Avoidance learning circuits: Basic mechanisms and implications for drug use and dependence

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Background: The tendency to attach negative emotional significance to events is a feature of multiple chronic pain, mood, and anxiety disorders, and a risk factor for continued dysfunction and compensatory drug use. Recent work suggests that such negative biases are learned adaptations implemented in medial frontal-striatal and frontal-brainstem circuits. These circuits determine the motivational significance of events—what we should pursue and what we should avoid—by integrating sensory information with memories of the past and expectations about the future. According to this view, chronic pain and mood disorders are similar in that they involve a vicious cycle of mutually reinforcing negative expectations and experiences, leading to a pattern of generalized avoidance.

Methods: I present two recent fMRI studies aimed at understanding two central features of negative expectancy-avoidance cycles—avoidance learning and confirmation biases—using pain as a model system. First, by combining computational circuit-dynamics modeling and fMRI, we examined how pain expectancies are compared with sensory input to generate prediction errors that drive avoidant behavior. Second, we examined expectancy effects on pain-related physiology and brain responses, and whether they produce a confirmation bias in learning that can lead to self-perpetuating 'vicious cycles.'

Results: Computational modeling applied to Study 1 revealed frontal-brainstem circuit dynamics underlying pain avoidance learning. The model suggests that pain expectancies are encoded in the ventromedial prefrontal cortex (vmPFC) and an associated striatal and parahippocampal circuit. Expectations are compared with pain-related input in the periaqueductal gray (PAG), which updates expectations in vmPFC and action policy information in the anterior cingulate (ACC). Animal models show parallel effects, and further implicate the opioid system as critical for canceling out expected pain signals in the PAG—a process critical for preventing positive feedback cycles of hyper-avoidance. As long-term opioid likely results in downregulation of opioid sensitivity, the prefrontal-PAG avoidance learning system is a potential biological substrate for dysfunctional outcomes with long-term opioid use. Study 2 provides direct evidence for a positive feedback cycle whereby negative expectations enhance pain, which leads to increased negative expectations. Conversely, positive expectations reduce pain, and increase subsequent positive expectations. Two independent mechanisms, sensory modulation and a confirmation bias in learning, maintain this feedback loop.

Conclusion: Fronto-striatal and frontal-PAG circuits are motivational learning systems that are sensitive to expectations and influence subsequent pain avoidance. The dynamics of these circuits are such that they are vulnerable to positive feedback loops, resulting in 'self-fulfilling prophecies' in pain experience. If initial expectations are positive, this is advantageous; but if they are negative, it is harmful. In patients with chronic pain and mood disorders, initial negative expectations may create a 'vicious cycle' of avoidance, pain, and resistance to

otherwise effective treatment. Prolonged opioid use may induce a vulnerability to such adverse feedback cycles.

References:

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