

Identifying the shared genetic signal from genome-wide association studies of externalizing behavior and locomotor activity

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Network propagation approach to integrating cross-species GWAS signal



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Cell Reports

Article

Genome-wide association studies of human and rat BMI converge on synapse, epigenome, and hormone signaling networks

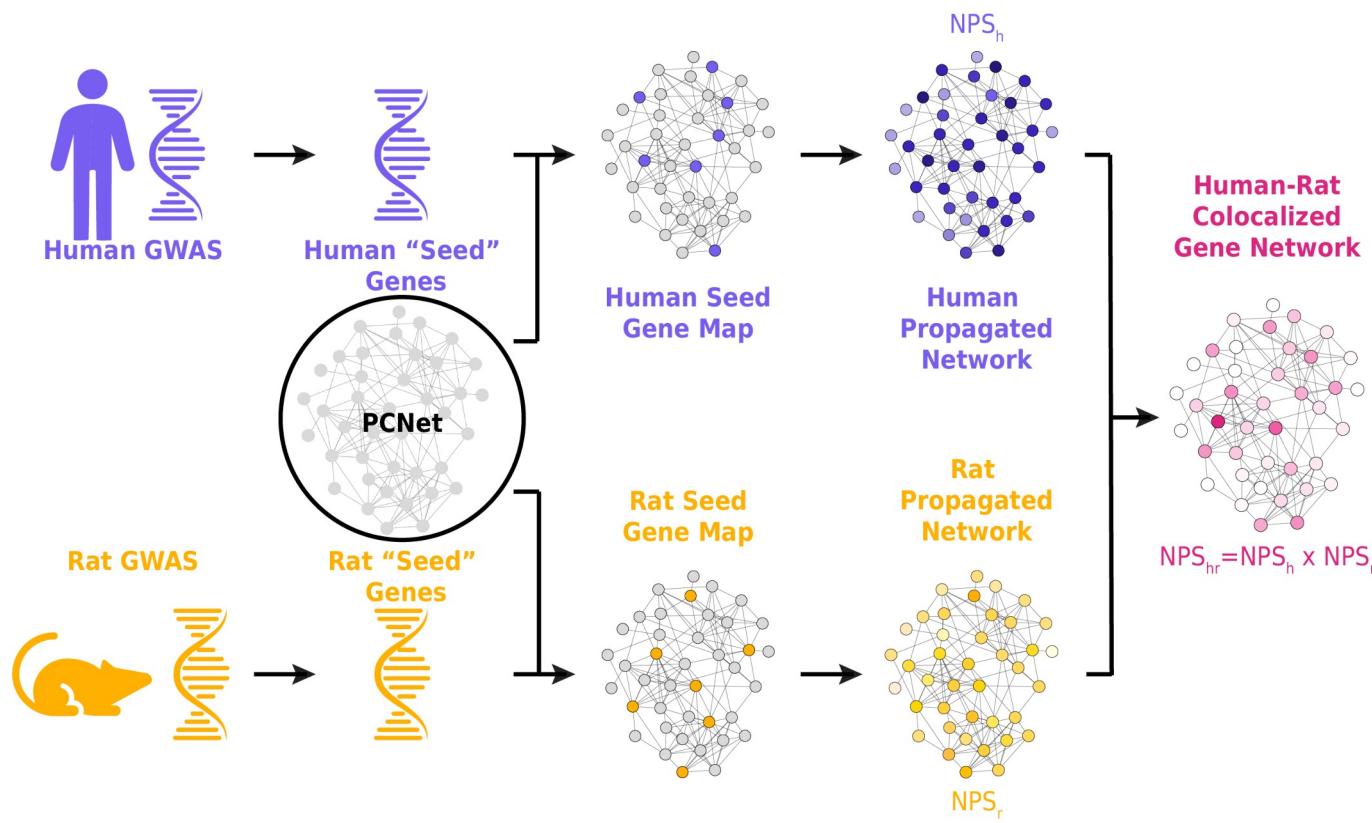
Graphical abstract

The graphical abstract illustrates the study's findings. It shows Human BMI GWAS (blue bar chart) and Rat BMI GWAS (purple bar chart). These results are integrated into a "Propagated Human Network" (blue circles) and a "Propagated Rat Network" (pink circles). A central "Conserved BMI Network" (orange circles) is identified where the two networks overlap. This network is further refined into a "Conserved BMI System Map" (orange circle), which includes nodes for "Synaptic Signaling" (yellow circle) and "Hormone Signaling" (red circle), and is connected to the Epigenome (pink circle).

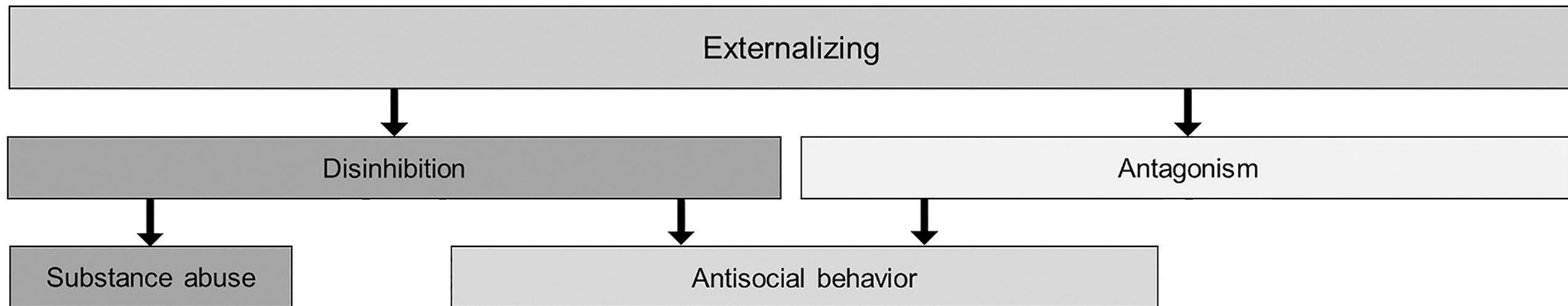
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In brief
Wright et al. identify a conserved molecular network underlying body mass index in humans and rats. Genes in this network, which are also associated with body-size phenotypes in mice, describe key processes including neuronal, epigenetic, and hormonal regulation. This work advances a general paradigm for cross-species GWAS translation.



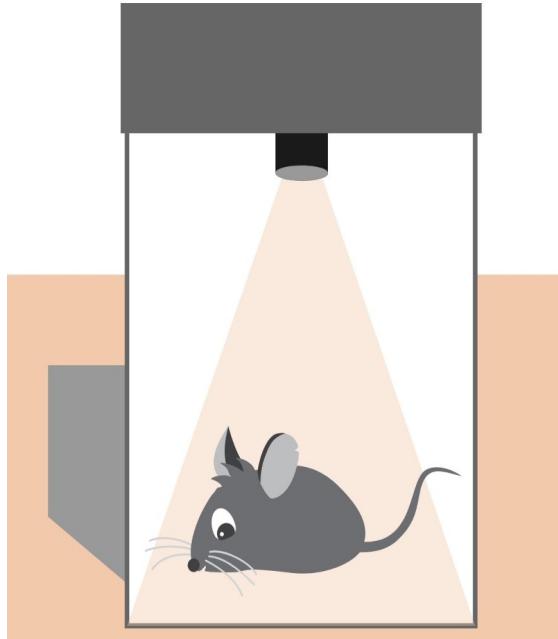
What is externalizing behavior?



Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): II. Externalizing superspectrum

Robert F. Krueger¹, Kelsey A. Hobbs¹, Christopher C. Conway², Danielle M. Dick³, Michael N. Dretsch⁴, Nicholas R. Eaton⁵, Miriam K. Forbes⁶, Kelsie T. Forbush⁷, Katherine M. Keyes⁸, Robert D. Latzman⁹, Giorgia Michelini¹⁰, Christopher J. Patrick¹¹, Martin Sellbom¹², Tim Slade¹³, Susan C. South¹⁴, Matthew Sunderland¹³, Jennifer Tackett¹⁵, Irwin Waldman¹⁶, Monika A. Waszczuk¹⁷, Aidan G.C. Wright¹⁸, David H. Zald¹⁹, David Watson²⁰, Roman Kotov¹⁷; HiTOP Utility Workgroup*

Novelty-induced exploratory locomotion



Measurement: Total distance traveled by the rat during open field test in novel location.

