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Preview

Reward learning in the development and maintenance of chronic back pain

Li-Bo Zhang[1,2] and Li Hu[1,2,*]
[1]CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, 100101 Beijing, China
[2]Department of Psychology, University of Chinese Academy of Sciences, 100101 Beijing, China
*Correspondence: huli@psych.ac.cn
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Treating and preventing chronic pain require our understanding of how it develops and maintains. Löffler et al. (2022)[1] demonstrate that distinct operant learning signals in the vmPFC-NAc pathway predict the development and maintenance of chronic back pain.

Chronic pain, which persists for more than three months after injury recovery,[2] has been consistently ranked as one of the most burdensome nonfatal diseases for decades.[3] Understanding how chronic pain develops from acute pain and how it maintains is the key to successful treatment and prevention of the debilitating disease. Operant conditioning has long been proposed as a potential mechanism of pain chronicity.[4] The ventromedial prefrontal cortex (vmPFC)-nucleus accumbens (NAc) pathway underlies crucial aspects of operant conditioning, for example, expectation and prediction error (i.e., the difference between what is expected and what actually happens).[5–7] However, it is still unclear how operant learning processes encoded in the vmPFC-NAc pathway contribute to the development and maintenance of chronic pain.

In this issue of *Cell Reports Medicine*, using fMRI, Löffler et al.[1] demonstrate that different operant learning-related neural responses in the vmPFC-NAc pathway predict the transition from subacute back pain (SABP) to chronic back pain (CBP) and the maintenance of CBP (Figure 1). They followed 50 SABP patients for 6 months and enrolled 29 CBP patients and 29 healthy individuals. All participants completed an operant reward learning task in the scanner, where they responded to two colored arrow symbols as quickly as possible to win a monetary reward or pain relief. These two types of rewards were delivered with a probability of 50%. As a result, the absence of reward would indicate a negative prediction error (NPE) and the presence of reward a positive prediction error (PPE). This study design enables the authors to identify which reward learning signals in the vmPFC and NAc predict the development and maintenance of CBP and determine whether the predictors differ between the two stages of chronic pain.

To identify predictors of pain chronicity, Löffler et al. conducted a series of correlation and pattern decoding analyses using learning task-based fMRI responses and resting-state fMRI data. They quantified the persistence of pain in SABP patients by computing percentage changes in pain severity scores between the baseline and follow-up. In the reward learning task, blood-oxygen-level-dependent (BOLD) responses in the left NAc during monetary PPE (i.e., presence of monetary rewards) and NPE (i.e., absence of monetary rewards) correlated positively with pain persistence and discriminated between SABP patients who recovered and those who still suffered from pain after six months. Moreover, larger connectivity between right NAc and vmPFC during monetary NPE also predicted pain persistence. By analyzing resting-state fMRI data, Löffler and colleagues showed that the left NAc-vmPFC connectivity *per se* predicted the transition to chronic pain. Additional pattern decoding analysis revealed that the activity pattern in the right NAc during the presentation of discriminative stimuli (i.e., colored arrow symbols) associated with pain relief could distinguish persistent and recovered SABP patients.

Next, Löffler et al. compared CBP patients and healthy controls to identify predictors of chronic pain maintenance. Compared with healthy individuals, CBP patients exhibited decreased vmPFC activity during monetary PPE, increased left NAc-vmPFC connectivity during monetary PPE, and increased vmPFC activity during the presentation of discriminative stimuli for monetary rewards. However, no significant NAc-vmPFC connectivity differences were found at rest. Further analysis also failed to predict pain severity in CBP patients with neural responses in the vmPFC-NAc pathway.

Altogether, this study shows that reward signals in the vmPFC-NAc pathway can predict the development and maintenance of CBP. Notably, findings from CBP patients contrast with those from SABP patients (Figure 1). For example, pain persistence was associated with larger left NAc responses during monetary PPE, but not vmPFC responses, which nevertheless differed between CBP patients and healthy participants. On the other hand, larger vmPFC responses during the presentation of discriminative stimuli for monetary rewards were observed in CBP patients, but these responses did not predict pain persistence for SABP patients. The authors inferred from these findings that the development and maintenance of CBP are characterized by the exploration-exploitation dilemma reflected in the vmPFC-NAc pathway. Specifically, the transition from SABP to CBP is predicted by the exploration of reward feedbacks, the period when prediction error is processed in areas like the NAc. The maintenance of CBP, however, is associated with the exploitation of past reward signals, as indicated by the enhanced

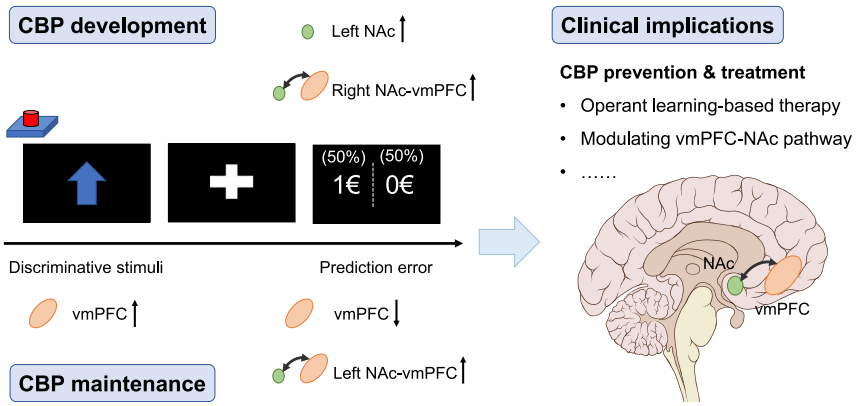

Figure 1. Roles of the vmPFC-NAc pathway in chronic back pain development and maintenance and their implications

In different stages of operant reward learning, activations and connectivity in the vmPFC-NAc pathway predict the development and maintenance of chronic back pain (CBP). Accordingly, operant learning-based therapies and modulating the vmPFC-NAc pathway may contribute to the prevention and treatment of CBP.

vmPFC responses to discriminative stimuli for monetary reward.

The importance of the vmPFC-NAc pathway in chronic pain has been highlighted previously.[8,9] Löffler et al. provide a precious opportunity to investigate how the vmPFC-NAc pathway distinctly contributes to the development and maintenance of CBP by following SABP patients for half a year and recruiting both CBP patients and healthy individuals. This study has clear clinical significance. For example, operant learning-based therapies or modulating brain activities in the vmPFC-NAc pathway may help prevent the transition to or maintenance of CBP. A recent preliminary study has shown that the transition from subacute to chronic back pain in females can be prevented by a 3-month treatment with Levodopa combined with naproxen, which targets dopaminergic neurons in the NAc.[10] One limitation in Löffler et al. is that they did not collect fMRI data from SABP patients in the follow-up. Had they done so, more insights into pain chronicity could have been gained by directly comparing brain responses between persistent and recovered SABP patients in the follow-up period or between persistent SABP patients and CBP patients. For a better treatment of chronic pain, more studies with larger sample sizes are needed to replicate Löffler et al.'s findings and further untangle the causal relationship between the vmPFC-NAc pathway and pain chronicity. Nevertheless, Löffler et al. still deepen our understanding of how operant learning and pain chronicity interact, and they present positive evidence that the vmPFC-NAc pathway may be a potential target for treating and preventing chronic pain.

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