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The brain remembers where and how inflammation struck

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Our immune system and brain interact on multiple scales, but how the brain represents and remembers immune challenges remains unclear. In this issue of *Cell*, Koren et al. (2021) reveal that the brain's insular cortex stores information about inflammation in the body. Strikingly, these immunological "memory engrams" can restore the initial disease state when reactivated.

The brain and immune system communicate at many levels of organization, and in both directions: from the body to the brain and vice versa. This neuroimmune communication is believed to underlie an immunoregulatory role of the brain and a sensory function of the immune system and occurs through both humoral but also neuronal pathways (Dantzer, 2018).

However, how the brain represents and stores information about immune challenges that occurred in the periphery remains largely unknown. In this issue of *Cell*, Koren et al. (2021) demonstrate that the brain's insular cortex stores information specific to the anatomical location and nature of a peripheral immune responses. Strikingly, reactivating the same neuronal ensembles, which were activated during the initial inflammation, is sufficient to reinstate the same disease in the body even after complete recovery (Figure 1).

Koren et al. (2021) initially explored which neuronal ensembles in the brain are activated by a bodily inflammation. The authors used a well-established experimental model of colitis to induce acute colon inflammation in mice and employed a genetic trick called "TRAP" (transgenic targeted-recombination-in-active populations) (DeNardo et al., 2019) to identify and further manipulate the neuronal ensembles that were active during the inflammation. The authors identified several brain regions that contain colitis-activated neurons. Among those were the insular cortex (InsCtx). Given the existing literature on this brain region as a major hub for bidirectional brain-body interactions (Gogolla, 2017), the authors decided to focus on this area for the remainder of their study.

The finding that neurons in a given brain region increase their activity during peripheral inflammation could have multiple explanations. For instance, the InsCtx is known to be highly multisensory, relevant to the processing of pain and valence (Gogolla, 2017). Therefore, the authors sought to address whether the "Trapped" InsCtx neurons truly encoded immunological-relevant information. They tested what happened when the same neurons as captured during the initial disease state were experimentally reactivated after complete healing of the inflammation. The authors expressed activating DREADDs (designer receptors exclusively activated by designer drugs) specifically in the colitis-activated neurons of the right InsCtx. Strikingly, reactivating these neuronal ensembles several weeks after the initial inflammation led to a second bout of inflammation in the colon. Of note, this second inflammation was solely caused by the reactivation of the neurons in the InsCtx in absence of any inflammatory substance in the periphery. Even more remarkable, the authors did not re-induce any peripheral immune response when they reactivated InsCtx neurons that were TRAPed outside (before or after) the acute inflammation. Similarly, activating a larger but unspecific pool of InsCtx neurons, targeted randomly and consisting of approximately twice as many neurons as captured during colitis, also did not cause peripheral inflammation.

To investigate the specificity of the immunological memory in the InsCtx further, Koren et al. (2021) experimentally induced a different inflammatory response, peritonitis, which elicits a well-defined yet distinct immune response from colitis and affects a different visceral area (the peritoneum). As before, the authors captured the neurons active during peritonitis in the InsCtx using TRAP and reactivated the same neurons once the inflammation had healed. Consistent with the previous experiments, they observed immunological changes in the periphery that were highly similar to the initial peritonitis but different from colitis. Intriguingly, the information thus stored in the distinct InsCtx ensembles is highly specific, leading to distinct immune profiles dependent on which immune challenge they were captured at. Furthermore, the information is also anatomically specific, as the effects of the reactivation of the neuronal ensembles led to changes only in the visceral compartment that was affected during the initial disease. Together, these results indicate a striking specificity of the neuronal ensembles in the InsCtx and a form of "memory specificity" that is reminiscent of memory engrams in other brain regions (Josselyn and Tonegawa, 2020).

Previous literature on memory engrams suggested that these are highly dynamic cellular ensembles (Sweis et al., 2021). Intriguingly, when the authors compared the neuronal ensembles captured in two subsequent peritonitis events, the ensembles were highly non-overlapping, suggesting that a dynamic pool of immune-responsive neurons uniquely captures each immune experience.