Implications: High sensation seeking is measured by high novelty-induced exploratory locomotion. Novelty-induced exploratory locomotion can be indexed using total distance in open field.

Alignment to externalizing: high sensation seeking is a key predictor of



| Lab | Short hand | Length | Method | Mean Age (days) |
|-----------------|------------|--------|-------------|-----------------|
| Hao Chen | TN | 15 min | video | 32 |
| Shelly Flagel | UMICH | 15 min | | 77 |
| Peter Kalivas | MUSC | 15 min | beam breaks | 68 |
| Suanne Mitchell | OHSU | 15 min | | 90 |
| David Dietz | NY | 18 min | | 61 |
| Tom Jhou | UMD | 20 min | | 90 |

Genomic structural equation modeling

nature
human behaviour

ARTICLES

<https://doi.org/10.1038/s41562-019-0566-x>

Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits

Andrew D. Grotzinger^{ID 1*}, Mijke Rhemtulla², Ronald de Vlaming^{ID 3,4}, Stuart J. Ritchie^{5,6},
Travis T. Mallard¹, W. David Hill^{5,6}, Hill F. Ip^{ID 7}, Riccardo E. Marioni^{5,8}, Andrew M. McIntosh^{ID 5,9},
Ian J. Deary^{5,6}, Philipp D. Koellinger^{3,4}, K. Paige Harden^{1,10}, Michel G. Nivard^{ID 7,11} and
Elliot M. Tucker-Drob^{1,10,11}

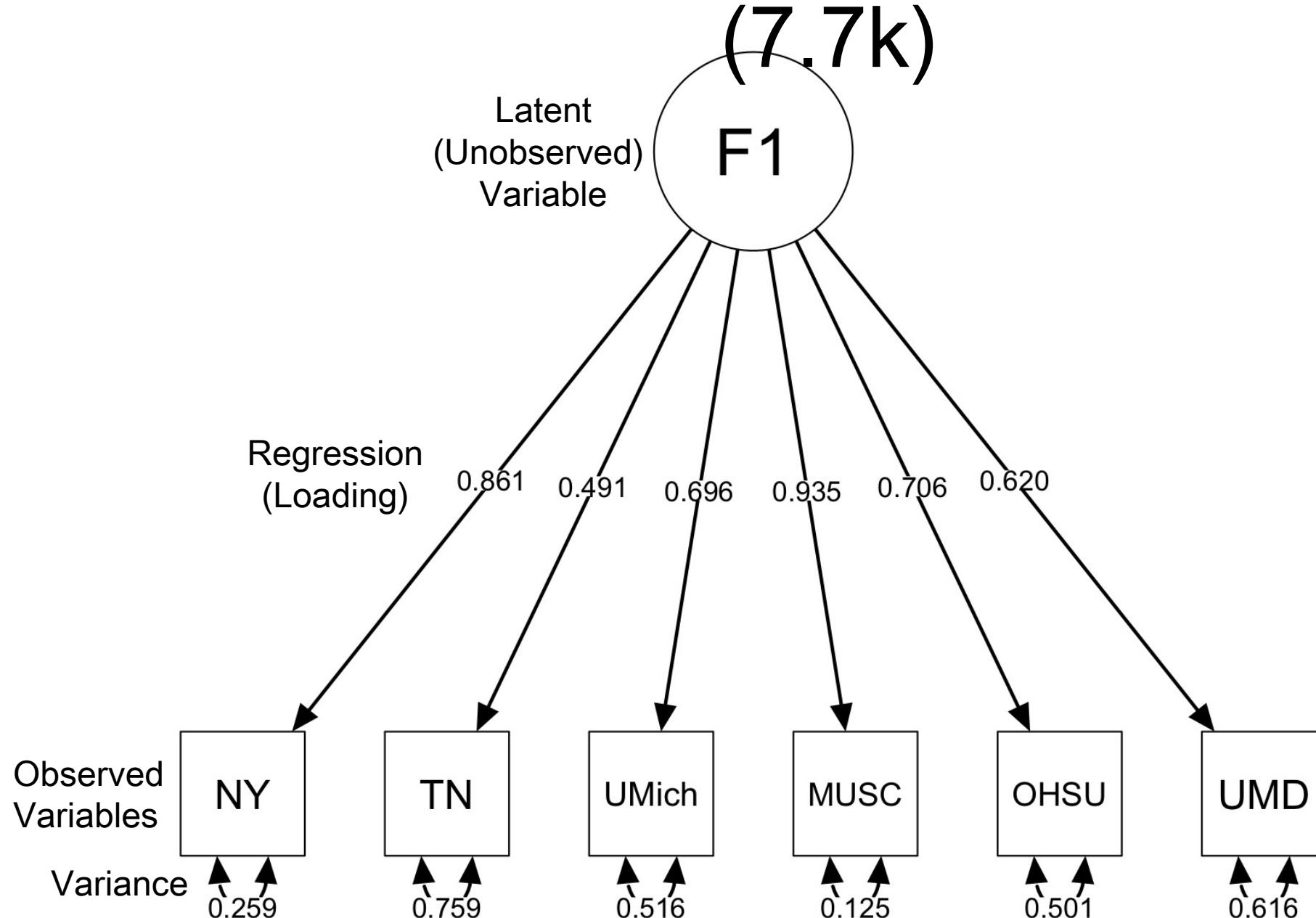
Genomic Structural Equation Modeling: method used to analyze the joint genetic architecture of traits based on variance and covariance between the observed traits

Common Factor: flexible model where observed variables share variance due to an underlying latent variable or factor

Multivariate analysis of locomotor activity (7.7k)



