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Compulsive behaviors in *C. elegans* as a model to study Substance Use Disorders

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The neural substrate(s) underlying risky decision-making and compulsivity despite the catastrophic consequences is a fundamental characteristic of Substance Use Disorders (SUD) and comorbidities but the molecular mechanism of these behaviors remains largely elusive. To model the development of compulsive engagement of reinforcing stimuli, we exploit two distinct motivated behaviors against aversive stimuli. The development of compulsivity is hypothesized to be imbalanced between enhanced motivational state for reward and loss of controlling avoidance program. To address sophisticated behavioral paradigms in the simplest and most completely defined connectome with fast genetic workflow, we used *C. elegans* as a model. We represented male copulation behavior, pursuing natural reward such as sexual drive, against aversive blue light irritant and ethanol seeking, which hijacked brain reinforcement circuits in mammals, over the aversive chemical barrier respectively.

We conducted the High-throughput screen to isolate genetic variants that increase the neuromodulation of behavioral arousal at downstream of sensory perception possibly affecting the stimulation threshold of interneurons and predispose the animal to SUD. By genetic manipulations, microsurgeries, electrophysiological recordings, and optogenetic control, we discovered the neuropeptide corticotropin-releasing factor (CRF) receptor ortholog GPCR in *C. elegans* enhance motivational state resulted in compulsive engagement which *C. elegans* NALCN (Sodium leak channel) activity is required for. To elucidate the molecular pathway, we are screening for differentially expressed genes in constitutively activated stress model and pursuing novel targets by characterizing two additional genetic variants representing compulsive engagement in both sexual behavior and ethanol seeking.