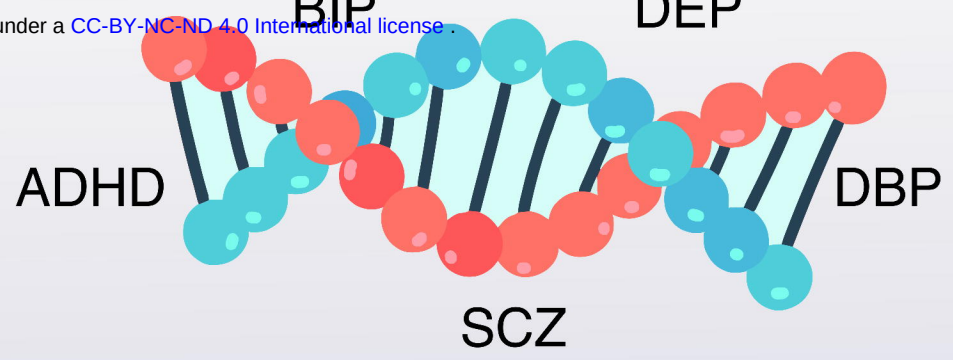
1. Candidate drug identification

Drug database

GWAS summary statistics



GSA-MiXeR

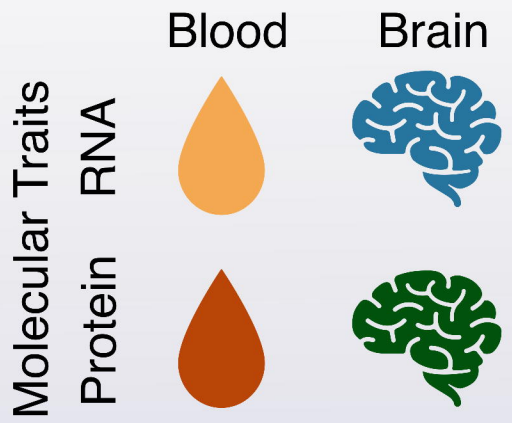
MAGMA

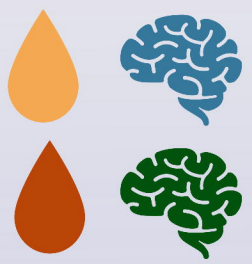
Enrichment

Candidate drugs

2. Candidate target identification

Functional data

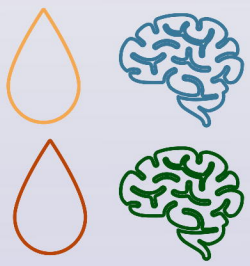




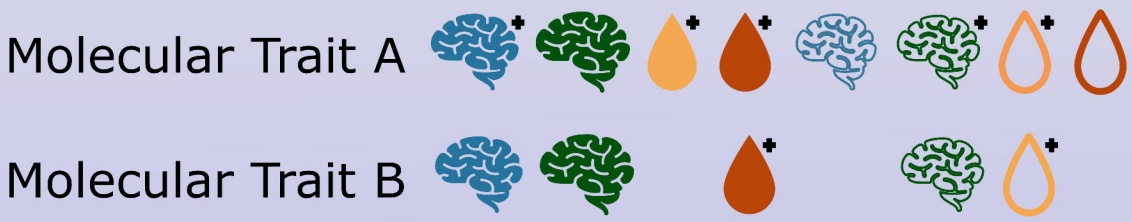
XWAS

MR

coloc+



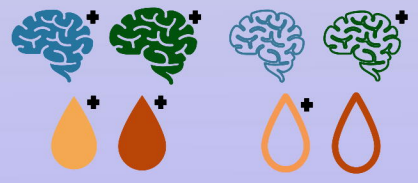
Candidate drug targets



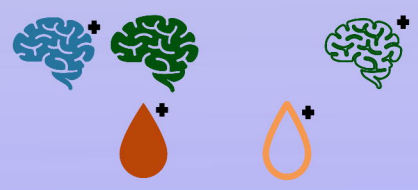
3. Drug prioritization

Candidate drugs and targets

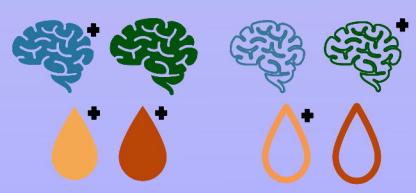
Molecular Trait A
Molecular Trait B
Molecular Trait C