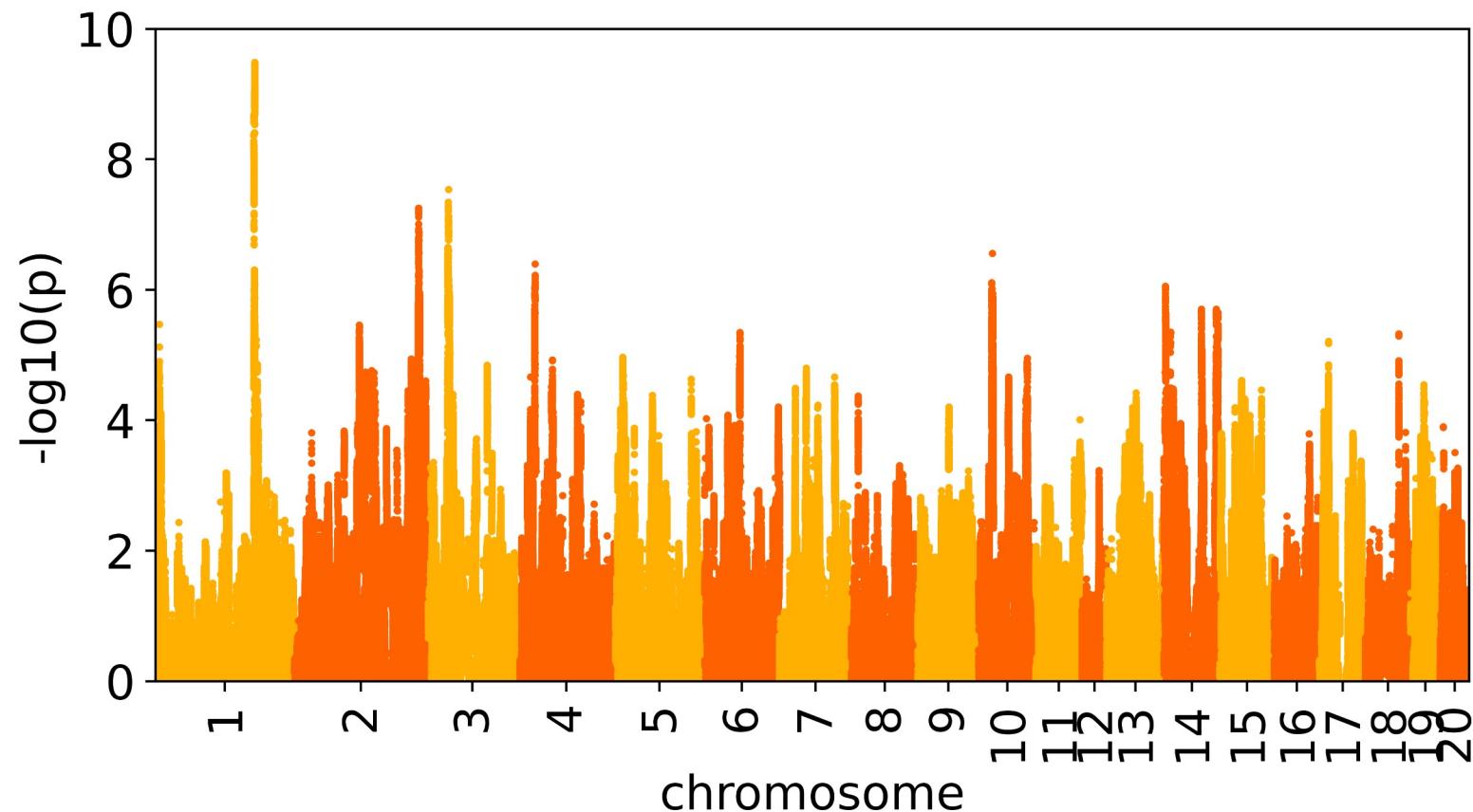
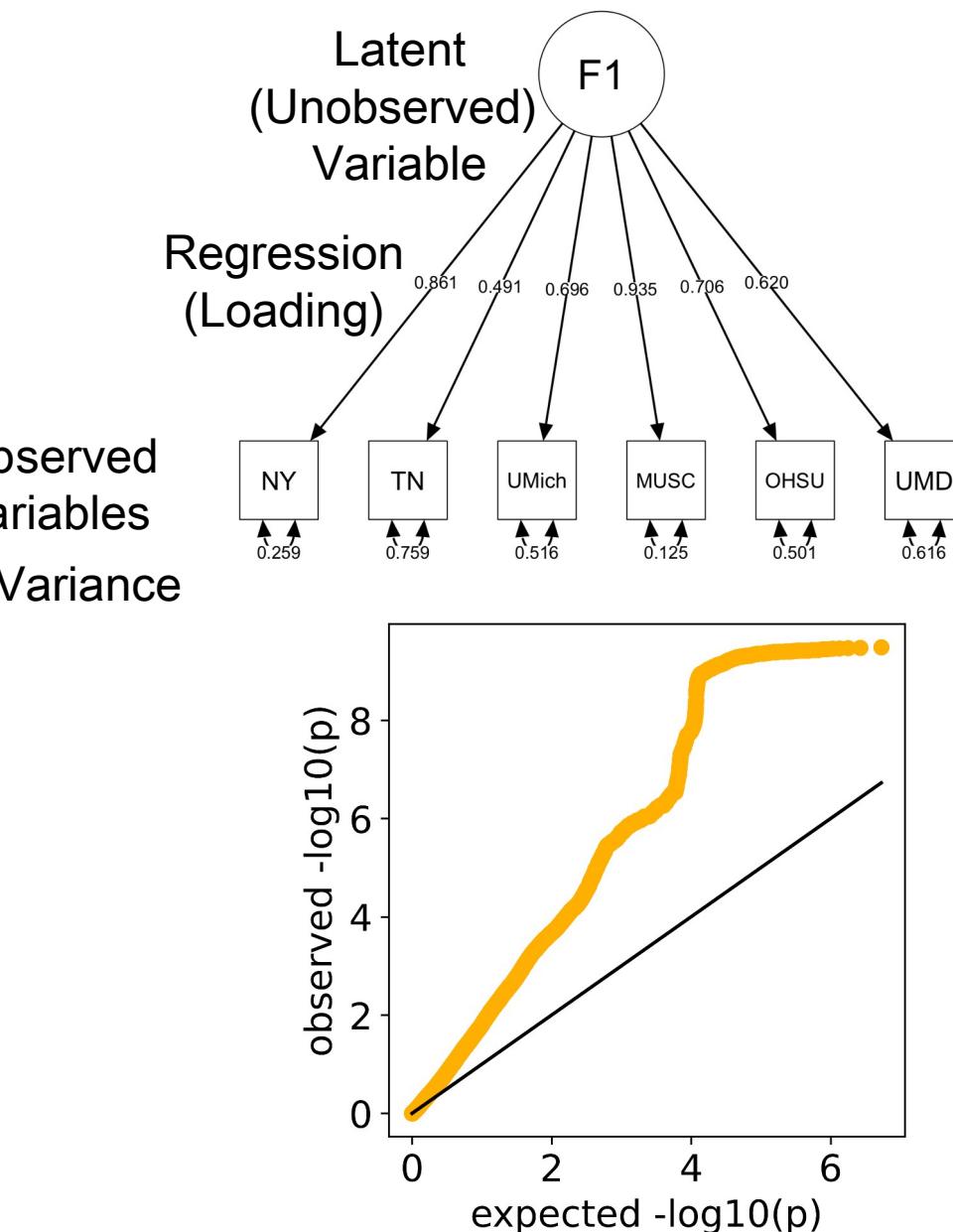
Apurva Chitre



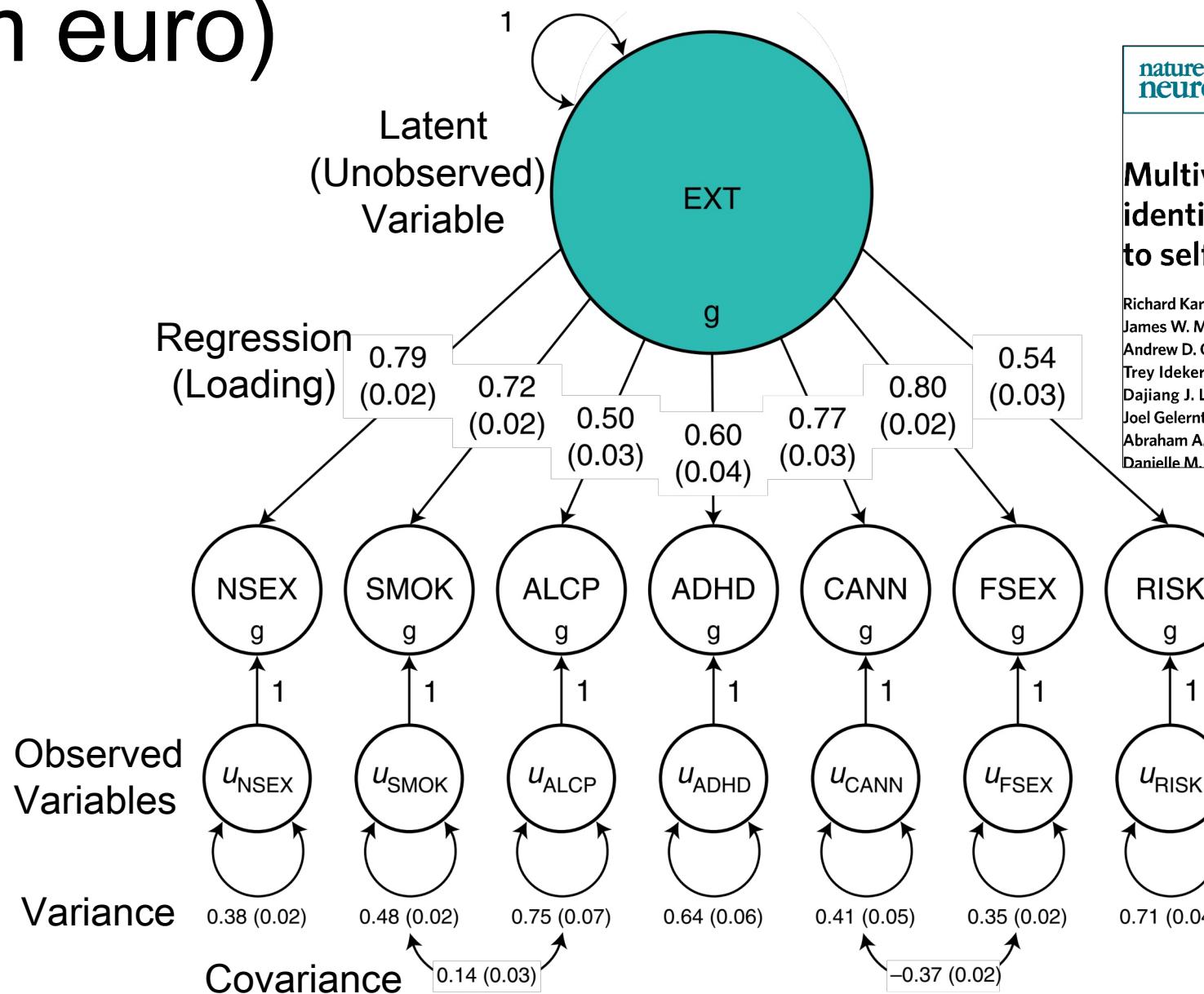
Multivariate analysis of locomotor activity



