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Getting the Run Around: Is the Locomotor Response to a Novel Environment Behavior Model a Model of Human Externalizing Behavior?

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Externalizing refers to a spectrum of behaviors and disorders related to impulse control that are associated with a variety of behaviors across the lifespan. In rodents, novelty-induced exploratory locomotion is among the most heavily studied behaviors and has been proposed as a model of human externalizing behavior; however, this hypothesized relationship has been difficult to objectively evaluate using empirical data. We leveraged biological knowledge networks to identify overlapping genetic signal from GWAS of externalizing in humans and locomotor behavior in heterogeneous stock (HS) rats. Specifically, we used findings from multivariate analyses of externalizing in ~1.5 million humans subjects, and of total distance traveled in the open field in almost 10,000 HS rats. Gene-level analysis using MAGMA revealed few overlapping genes (n=15, p=0.14). However, after network propagation using the PCNet2.0 interactome, we found that the networks interconnecting these two traits showed substantial and highly significant overlap (p=1.25x10-5), suggesting that the underlying biology of these two traits is conserved across species. We validated our network with independent genetic perturbation data from the International Mouse Phenome Consortium. The shared network showed enrichment for genes that function in the nervous system and that are associated with behavioral traits. To identify specific gene communities with conserved function across species, we identified modules within the conserved network using hierarchical clustering. These modules identified multiple functions including transmitter-gated channels, axonogenesis, phospholipid scrambling, and protein side-chain deglutamylation. Our results provide genetic evidence supporting the claim that rodent locomotor activity models aspects of human externalizing behavior, supporting a large body of work that has used locomotor behavior to probe the molecular genetic basis of substance use disorders.