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Comorbidity of chronic pain and anxiodepressive disorders: Deciphering underlying brain circuits.

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Chronic pain and anxiodepressive disorders are well-known for being intimately related and for influencing each other, but the mechanisms underlying this clinically significant comorbidity remain largely unknown. In this issue, Bravo *et al.* (2020) address this challenging topic by focusing on brain structures implicated in their bidirectional relationship. By reviewing lesion, pharmacologic, optogenetic or chemogenetic studies, they nicely recapitulate the role of individual brain structures (such as the prefrontal cortex - PFC, the amygdala, the nucleus accumbens - NAc, the locus coeruleus - LC, and the hippocampus) in the anxiodepressive disorders-pain dyad.

Even though studies focusing on individual brain regions improve our understanding of pathophysiology, it is also essential to reach circuitry level of understanding. Indeed, most central nervous system disorders are linked to alterations in brain circuits rather than to changes occurring in single structures. While this issue was difficult to explore until recently, the rapid development of optogenetic and chemogenetic tools now allows the targeting of anatomically defined neuronal pathways (Fig 1A). Regarding chronic pain-induced emotional dysregulation (CPED), a few preclinical studies have started to unravel critical brain circuits (Fig. 1B), which link together some of the brain regions highlighted by Bravo et al.

Lee and collaborators (2015) first showed that optogenetic activation of PFC neurons terminals within the NAc blocks both nociceptive and negative affective

behaviors in neuropathic animals (Fig. 1A). To further identify the neurochemical identity of this pathway, they combined optogenetic and pharmacological manipulations, and infused an AMPA receptor antagonist into the NAc, which blocked the effects of the optogenetic modulation.

The amygdala is another major hub for CPED. Llorca-Torrallba and colleagues (2019) demonstrated that chemogenetic silencing of LC noradrenergic neurons projecting to the basolateral amygdala (Fig. 1A) relieved pain-induced anxiety-like behaviors in neuropathic rats, without affecting mechanical hypersensitivity.

To decipher potentially divergent contributions from subpopulations of neurons located in the same brain structure but sending projections to distinct target sites, Hirschberg and colleagues highlighted another approach (2017). The authors used retrograde viruses injected in the PFC or spinal cord (SC) to target ascending and descending projections from noradrenergic neurons of the LC, respectively (Fig. 1A). They showed that chemogenetic activation of the LC-SC pathway had an anti-nociceptive effect, while the activation of LC-PFC projections enhanced aversive and anxiety-like behaviors. This study along with that of Llorca-Torrallba *et al.* (2019) point out that refining the analysis of specific neuronal subpopulations based on their efferences can reveal distinct and even functionally opposite effects in the modulation of the sensory and affective components of pain.

While the different studies discussed so far assessed pathways involving two brain structures, circuits underlying pain perception and emotional regulation are likely to be more complex. Recently, Zhou and collaborators (2019) dissected an ascending pathway involved in pain-induced depressive-like behavior that is composed of the dorsal raphe nucleus (DRN), the central nucleus of the amygdala (CeA), and the lateral habenula (LHb), using both chemo- and optogenetics. Their results demonstrated that inhibition of serotonergic DRN neurons terminals in the CeA (Fig. 1A) resulted in depressive-like behavior in naive mice, while activation of this pathway in neuropathic animals produced antidepressant-like and antinociceptive effects. DRN serotonergic neurons preferentially target somatostatin neurons in the CeA, which in turn project to the LHb. Surprisingly, electrophysiological recordings showed that activation of CeA somatostatin fibers elicited excitatory responses in the LHb. Indeed, even though most somatostatin neurons are GABAergic, a small population of them is in fact excitatory. Silencing those fibers in the LHb (Fig. 1A) rescued chronic pain-induced depressive-like

behavior, while activation of this pathway in naive animals conversely induced depressive-like behavior. Finally, by combining optogenetics with neuronal tracing and electrophysiology, they assessed the whole DRN-CeA-LHb circuit and showed that CPED in their model stems from the loss of serotonergic inhibition of LHb-projecting neurons of the CeA.