Apurva Chitre



Multivariate analysis of externalizing behavior (1.5m euro)



nature
neuroscience

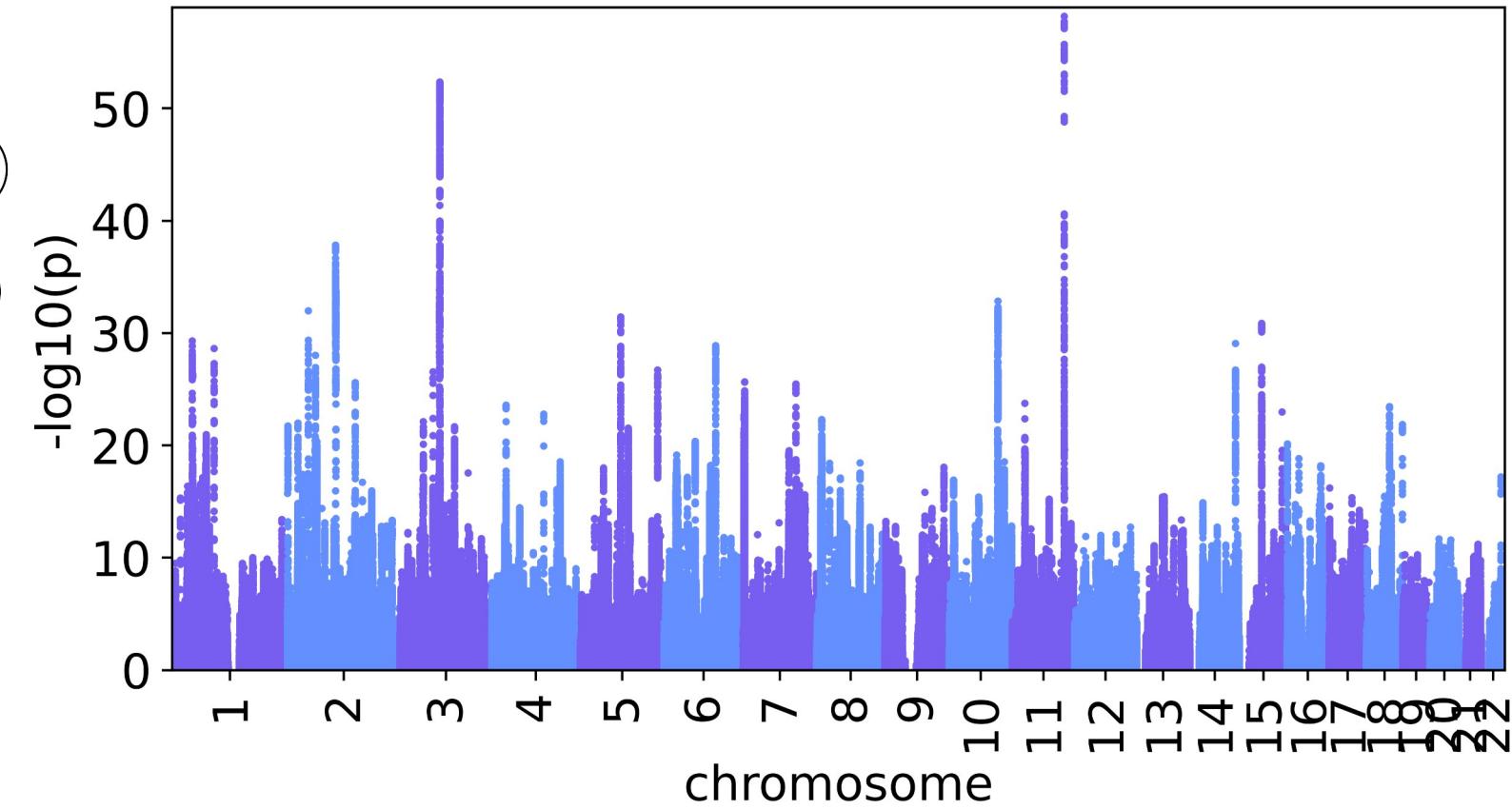
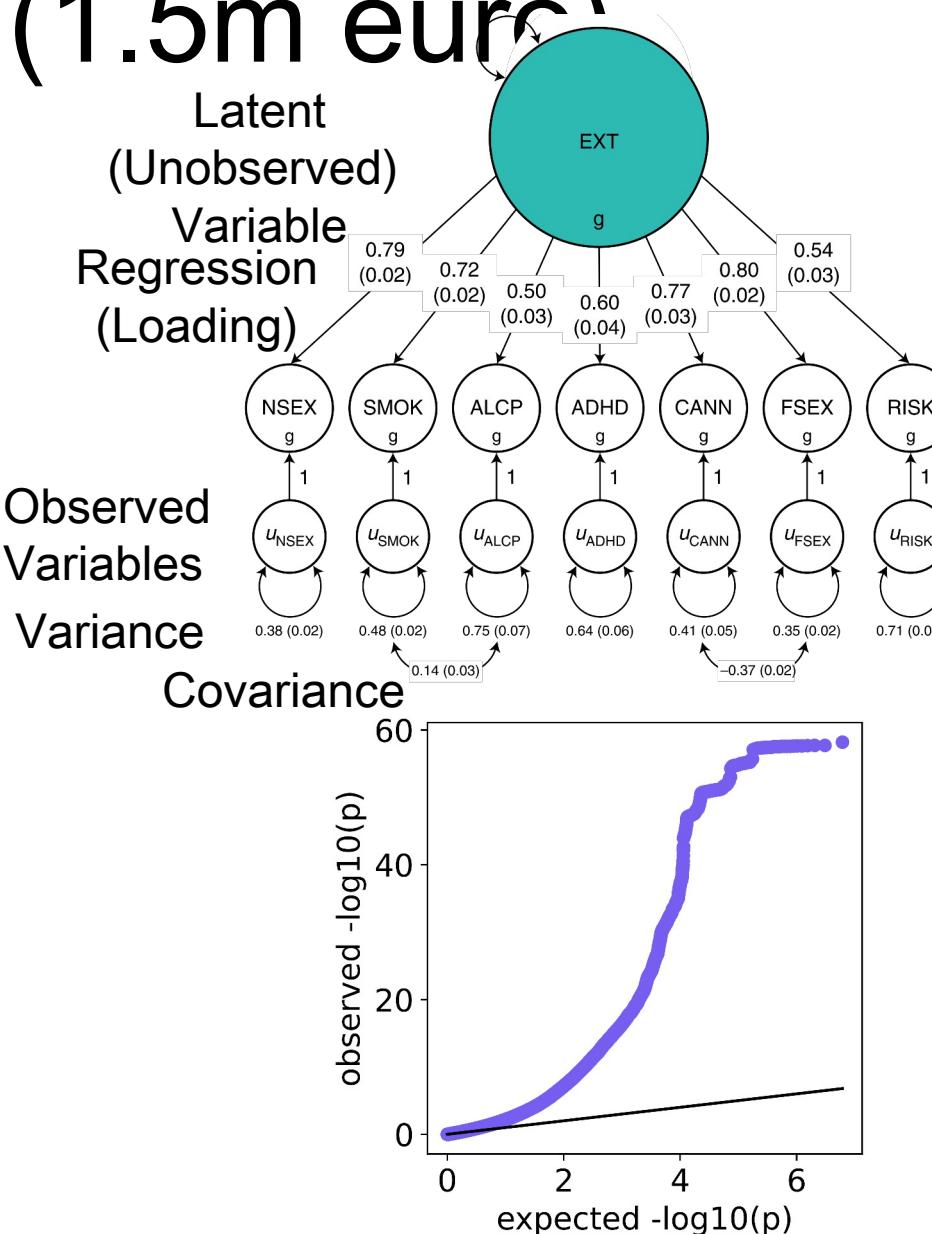
ARTICLES