The InsCtx is known to be important for both the sensory-discriminative and affective-motivational aspects of pain (Lu et al., 2016). To address whether pain is a significant component of the immunological memory trace in the InsCtx, the

authors administered painkiller acetaminophen during TRAPing. Interestingly, while parts of the immune response induced by reactivating neurons captured during inflammation in the presence of analgesia were attenuated, others were preserved, suggesting that the neuronal ensembles captured in the InsCtx are engaged by a mixture of pain and inflammatory signals.

How does the gut receive signals from the brain? To elucidate the anatomical pathways enabling the communication between the InsCtx and the body, the authors used polysynaptic viral-labeling techniques to highlight a pathway by which the InsCtx polysynaptically innervates the colon. Indeed, using TRAP, the authors demonstrated that neurons included in the InsCtx neuronal ensemble activated by an immune response in the colon were also polysynaptically connected to this region of the gut. Further experiments highlighted that possible hubs in the pathway from the brain to the periphery may be the dorsal motor nucleus of the vagus nerve and the medulla, indicating that the InsCtx engages the autonomic nervous system to mediate its effects on the body.

In a final experiment, the authors demonstrated that non-specifically inhibiting the InsCtx using DREADDs is sufficient to attenuate an experimentally induced inflammation of the colon. This result reveals a bidirectional role of the insular cortex in regulating peripheral immune responses.

Taken together, the findings by Koren et al. (2021) establish clear evidence that the brain's InsCtx communicates with the immune system, represents specific information about inflammation in the body, and regulates peripheral immune responses. These striking observations immediately raise several further intriguing questions: are there physiological conditions under which the inflammation-specific InsCtx ensembles are reactivated and re-evoke the disease, and if so, under which circumstances? What happens to immunological memories in the InsCtx upon chronic inflammation? Can the brain-body interplay become a vicious circle? How long do inflammation memories stay stable and can they be altered? Are immunological memories extinguishable? Can better pain management help in weakening immunological memories and attenuate relapse?

The implication of the InsCtx in immunological memory and immune system regulation is particularly intriguing since the InsCtx is known as a major hub in emotion regulation and memory, multisensory integration, and valence processing (Gogolla, 2017). Psychological factors, stress, and emotions are known to influence onset and progression of all kinds of diseases, including but not limited to allergies, cancers, autoimmune diseases, and infectious diseases (Dantzer, 2018; Dantzer et al., 2008). Thus, future research may be required to address how other relevant information streams represented in the InsCtx may be integrated with the inflammation-specific engrams and whether and how they can cause or influence their reactivation. Do stress and anxiety lead to reactivation, per se, or change how many cells are recruited into an immunological engram? Can emotionally salient events known to activate the InsCtx trigger reactivation of immunological memories and elicit peripheral inflammation?

A further fascinating link may exist between immunological memories stored in the InsCtx and psychiatric conditions. Strikingly, the insular cortex is affected in function and anatomy across many diverse psychiatric conditions (Goodkind et al., 2015). Furthermore, it has been long appreciated that bodily disease can

