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

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In rodent models, novelty-induced exploratory locomotion has been proposed as a model of human externalizing behavior. However, there is little empirical data available that can rigorously evaluate this assertion. We used biological knowledge networks to investigate the overlapping genetic signal from these parallel traits. We use findings from a multivariate genome-wide association study (GWAS) of externalizing in ~1.5M human subjects, and a meta-analysis GWAS of total distance traveled in the open field in ~7.7K heterogeneous stock rats. After translating these data into gene-level signal using MAGMA, we found little overlap (p=0.5) between the lists of implicated genes. However, after we projected these gene lists into a network space using a random walk

approach (NetColoc), we identified a highly significant overlap between these two propagated networks (p=1.8x10^{-9}). The overlapping gene sets highlighted common mechanisms, including neurological development and synaptic signaling, particularly GABAergic signaling. We also identified species-specific processes, including mitochondrial energy production and muscular and skeletal development in rats, and amino acid metabolism and histone H3K9 demethylase activity in humans. This study supports a biological relationship between locomotor activity and externalizing, and demonstrates a broadly applicable paradigm for empirically determining whether and how phenotypes measured in model species recapitulate uniquely human behavioral and psychiatric traits.