<https://doi.org/10.1038/s41593-021-00908-3>

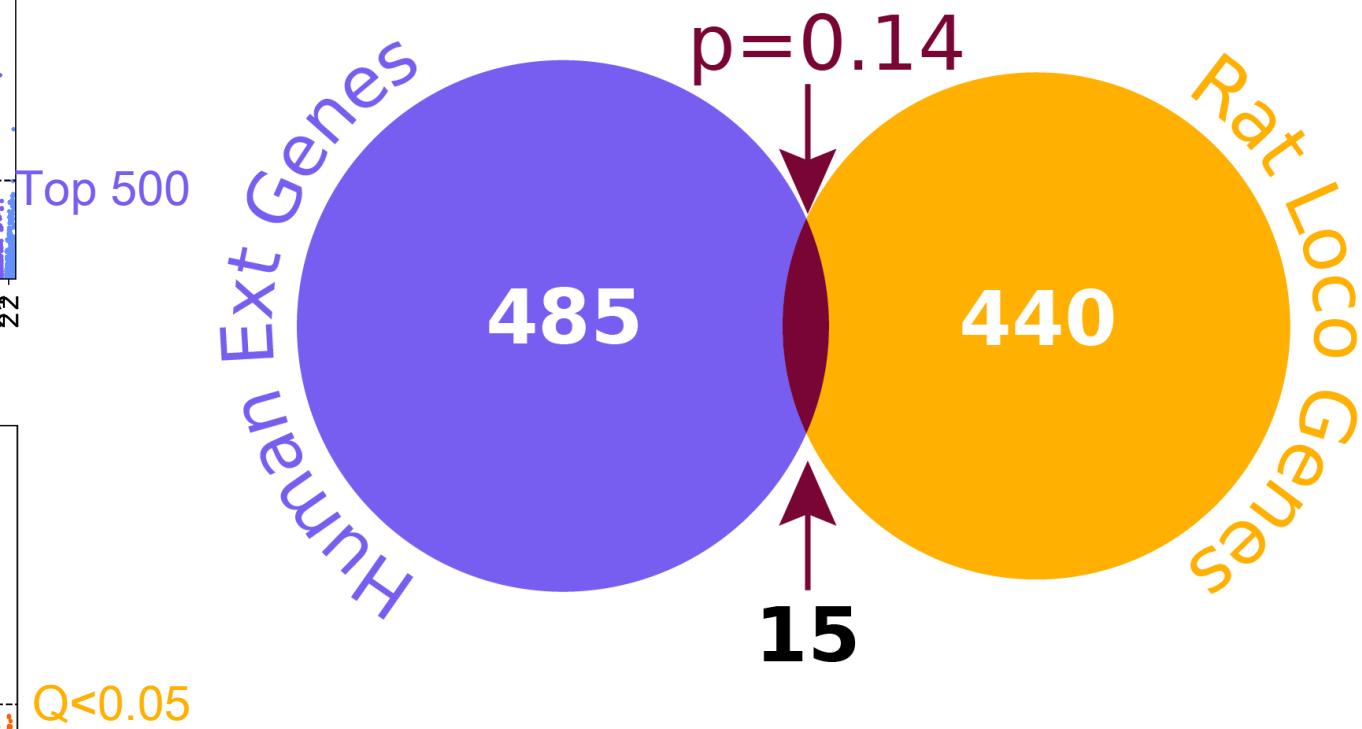
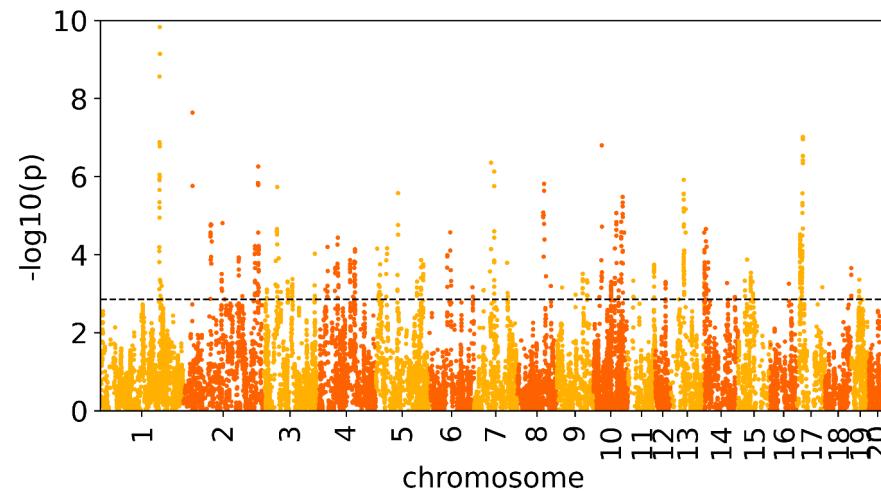
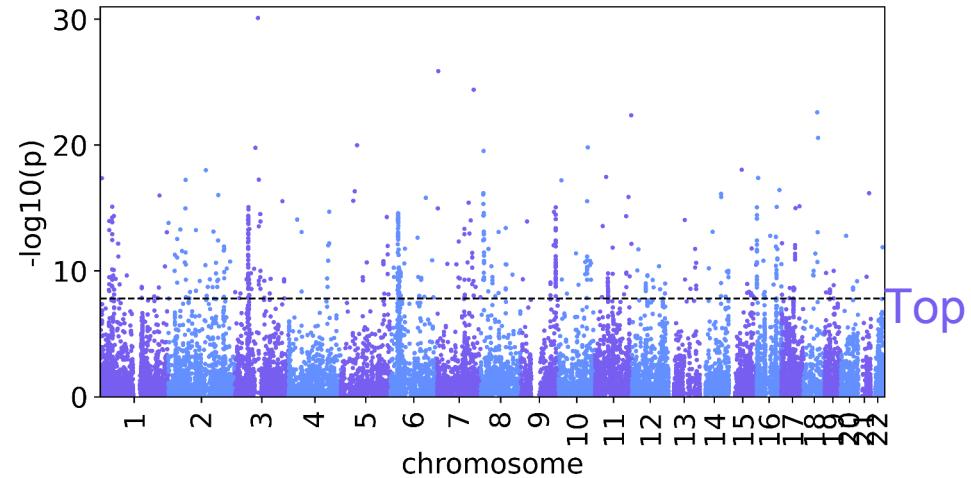
Multivariate analysis of 1.5 million people identifies genetic associations with traits related to self-regulation and addiction

Richard Karlsson Linnér^{1,41}, Travis T. Mallard^{2,41}, Peter B. Barr^{3,41}, Sandra Sanchez-Roige^{4,5,41}, James W. Madole², Morgan N. Driver⁶, Holly E. Poore⁷, Ronald de Vlaming¹, Andrew D. Grotzinger¹², Jorim J. Tielbeek⁸, Emma C. Johnson⁹, Mengzhen Liu¹⁰, Sara Brin Rosenthal¹¹, Trey Ideker¹², Hang Zhou^{13,14}, Rachel L. Kember^{15,16}, Joëlle A. Pasman¹⁷, Karin J. H. Verweij¹⁸, Dajiang J. Liu^{19,20}, Scott Vrieze¹⁰, COGA Collaborators*, Henry R. Kranzler^{15,16}, Joel Gelernter^{13,14,21,22}, Kathleen Mullan Harris^{23,24}, Elliot M. Tucker-Drob^{2,25}, Irwin D. Waldman^{7,26}, Abraham A. Palmer^{14,27,42}, K. Paige Harden^{2,25,42}, Philipp D. Koellinger^{1,28,42} and Danielle M. Dick^{1,3,6,42}