Molecular Trait B
Molecular Trait D



Molecular Trait A
Molecular Trait D



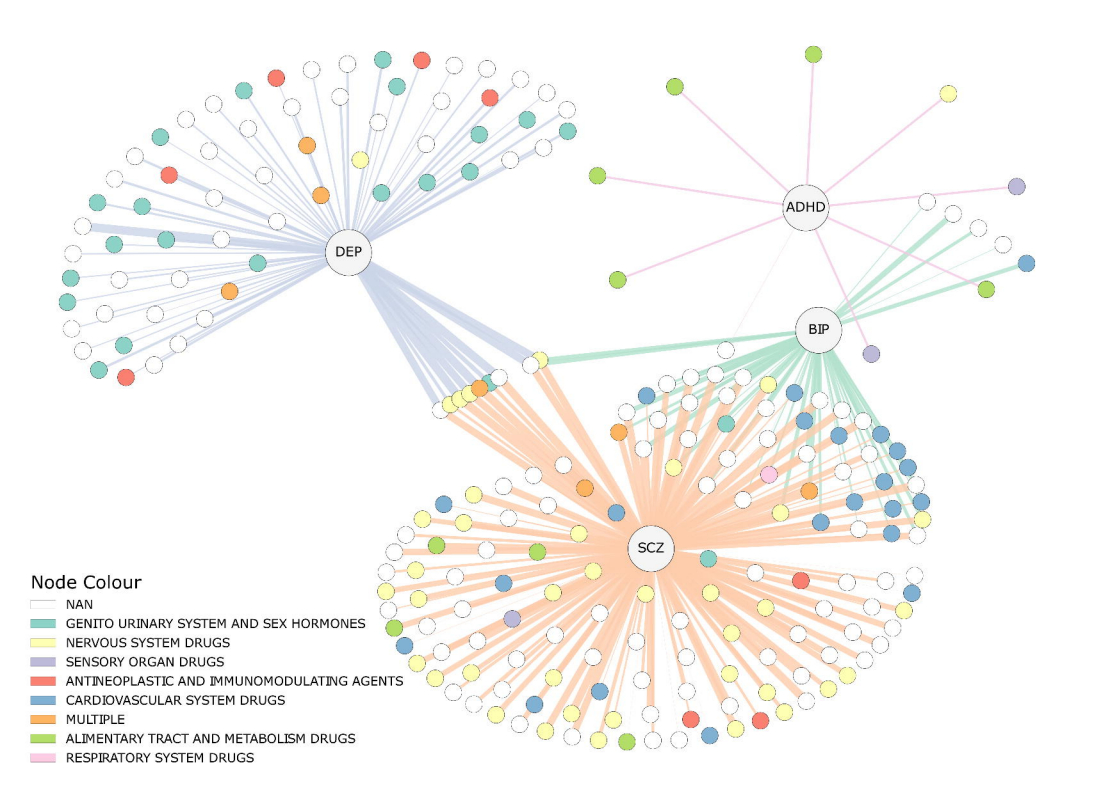
+ negative correlation*

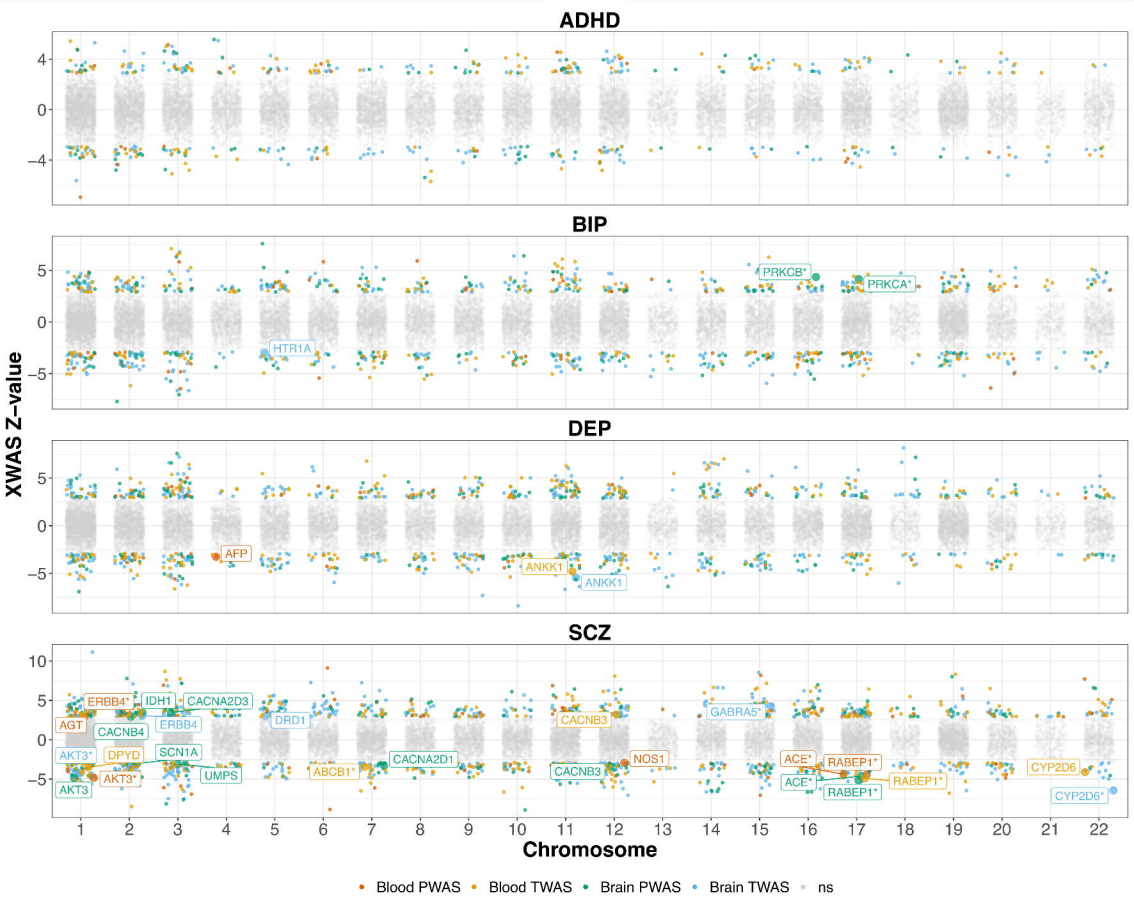