Taken altogether, these results deepen our understanding of the interconnected pathways that differentially modulate affective and sensory components of pain. Nevertheless, more research will be needed to better understand the big picture of CPED. While existing studies have proven the strength of opto- and chemogenetics in combination with pharmacological or electrophysiological approaches, future studies should consider additional levels of analysis. Within this line, cell-type, pathway-specific, or single-cell RNA-sequencing all have the potential to reveal underlying molecular mechanisms. On the other hand, techniques such as fiber photometry or calcium imaging, which are now more and more used *in vivo* and even in freely-moving rodents, give more precise information at cellular and cell-specific levels. Finally, the use of functional magnetic resonance imaging (fMRI) or diffusion tensor imaging could give a more global insight in brain pathway alterations in CPED. Such non-invasive approaches allow for longitudinal studies and offer promising perspectives when considering that temporality is crucial when it comes chronic pain and its affective consequences.

We believe that the leap forward in novel technics and their combination with more classical approaches will lead to a better understanding of the circuits underlying the anxiodepressive disorders-pain dyad.

Acknowledgments

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Figure 1. Tools and approaches used to dissect neuronal circuitry underlying chronic pain-induced emotional dysregulation. A. Optogenetic and chemogenetic technics used to dissect brain circuits. *Upper left panel:* mPFC-NAc specificity reached by injection of anterogradely transported opsin in the PFC and by an optic fiber

implantation in the NAc (Lee et al., 2015). *Upper right panel:* Cell-type specificity by promoter-dependent expression: injection in the PFC or SC of a retrograde virus expressing DREADD under the synthetic promoter PRS targeting noradrenergic (NA) neurons. Cell bodies of NA neurons expressing DREADD and projecting either the PFC or SC are stimulated by CNO injection in the LC through a cannula (Hirschberg *et al.*, 2017). *Lower panel:* Cell-type specificity by Cre-dependent expression. *Left:* Injection of an anterogradely transported DREADD in the LC. DREADD will be expressed in neurons expressing the Cre recombinase under the TH promoter. Axon terminals expressing DREADD in the BLA are stimulated by CNO injection through a cannula (Lorca-Torralba *et al.*, 2019). *Right:* Injection of an anterogradely transported opsin or DREADD in the DRN or the CeA. The opsins/DREADD will only be expressed in neurons expressing Cre-recombinase under the Pet-1 (5HT neurons, injected in the DRN) or SOM (injected in the CeA) promoters. Axon terminals expressing opsin/DREADD in the CeA or the LHb are stimulated by light/CNO injection through an optic fiber/cannula (Zhou *et al.*, 2019). **B.** The figure depicts neuronal circuits underlying the comorbidity between pain and depression/anxiety, as dissected using optogenetics/DREADD in the following publications (see main text for details): mPFC-NAc pathway, see Lee *et al.*, 2015; LC-mPFC and LC-spinal cord pathways, see Hirschberg *et al.*, 2017; LC-AMY pathway, see Llorca-Torralba *et al.*, 2019; DRN-AMY-LHb pathways, see Zhou *et al.*, 2019. Abbreviations: 5-HT: serotonin; AMY: amygdala; BLA: basolateral amygdala; CeA: central nucleus of the amygdala; CNO: clozapine-N-oxide; DREADD: designer drug exclusively activated by a designer drug; DRN: dorsal raphe nucleus; LC: locus coeruleus; LHb: lateral habenula; PFC: prefrontal cortex; PSAM: pharmaco-selective actuator module; NA: noradrenaline; NAc: nucleus accumbens; SC: spinal cord; SOM: somatostatin; TH: tyrosine hydroxylase.