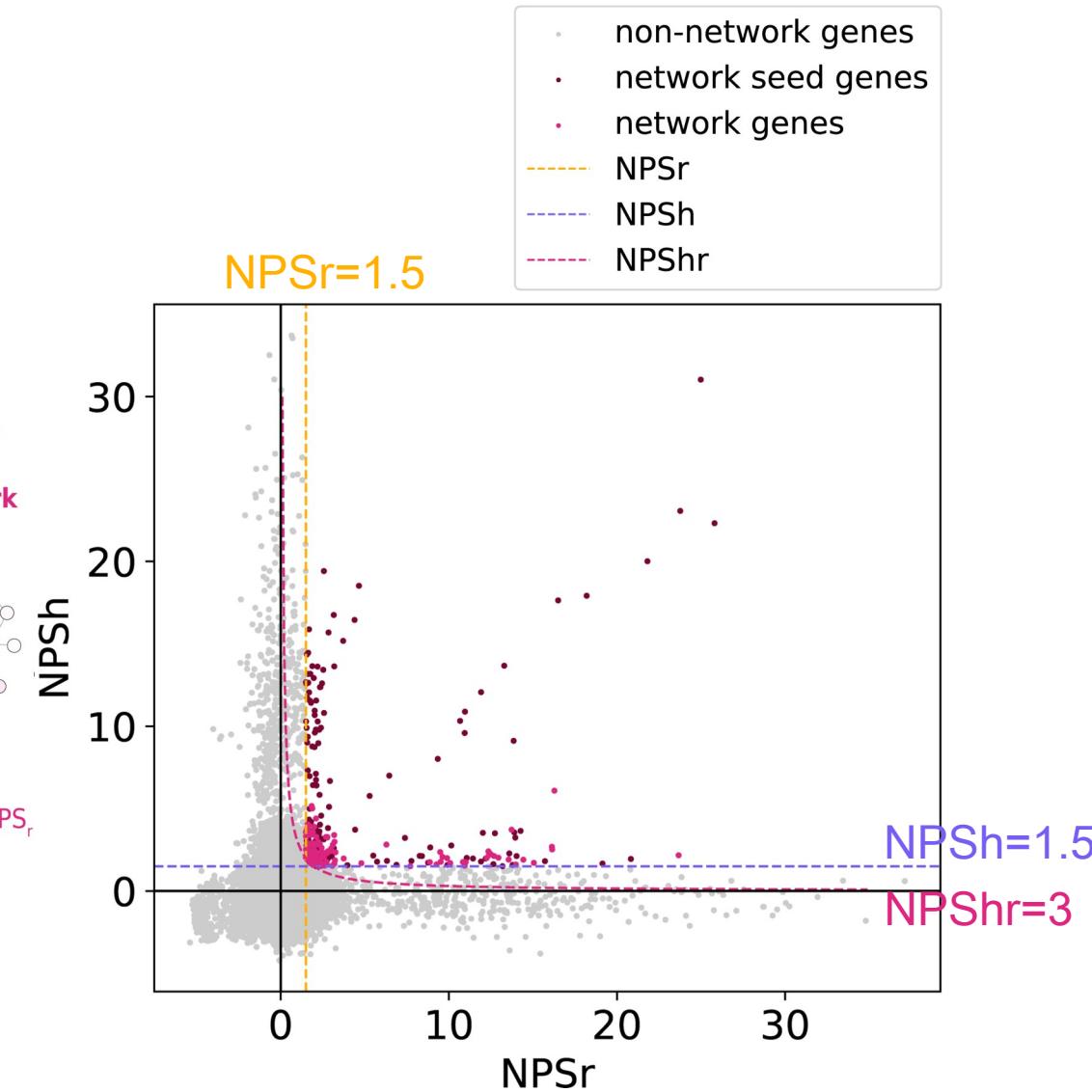
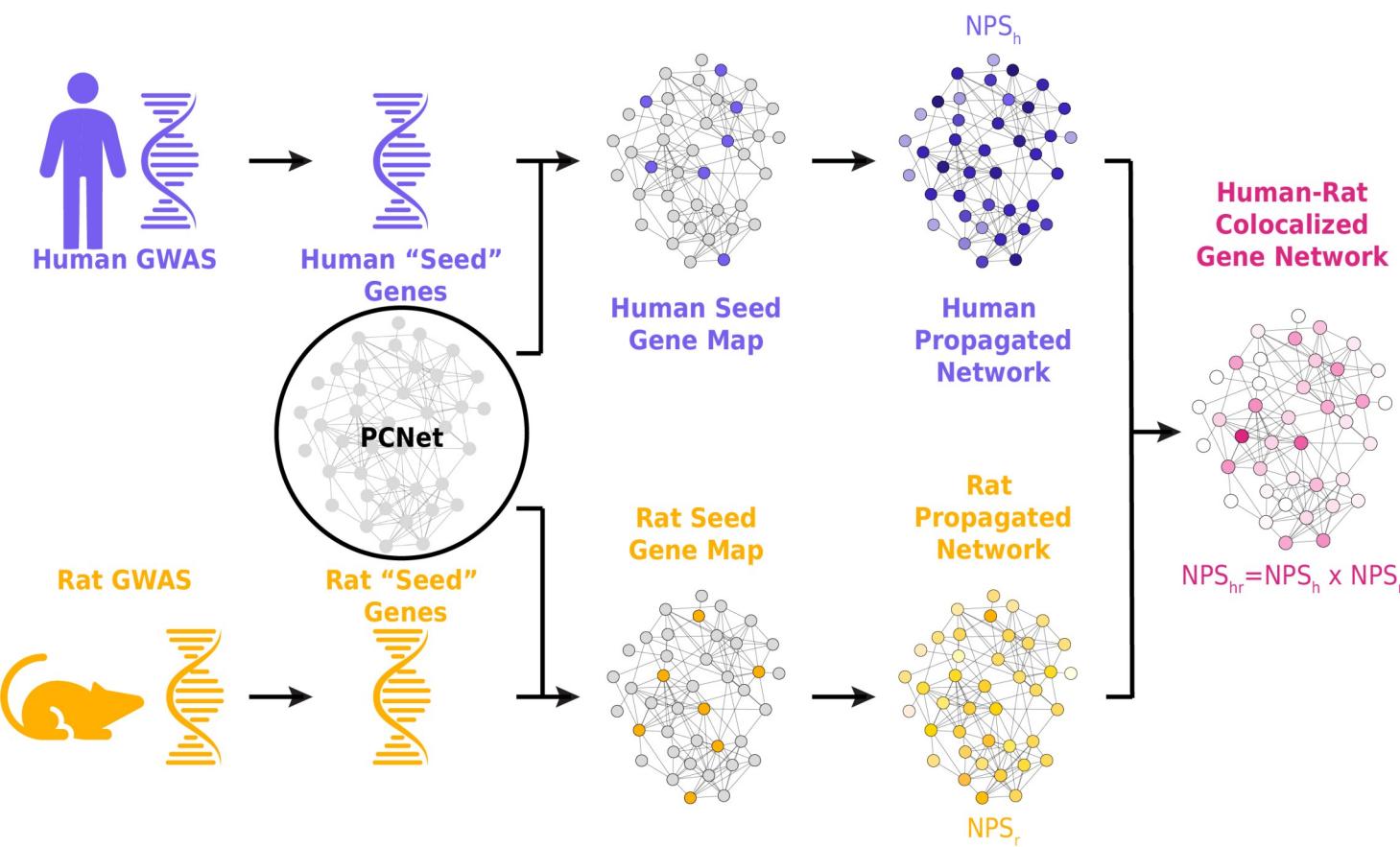
Multivariate analysis of externalizing behavior (1.5m euro)



