Introduction

- Many individuals with psychiatric disorders also exhibit substance abuse disorders:
  - More than 80% of individuals with schizophrenia are nicotine dependent1
  - 25% of patients with major depressive disorder also exhibit alcohol use disorder2
- Genome-Wide Association Studies (GWAS) capture genetic variants associated with specific traits, but given that most risk variants reside in non-coding regions of the genome, deciphering their target genes and neurobiological mechanisms remains a challenge3
- The Won Lab recently developed H-MAGMA, a computational framework that uses the gene mapping tool MAGMA and data from Hi-C chromatin interaction experiments to assign non-coding SNPs to their cognate genes4-5.
- By performing different analyses on the genes associated with different psychiatric and substance-use disorders, we gain insights into the common neurological mechanisms between these disorders. These insights could lead to better, more targeted treatments for these comorbidities.

Methods

H-MAGMA transforms SNP-level p-values to gene-level p-values. Exonic SNPs from individual GWAS were directly assigned to the genes in which they reside, while SNPs residing in non-coding regions were assigned to target genes based on chromatin interaction from disomic (DN) neurons. To identify pleotropic gene lists, RRHD was run on pairs of psychiatric and substance-use disorders. To identify specific cell-types underlying this comorbidity, we mapped the cellular expression profiles of pleiotropic genes.

Figure 1. Genetic Correlation Between SUD and Psychiatric Disorders. Darker and larger squares in the top right side correspond to higher genetic correlation, lighter and smaller squares correspond to lower genetic correlation. Bottom left side shows exact values for genetic correlation. Results that were not significant at |r| < 0.05 were removed. ADHD - Attention Deficit/Hyperactivity Disorder, ASD - Autism Spectrum Disorder, BP - Bipolar Disorder, MDD - Major Depressive Disorder, SCZ - Schizophrenia, CPD - Cigarettes Per Day, FTND - Fagerstrom Test for Nicotine Dependence, PAU - Problematic Alcohol Use, DPW – Drinks Per Week

Figure 2. Circuit Mapping

Figure 3. Cellular expression profiles of pleiotropic genes in the nucleus accumbens. Darker red areas indicate higher expression of pleiotropic genes in that cell type and darker blue areas indicate lower expression. The major neuron types are Inhibitory, and medium spiny neurons (MSN). MSNs were also further broken down into two categories based on whether they more highly expressed the marker gene DRD1 (MSN.D1) or DRD2 (MSN.D2)

Figure 4. Circuit-mapping profiles of pleiotropic genes. Darker red areas indicate higher expression of pleiotropic genes in that brain region and darker blue areas indicate lower expression. The pleiotropic gene list was made from the intersection of two gene lists: for psychiatric and substance use disorders. The psychiatric gene list was made from genes that were present in H-MAGMA results from 3 out of five of: ADHD, ASD, BP, MDD, and SCZ. The substance-use disorder was made using the same criteria for 3 of 4 of CPD, FTN, PAU, and DPW.

Conclusion

- Cell-type specific H-MAGMA identifies risk genes associated with psychiatric and substance-use disorders.
- Cellular expression profile highlights neurons as the primary cell types underlying this comorbidity, with Medium Spiny Neurons possibly being more influential than Inhibitory Neurons.
- Circuit mapping profiles indicate that the Cortex, Thalamus, and Amygdala (and surprisingly, not the Midbrain), could be particularly influential in these comorbidities.

Reference