Prioritized drugs

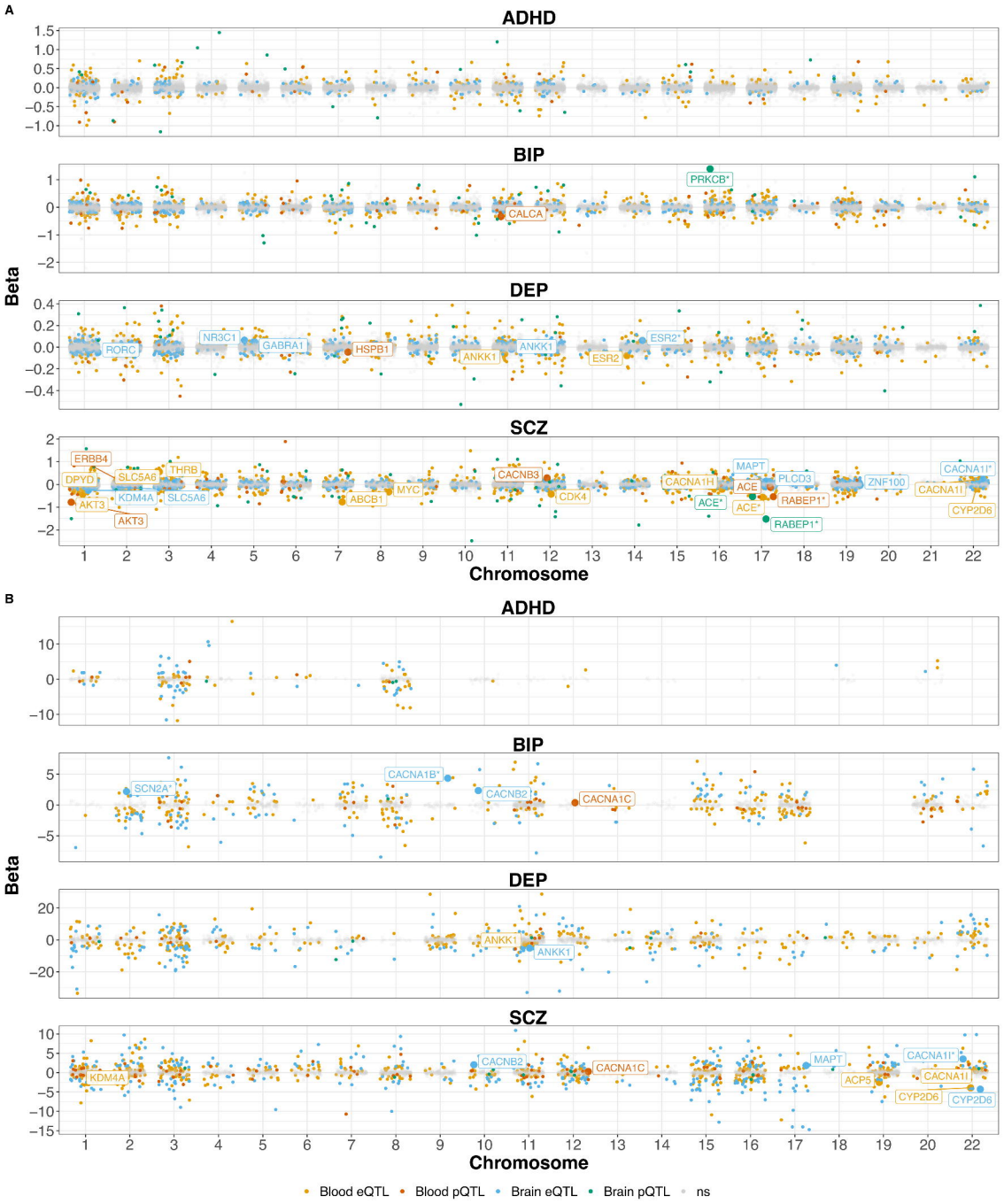
Drug 1*

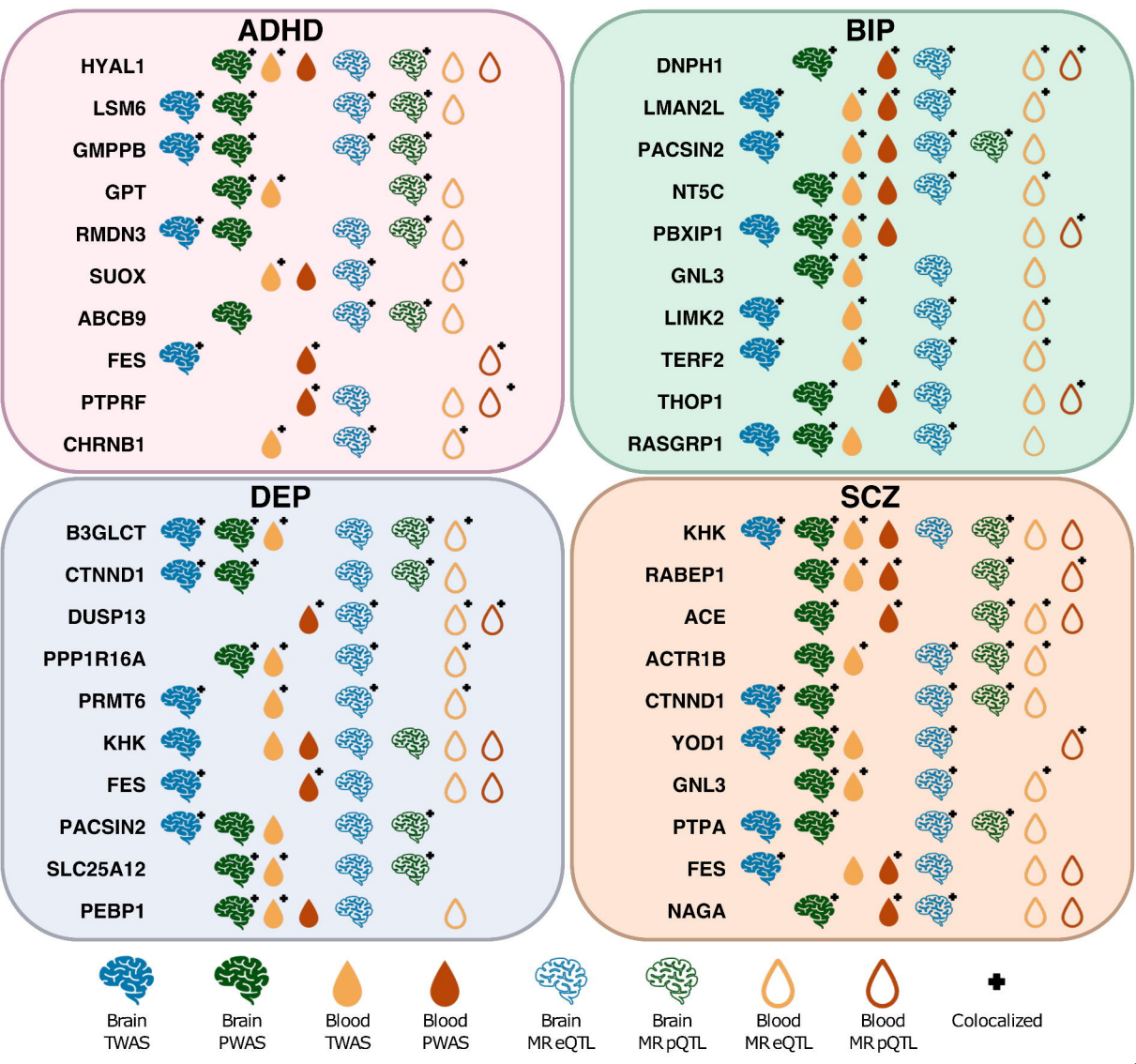
Drug 2

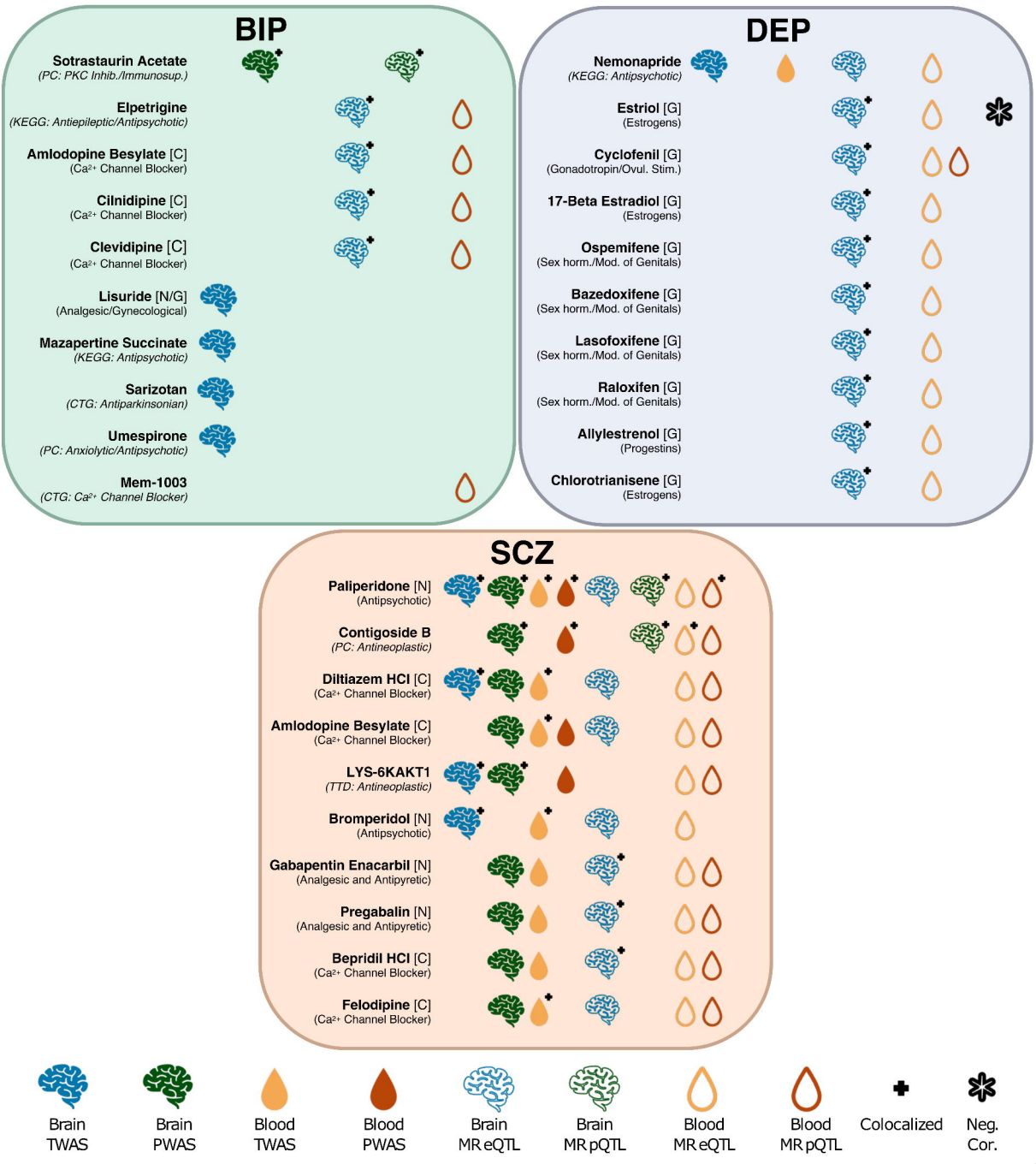
Drug 3


DEP
ADHD
BIP
SCZ
Node Colour
NAN
GENITO URINARY SYSTEM AND SEX HORMONES
NERVOUS SYSTEM DRUGS
SENSORY ORGAN DRUGS
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
CARDIOVASCULAR SYSTEM DRUGS
MULTIPLE
ALIMENTARY TRACT AND METABOLISM DRUGS
RESPIRATORY SYSTEM DRUGS


ADHD
BIP
DEP
SCZ
XWAS Z−value
Chromosome
PRKCB*
PRKCA*
HTR1A
AFP
ANKK1
ANKK1
ERBB4*
IDH1
CACNA2D3
AGT
CACNB4
ERBB4
DRD1
AKT3*
DPYD
SCN1A
AKT3*
AKT3
UMPS
ABCB1*
CACNA2D1
CACNB3
CACNB3
NOS1
GABRA5
ACE*
ACE*
RABEP1*
RABEP1*
RABEP1*
CYP2D6
CYP2D6*
Blood PWAS
Blood TWAS
Brain PWAS
Brain TWAS
ns