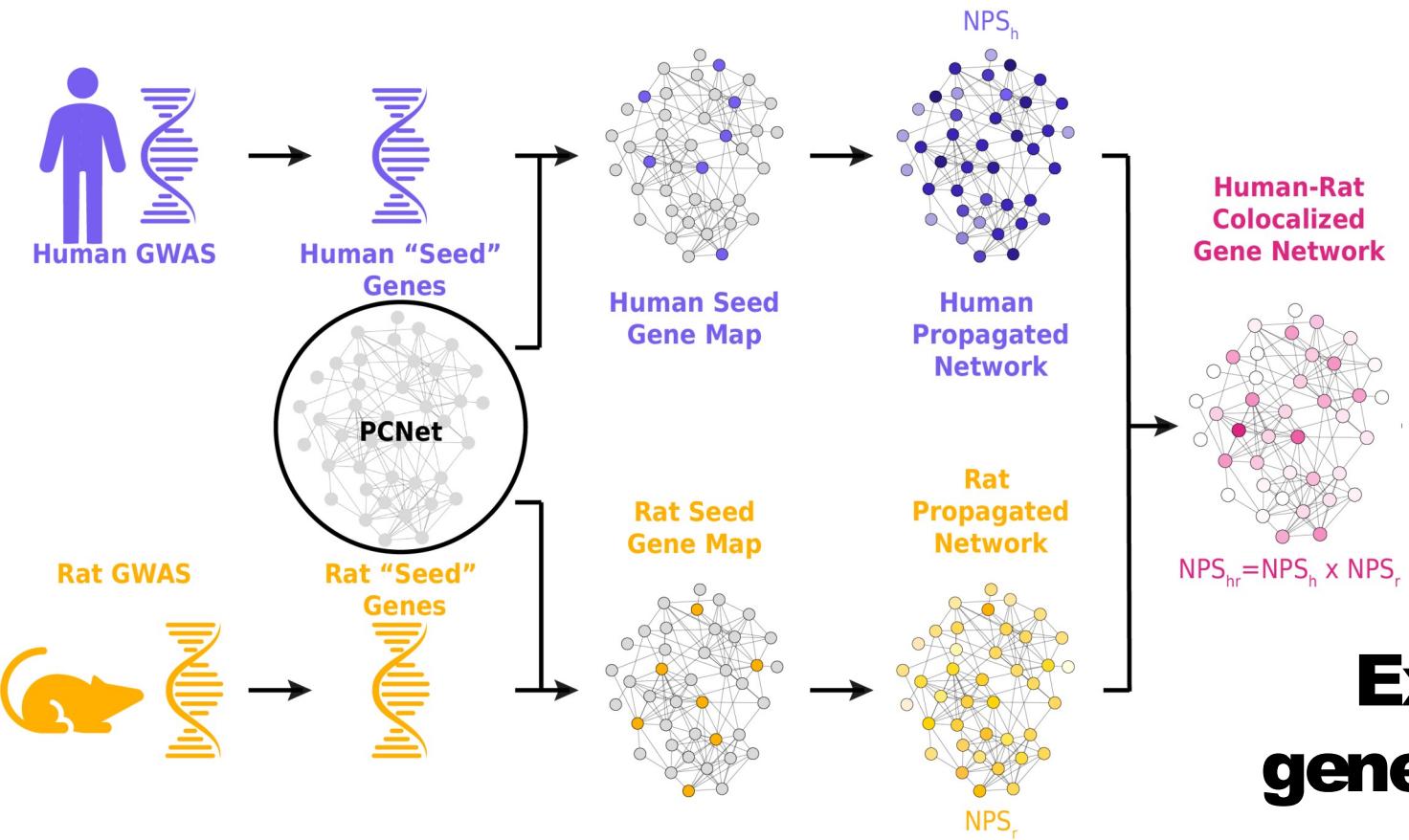
Externalizing and locomotor share 15 “seed” genes



Network propagation of externalizing and locomotor seed genes

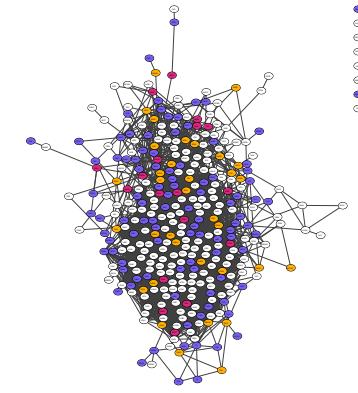
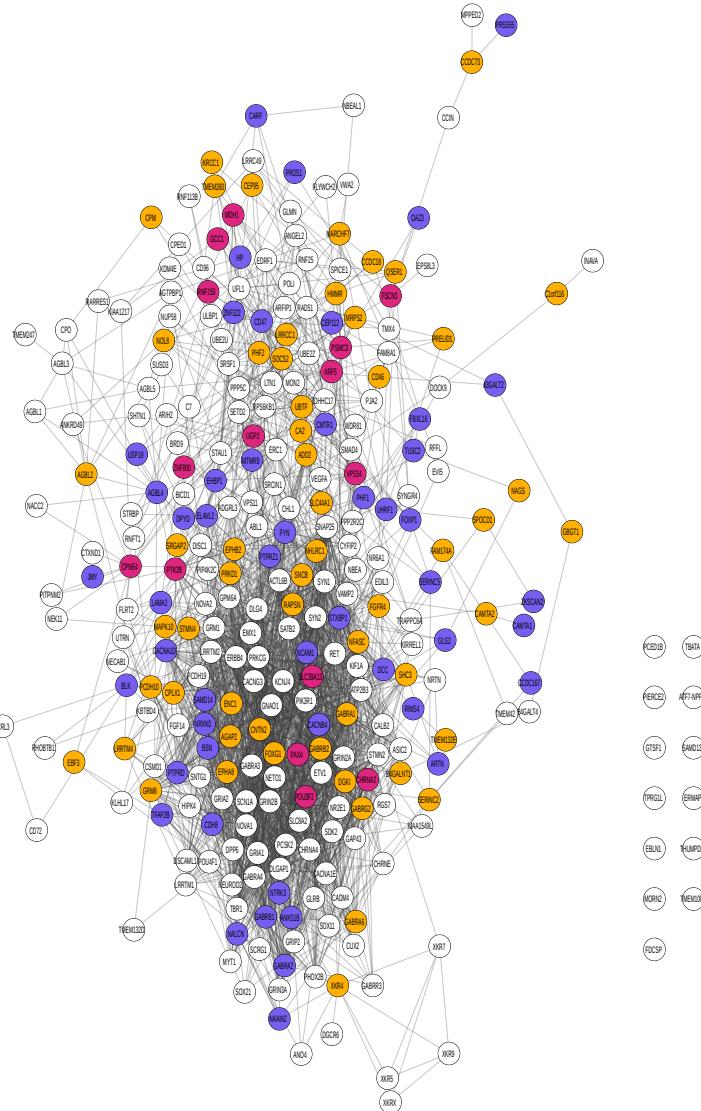


Network propagation of externalizing and locomotor seed genes



Externalizing and Locomotor genes are significantly more network colocalized than expected.

