Leveraging Evolution to Unravel the Neuromolecular Interactions in the Amygdala between Psychiatric and Substance Use Disorders

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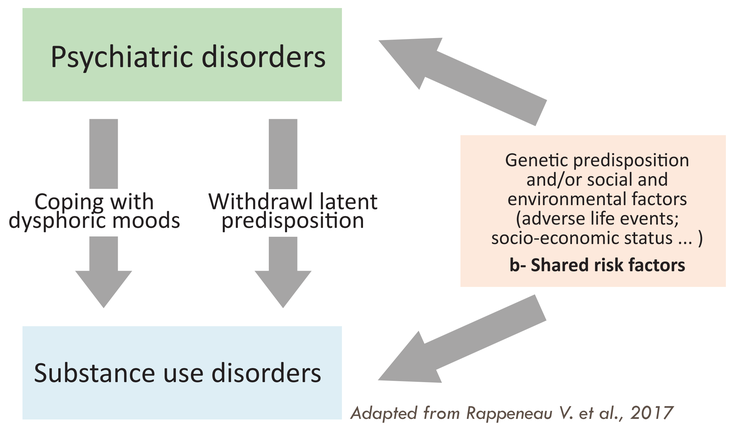
Question:

About half of individuals who experience a mental illness also suffer from a substance use disorder, often with more severe outcomes. What is the neuromolecular basis of this comorbidity? And what is the relationship between genes dysregulated in psychiatric disorders and those dysregulated in substance use disorders?



Adapted from Rappeneau V. et al., 2017

a- Causal relationships between the two disorders

The mammalian amygdala: An evolutionarily conserved brain region involved in processing of memory, decision-making and emotional responses. A growing body of evidence suggests that the amygdala is dysregulated in both mental disorders and substance use disorders

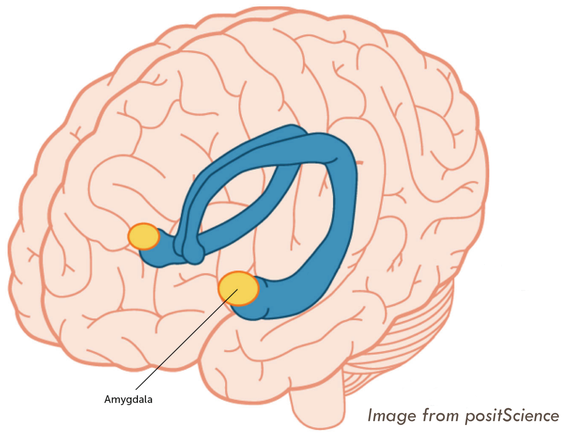
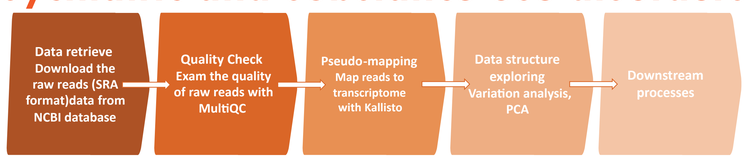


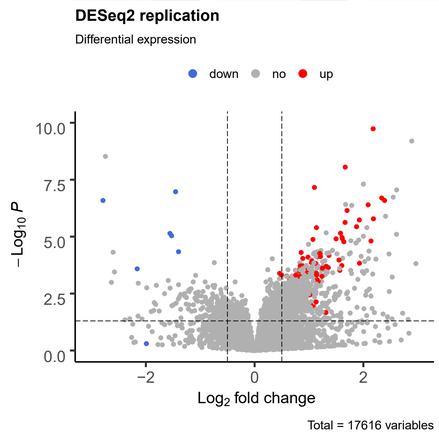
Image from positScience

Approach:

Transcriptome analyses in human post mortem brains have identified dysregulation of several pathways in both psychiatric disorders and substance use disorders. However, the interaction of these disorders at the molecular level has not been examined systematically, and little work has been done in the amygdala.