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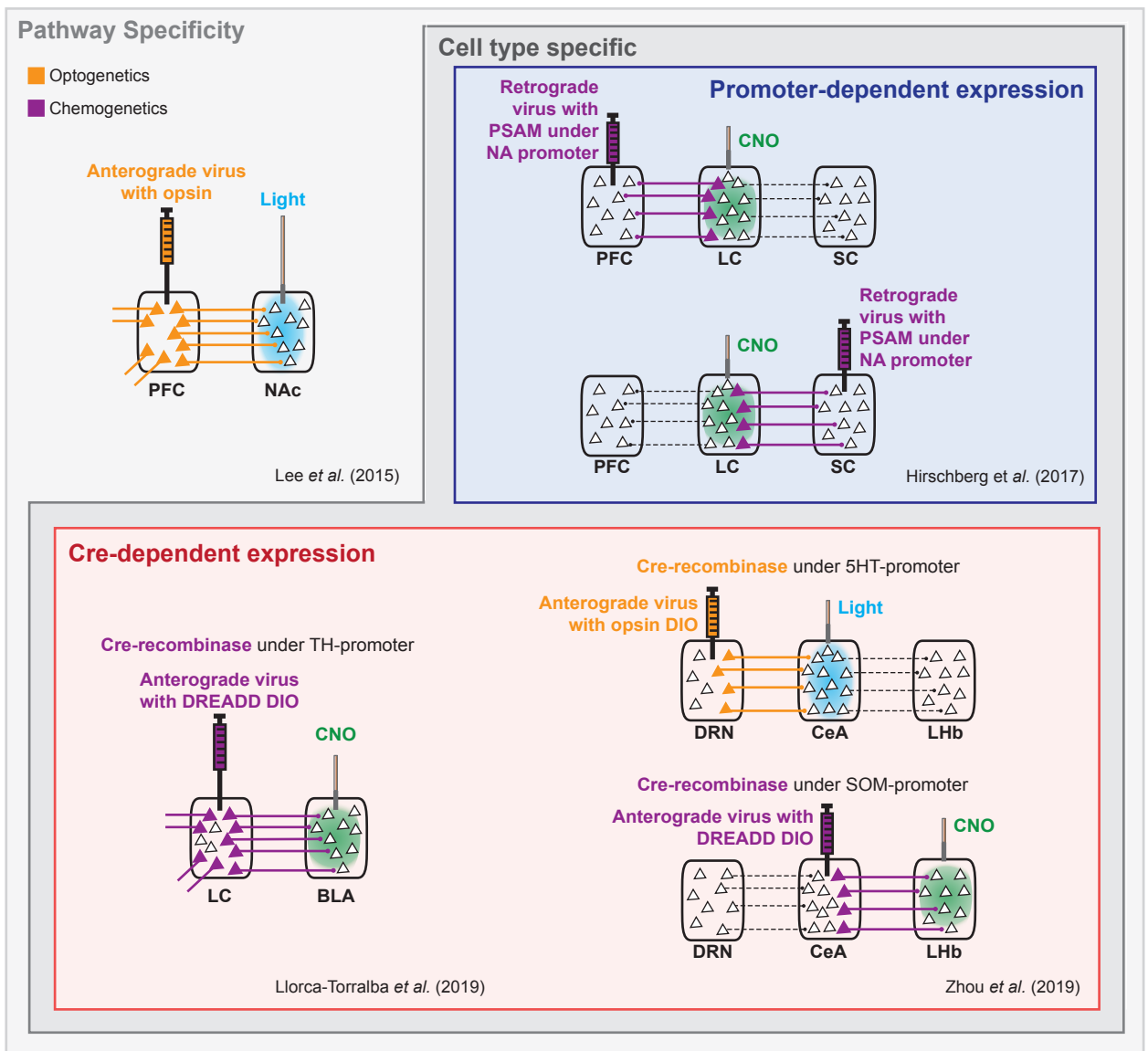
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