A
ADHD
BIP
DEP
SCZ
Beta
PRKCB*
CALCA
RORC
NR3C1
GABRA1
HSPB1
ANKK1
ESR2*
ERBB4
DPYD
SLC5A6
THRB
KDM4A
AKT3
ABCB1
MYC
CACNB3
CDK4
CACNA1H
MAPT
ACE
PLCD3
RABEP1*
ZNF100
CACNA1I*
CYP2D6
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome
B
ADHD
BIP
DEP
SCZ
Beta
SCN2A*
CACNA1B*
CACNB2
CACNA1C
ANKK1
MAPT
ACP5
CACNA1I
CYP2D6
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 22
Chromosome
Blood eQTL
Blood pQTL
Brain eQTL
Brain pQTL
ns


ADHD
HYAL1
LSM6
GMPPB
GPT
RMDN3
SUOX
ABCB9
FES
PTPRF
CHRNB1
BIP
DNPH1
LMAN2L
PACSIN2
NT5C
PBXIP1
GNL3
LIMK2
TERF2
THOP1
RASGRP1
DEP
B3GLCT
CTNND1
DUSP13
PPP1R16A
PRMT6
KHK
FES
PACSIN2
SLC25A12
PEBP1
SCZ
KHK
RABEP1
ACE
ACTR1B
CTNND1
YOD1
GNL3
PTPA
FES
NAGA
Brain TWAS
Brain PWAS
Blood TWAS
Blood PWAS
Brain MR eQTL
Brain MR pQTL
Blood MR eQTL
Blood MR pQTL
Colocalized


BIP
Sotrastaurin Acetate
(PC: PKC Inhib./Immunosup.)
Elpetrigine
(KEGG: Antiepileptic/Antipsychotic)
Amlodopine Besylate [C]
(Ca2+ Channel Blocker)
Cilnidipine [C]
(Ca2+ Channel Blocker)
Clevidipine [C]
(Ca2+ Channel Blocker)
Lisuride [N/G]
(Analgesic/Gynecological)
Mazapertine Succinate
(KEGG: Antipsychotic)
Sarizotan
(CTG: Antiparkinsonian)
Umespirone
(PC: Anxiolytic/Antipsychotic)
Mem-1003
(CTG: Ca2+ Channel Blocker)
DEP
Nemonapride
(KEGG: Antipsychotic)
Estriol [G]
(Estrogens)
Cyclofenil [G]
(Gonadotropin/Ovul. Stim.)
17-Beta Estradiol [G]
(Estrogens)
Ospemifene [G]
(Sex horm./Mod. of Genitals)
Bazedoxifene [G]
(Sex horm./Mod. of Genitals)
Lasofoxifene [G]
(Sex horm./Mod. of Genitals)
Raloxifen [G]
(Sex horm./Mod. of Genitals)
Allylestrenol [G]
(Progestins)
Chlorotrianisene [G]
(Estrogens)
SCZ
Paliperidone [N]
(Antipsychotic)
Contigoside B
(PC: Antineoplastic)
Diltiazem HCl [C]
(Ca2+ Channel Blocker)
Amlodopine Besylate [C]
(Ca2+ Channel Blocker)
LYS-6KAKT1
(TTD: Antineoplastic)
Bromperidol [N]
(Antipsychotic)
Gabapentin Enacarbil [N]
(Analgesic and Antipyretic)
Pregabalin [N]
(Analgesic and Antipyretic)
Bepridil HCl [C]
(Ca2+ Channel Blocker)
Felodipine [C]
(Ca2+ Channel Blocker)
Brain TWAS
Brain PWAS
Blood TWAS
Blood PWAS
Brain MR eQTL
Brain MR pQTL
Blood MR eQTL
Blood MR pQTL
Colocalized
Neg. Cor.