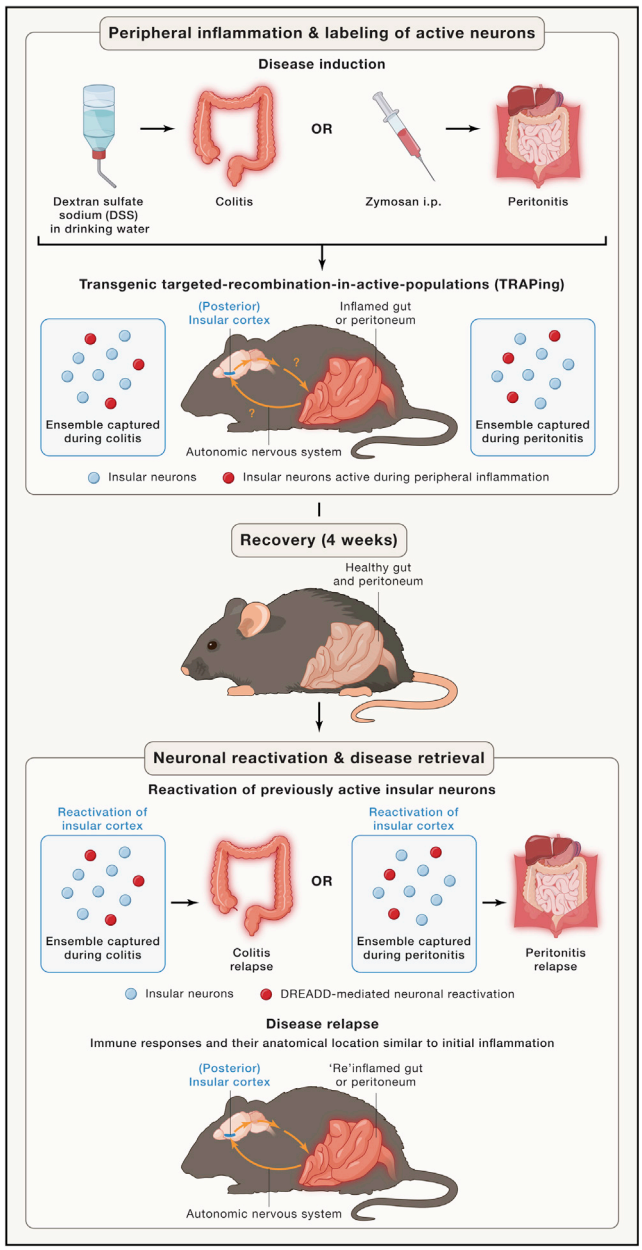

Figure 1. The insular cortex contains immunological engrams

Koren et al. (2021) induced inflammation in the body either using a dextran sulfate sodium (DSS)-induced model of colitis or a Zymosan-induced model of peritonitis. They then marked the activated neurons in the insular cortex. After complete recovery from the inflammation, the authors reactivated the inflammation-specific neuronal ensembles in the insular cortex and thereby recovered the initial disease state.

trigger or impact psychiatric conditions, including depression, anxiety or schizophrenia (Dantzer et al., 2008; Gibney and Drexhage, 2013). How does the role of the InsCtx in psychiatric disease, emotion processing and immune regulation overlap and cause interactions?

In conclusion, the observations by Koren et al. (2021) implicating the InsCtx in immunological memories may thus represent a novel avenue for better understanding of the interplay between emotion, psychiatric illness, and bodily disease.

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REFERENCES

Dantzer, R. (2018). Neuroimmune Interactions: From the Brain to the Immune System and Vice Versa. Physiol. Rev. *98*, 477–504.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., and Kelley, K.W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. *9*, 46–56.

DeNardo, L.A., Liu, C.D., Allen, W.E., Adams, E.L., Friedmann, D., Fu, L., Guenthner, C.J., Tessier-Lavigne, M., and Luo, L. (2019). Temporal evolution of cortical ensembles promoting remote memory retrieval. Nat. Neurosci. *22*, 460–469.

Gibney, S.M., and Drexhage, H.A. (2013). Evidence for a dysregulated immune system in the etiology of psychiatric disorders. J. Neuroimmune Pharmacol. *8*, 900–920.

Gogolla, N. (2017). The insular cortex. Curr. Biol. *27*, R580–R586.

Goodkind, M., Eickhoff, S.B., Oathes, D.J., Jiang, Y., Chang, A., Jones-Hagata, L.B., Ortega, B.N., Zaiko, Y.V., Roach, E.L., Korgaonkar, M.S., et al. (2015). Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry *72*, 305–315.

Josselyn, S.A., and Tonegawa, S. (2020). Memory engrams: Recalling the past and imagining the future. Science *367*.. https://doi.org/10.1126/science.aaw4325.

Koren, T., Rifa, R., Am, M., Krot, M., Boshnak, N., Ben-Shaanan, T.L., Azulay-Debby, H., Zalayat, I., Avishai, E., Hajjo, H., et al. (2021). Insular cortex neurons encode and retrieve specific immune responses. Cell *184*.. https://doi.org/10.1016/j.cell.2021.10.013.

Lu, C., Yang, T., Zhao, H., Zhang, M., Meng, F., Fu, H., Xie, Y., and Xu, H. (2016). Insular Cortex is Critical for the Perception, Modulation, and Chronification of Pain. Neurosci. Bull. *32*, 191–201.

Sweis, B.M., Mau, W., Rabinowitz, S., and Cai, D.J. (2021). Dynamic and heterogeneous neural ensembles contribute to a memory engram. Curr. Opin. Neurobiol. *67*, 199–206.