The Externalizing-Locomotor Network

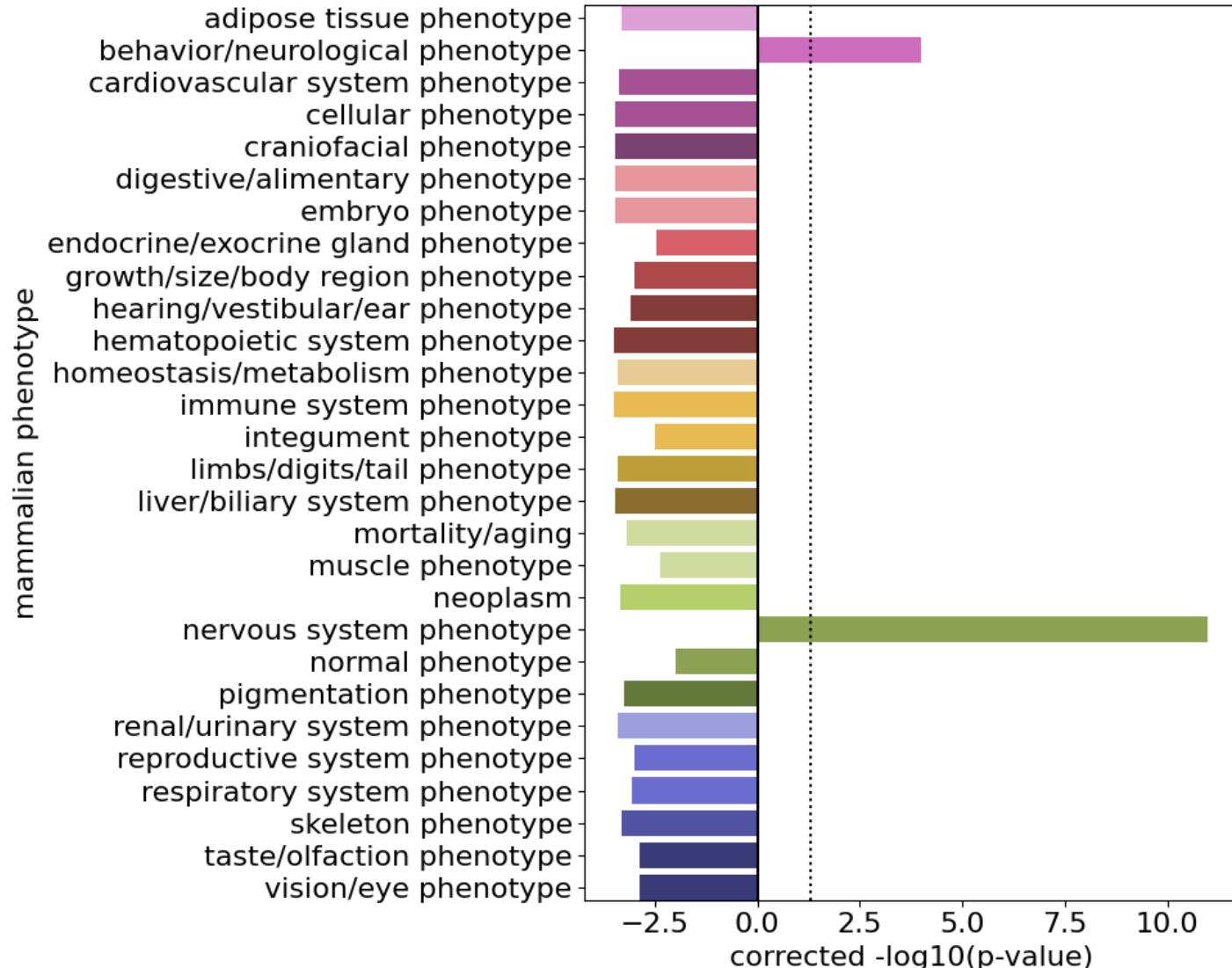


Nodes: 299
only locomotor seeds: 57
only externalizing seeds: 50
Shared seeds: 14
Edges: 3580

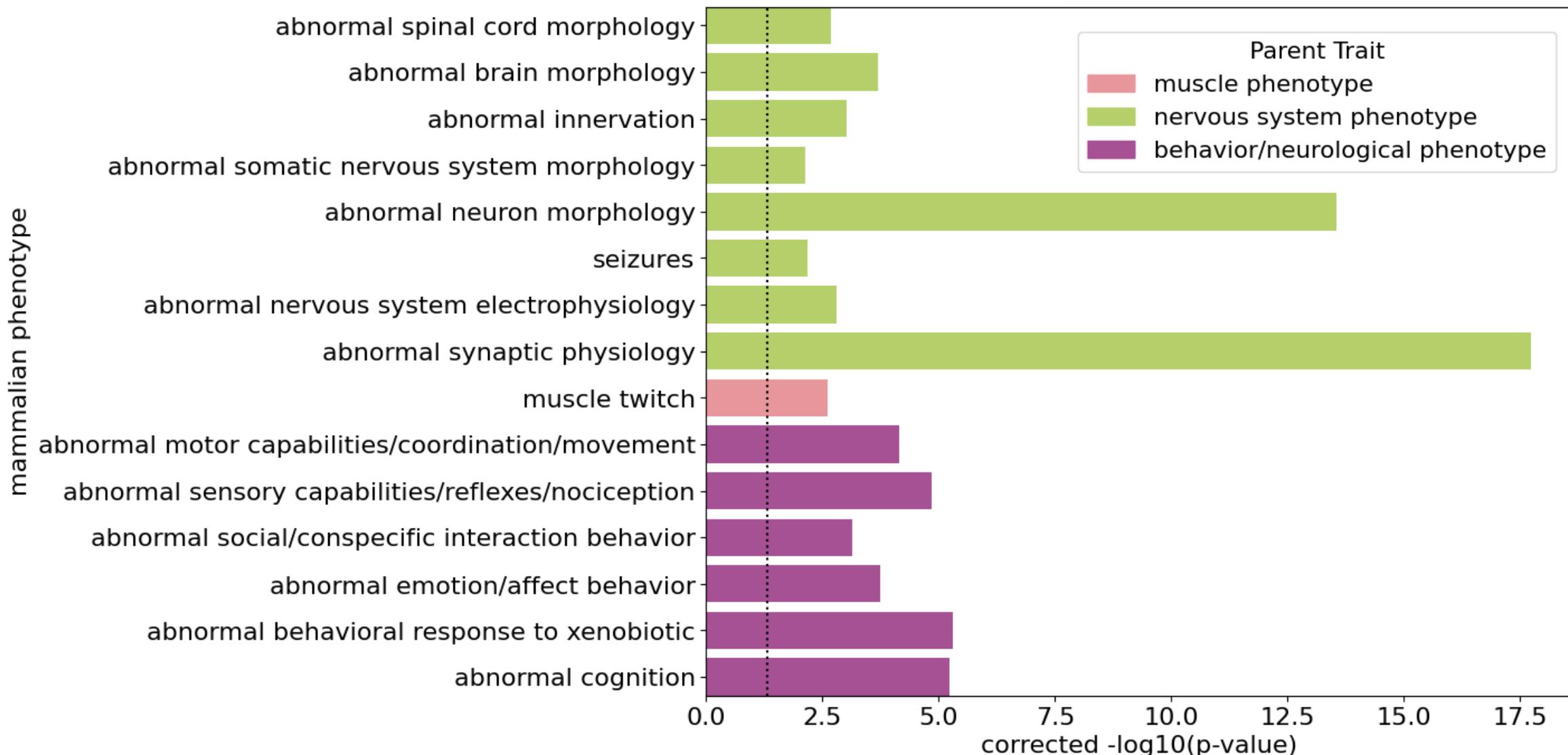
Validation using the Mouse Genome Informatics Database

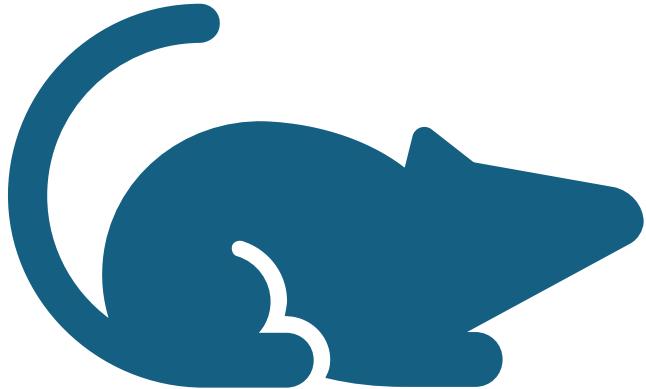


- manually curated genotype-phenotype database based on molecular perturbations
- uses the Mammalian Phenotypes Ontology
 - hierarchical structure
- significantly behavioral and



Validation using the MGI





Conclusions

- GWAS of externalizing behavior and locomotor activity identify numerous genes via MAGMA analysis, of which only 15 overlap
- Network propagation and colocalization identifies a conserved externalizing-locomotor network, with significantly higher overlap than is expected by chance
- The externalizing-locomotor network contains numerous genes related to neuropsychiatric function, suggesting conserved genes mediating both processes
 - This function is validated in the MGI and the GWAS catalog

Acknowledgments



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Genetics, Genomics, and Epigenetics
of Substance Use Disorders in Outbred Rats



National Institute of
General Medical Sciences