Illuminating the neural circuitry underlying context-dependent reward-seeking

By Julia Yu
(Supervisor: Dr. Jonathan Britt)

Our memory of a painful or pleasurable experience is defined by the surrounding context. Contexts provide structure and meaning to our experiences and affect how we interpret environmental cues. Considering that a given environment may be associated with both positive and negative events and that the emotional significance attached to a context can change over time, how do we judge when a stimulus might be relevant for signalling reward or danger? The ability to use contextual cues to respond flexibly across different situations is critical for a creature's survival, and a major goal in neuroscience is to understand how the brain acquires and uses these associations to generate adaptive behaviours.

Many mental illnesses involve deficits in the contextual regulation of behaviour, including drug addiction, schizophrenia, and post-traumatic stress disorder[1]. These diagnoses are often concurrent and are a leading cause of disability in Canada[2]. A compelling explanation for the high degree of comorbidity between substance use and psychiatric disorders is that they may share a common brain mechanism. One well-studied brain area that has been linked to a number of psychiatric conditions is the nucleus accumbens (NAc), which integrates contextual, emotional, and motivational cues to coordinate goal-directed behaviour[3,4]. A predominant excitatory projection to the NAc comes from the ventral subiculum (vSub), the main output region of the hippocampus[5]. Neurons in the ventral hippocampus and NAc encode information about spatial contexts[6,7] and are excited by both positively- and negatively-valenced stimuli such as food and foot shock[8-10]. While much is known about how these regions function independently, it is unclear how they interact to govern motivated behaviours, such as when to seek out rewards or avoid danger.

Here, we used a method called optogenetics to determine whether hippocampal inputs to the nucleus accumbens are necessary for regulating motivated behaviours depending on the emotional valence of a context. By using lasers to activate light-sensitive proteins (opsins) expressed in specific cell types, optogenetics allows researchers to switch neurons on or off with millisecond precision in awake, behaving mammals[11]. We sought to address this question by silencing hippocampal projections to the NAc while rats engaged in reward-seeking behaviour measured by the number of lever presses made to obtain a food reward. Prior to behavioural training, I injected a virus in the vSub that drove expression of a light-activated, inhibitory proton pump under a promoter expressed by excitatory glutamatergic neurons (AAV9-CaMKIIα-ArchT-GFP). I next implanted optical fibres above the shell subregion of the NAc to enable light-induced inhibition of vSub axon terminals (**Fig. 1a**). Rats were then trained to lever press for food before undergoing auditory fear conditioning, in which a neutral tone is associated with an aversive outcome through repeated pairings with a mildly painful foot shock (**Fig. 1b**). Each animal was tested 24 and 48 hours later with and without optogenetic inhibition. If the hippocampus-to-accumbens pathway is responsible for

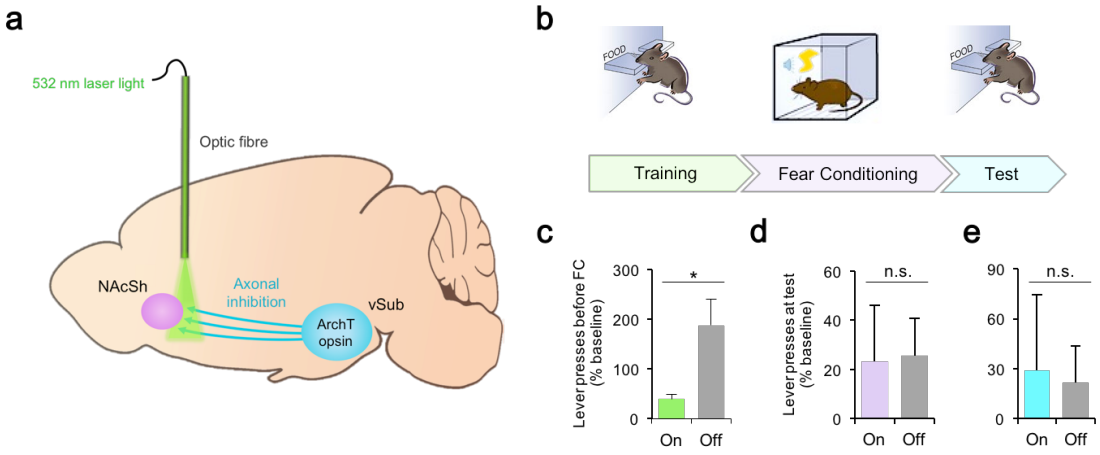
activating contextually relevant behaviours under bivalent conditions, then blocking vSub inputs in a context exclusively associated with the availability of food reward should reduce reward-seeking behaviour. Likewise, inactivating vSub terminals in a context associated with an aversive experience should block fearful behaviour and increase reward-seeking. We also asked if this pathway is involved in context-related fear learning by inhibiting during fear conditioning. If vSub-to-NAc afferents 're-wire' to dampen reward-seeking after an aversive event, then animals with these axons inhibited during fear conditioning should show less fear and lever-press more when tested without perturbation of this pathway.