Uncovering the interactions between psychiatric and substance use disorders

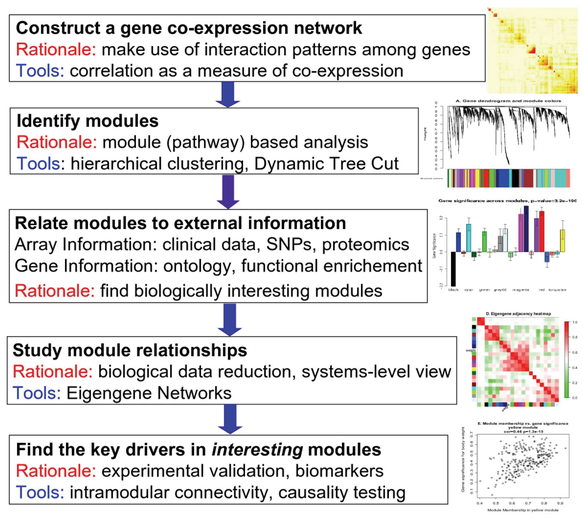




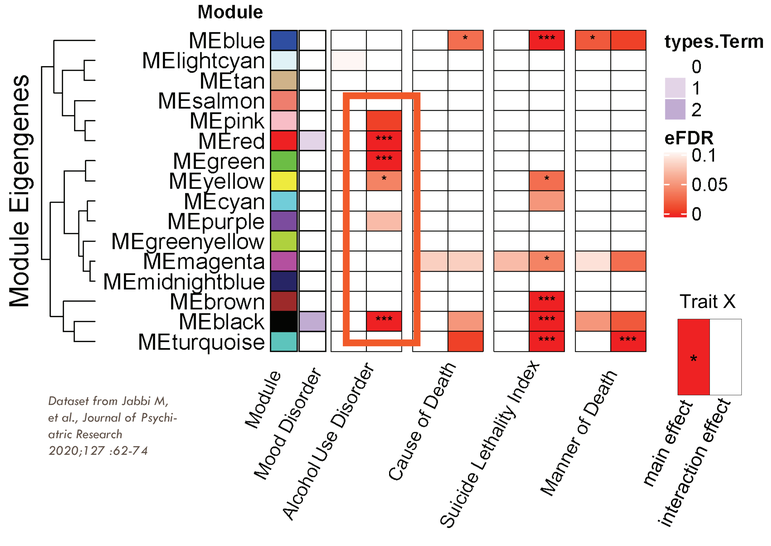
We examine publicly available amygdala transcriptome datasets from human and non-human animals:
- Careful replication of previous results (workflow shown above)
- Volcano plot demonstrates concordance with original results: 75% of differentially expressed genes (DEGs) were recovered

WGCNA identifies the gene expression network

Weighted correlation network analysis (WGNCA) is a popular analysis for finding clusters (modules) of highly correlated genes, for summarizing such clusters using the module eigengene and relate modules to one another or to external sample traits.

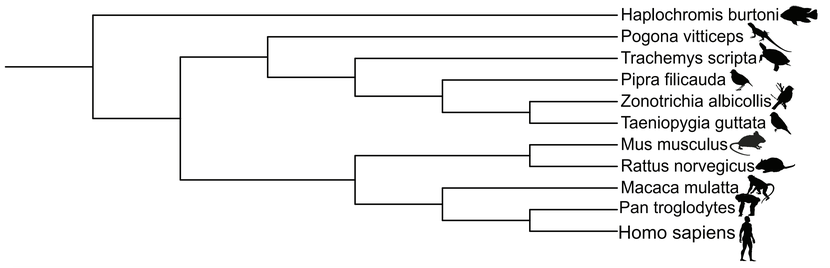


Linear modeling analysis reveals gene expression modules with interactions between psychiatric and substance use disorders

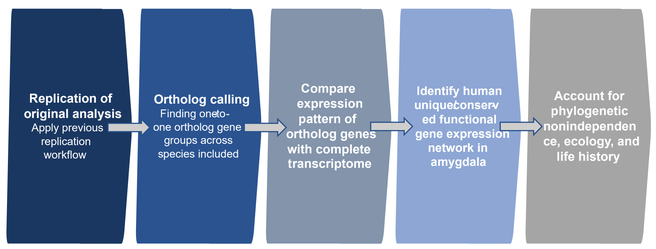


Dataset from Jabbi M, et al., Journal of Psychiatric Research 2020;127 :62-74

Phylogenetic comparative analysis of amygdala transcriptomes to identify the evolutionary origins of gene expression modules dysregulated in psychiatric and substance use disorders

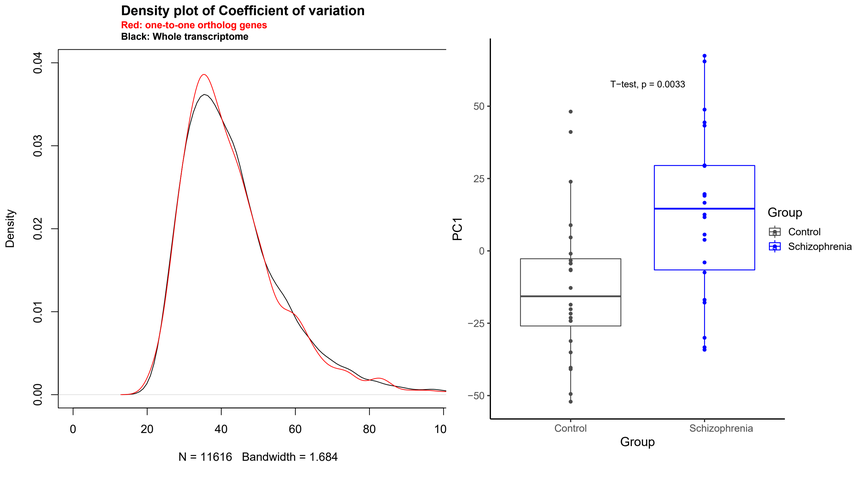


To provide fundamental explanations for the extreme complex phenotypes of psychiatric disorders, we set to compare the amygdala transcriptome (workflow shown below) across vertebrates. This approach will not only help us to understand how these phenotypes are evolved but also help with identifying the human-specific gene expression network dysregulated in psychiatric disorders.



Preliminary results: Primate-specific analysis

- 3877 one-to-one orthologs show similar variance distribution as the complete transcriptome(bottom right)
- PCA of orthologous gene set reveals that PC1 separates patients from controls even though the complete transcriptome does not (bottom left: box plots for of PC1 for both complete transcriptome and orthologous set)



Conclusions

-We can identify dysregulated gene sets with interactions between psychiatric and substance use disorders
- Comparative analysis is a promising approach for identifying both human-specific and conserved genes modules that are dysregulated in psychiatric disorders and substance use disorders

Acknowledgements:
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