We observed a significant decrease in reward-seeking when vSub-to-NAc projections were silenced before tone-shock exposure (**Fig. 1c**), raising the possibility that activity in this pathway may be required to initiate and sustain motivated responding in reward-predictive contexts. Interestingly, inhibiting these projections during fear conditioning did not disinhibit later reward-seeking when animals were tested without light, suggesting that plasticity between hippocampus-to-accumbens connections is not required for learning about the status of a context as a predictor of reward or pain (**Fig. 1d**). Lastly, vSub-to-NAc projections do not appear to be necessary for controlling motivated behaviours under aversive conditions, as inhibition did not affect lever-pressing after a shift in the emotional valence of a context from positive to negative (**Fig. 1e**). Together, our results indicate that hippocampal inputs to the nucleus accumbens may be essential for activating goal-directed behaviours in appetitive, but not aversive, contexts.

How might the hippocampus-to-accumbens pathway be important for promoting reward-seeking? The actions of dopamine and glutamate release in the NAc are necessary for sustaining motivated behaviour, and disrupting glutamatergic signalling by silencing hippocampal inputs may be enough to suppress motivated responding. This is consistent with the idea that aberrant processing of glutamatergic afferents to the nucleus accumbens from the hippocampus as well as the amygdala and prefrontal cortex may play a role in psychiatric disease states characterized by a dysregulation of dopamine[12-14].

In order to resolve the underlying pathophysiology of psychiatric disorders, we must first understand the neural circuits that regulate basic processes such as motivation and reinforcement learning. Many questions remain about how connections between brain regions that process bivalent stimuli such as the hippocampus and accumbens communicate to drive goal-directed action across diverse contexts. The powerful genetic tools available to today's neuroscientists are making it possible to start investigating these questions with unprecedented precision. Insights gained from a neural circuit-mapping approach carry far-reaching implications for the development of more specific therapeutic interventions to ultimately improve the lives of patients afflicted by mental illness.

Figure 1: Hippocampal Inputs to the Nucleus Accumbens Drive Motivated Responding to Appetitive but not Aversive Stimuli.



(a) Pathway-specific targeting of hippocampal afferents to the nucleus accumbens using optogenetics: virally-mediated expression of the light-sensitive inhibitory proton pump ArchT in the ventral subiculum of the hippocampus (vSub) with optic fibre implantation above the nucleus accumbens shell (NAcSh).
(b) Rats learned to lever-press for food before receiving repeated tone-foot shock pairings in the same chamber (fear conditioning). Reward-seeking behaviour was measured in two subsequent test sessions; each subject received one light-on session.
(c-e) Mean lever presses before and after tone-shock exposure, expressed as a percentage of the session immediately before fear conditioning (baseline). Coloured bars correspond to the session in which rats received light inhibition. **(c)** Inhibiting vSub-to-NAcSh terminals reduced reward-seeking in photostimulated rats (On) relative to light-off controls (Off). **(d)** Rats that received light inhibition during fear conditioning did not differ from controls in the number of lever-presses made when tested without light. **(e)** Inhibiting this pathway did not affect motivated responding when tested after shifting the emotional valence of a context from appetitive to aversive.

N.s., not significant. *$p < .05$. Error bars, s.e.m. Schematic images in (b), modified from [15, 16].

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