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# The Anterior Cingulate Cortex Is a Critical Hub for Pain-Induced Depression

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**ABSTRACT**

**BACKGROUND:** Besides chronic stress, chronic pain is a prevalent determinant for depression. Changes induced in specific brain regions by sustained pain may alter the processing of affective information, thus resulting in anxiodepressive disorders. Here, we compared the role of the anterior cingulate cortex (ACC) and the posterior insular cortex in the anxiodepressive, sensory, and affective aspects of chronic pain.

**METHODS:** Neuropathic pain was induced by cuffing the right sciatic nerve of C57BL/6J mice. Lesions were performed by local injection of ibotenic acid and chronic activation of the ACC by optogenetic stimulation. Anxiodepressive-related behaviors were evaluated through the novelty suppressed feeding, marble burying, splash, and forced swimming tests. Mechanical thresholds were determined using von Frey filaments, and the relief of spontaneous pain was determined by using place conditioning.

**RESULTS:** The ACC lesion prevented the anxiodepressive consequences of chronic pain without affecting the sensory mechanical allodynia. Conversely, the tonic or spontaneous pain and the anxiodepressive consequences of pain remained present after posterior insular cortex lesion, even though the mechanical allodynia was suppressed. Furthermore, optogenetic stimulation of the ACC was sufficient to induce anxiety and depressive-like behaviors in naïve animals.

**CONCLUSIONS:** Our results show that, at cortical level, the sensory component of chronic pain remains functionally segregated from its affective and anxiodepressive components. Spontaneous tonic pain and evoked allodynia can be experimentally dissociated. Furthermore, the ACC appears as a critical hub for mood disorders, including for the anxiodepressive consequences of chronic pain, and thus constitutes an important target for divulging the underlying mechanism.

*Keywords:* Anterior cingulate cortex, Anxiety, Behavior, Depression, Insular cortex, Neuropathic pain, Optogenetics

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Depression, the most common mental disorder, is a disabling and long-lasting medical condition, estimated to be the foremost contributor to the worldwide burden of disease by 2030 (1). Among several precipitating factors, chronic pain is a prevalent determinant for depression. Indeed, a mean prevalence rate of around 50% for major depressive disorder is reported in patients with chronic pain (2). The existence of pain-induced affective disorders is further supported by preclinical studies showing that chronic pain models can induce anxiety-like and/or depression-like behaviors in animals in a time-dependent manner (3–5). While it could be suggested that chronic pain may be a chronic inescapable stress (6), preclinical and clinical studies have shown that sustained neuropathic pain strongly differs from a simple stress regarding neuroendocrine hypothalamic-pituitary-adrenal (HPA) alterations, even if it induces similar behavioral consequences. Indeed, neuropathic pain does not modify the basal or stress-induced levels of corticosterone or the HPA axis negative feedback (4,7), while this is the case in the several models of stress-induced depression (8,9). Another hypothesis for pain-induced depression could be based on a shared neuroanatomical substrate, proposing that specific brain regions processing pain are also involved in mood-related processing and that the alterations induced in these regions by chronic pain may alter the processing of affective information, thus resulting in mental disorders. Among the candidates, the anterior cingulate cortex (ACC) and the insular cortex (IC) appear to be critical in the networks involved in both pain and mood (10–12).

The ACC is a relay that interconnects neurons from the frontal cortex, the thalamus, and the amygdala, integrating cognitive, emotional, and autonomic functions (10,11). Clinical imaging studies have shown the recruitment of the ACC in pain processing (13), and preclinical studies have more precisely associated the activation of the ACC neurons with pain-like aversive behavior, while the inhibition of these neurons blocks such behavior (14). The IC is another cortical area of interest since both human and animal studies have shown its recruitment in acute and chronic pain (15–17). The complexity of IC connectivity and the variability of pain-related

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activity between different IC subregions suggest that this cortical area may play a multifaceted role in pain processing. For example, some studies have reported a preferential pain activation of the posterior IC (pIC) (18), whereas others have also described it in the mid insula (19) or in the operculoinsular area (15,20). The activation of the IC has been implicated in both antinociceptive and pronociceptive processes (19), while its role in the aversive component of pain is still unclear.

Despite the lack of direct evidence, the ACC and the IC could also play a role in the anxiodepressive consequences of chronic pain. Indeed, both cortices are known to display functional and morphological alterations in depressive states (21–23), such as the observation of decreased connectivity (24), altered glucose metabolism (25), and reduced volume (26) in the ACC of depressed patients and also altered basal neuronal resting state activity in the IC (22). Studies showing the alleviation of depressive symptoms in treatment-resistant patients by ablative surgery (27) or deep brain stimulation (28) of the ACC further support the implication of this region in major depression. However, these data come from the psychiatric field and the involvement of these regions in the affective consequences of chronic pain has not yet been studied.

Although clinical and preclinical studies strongly suggest a role of the ACC and the IC in pain processing, respective functions of these cortical areas in the anxiodepressive consequences as well as in the sensory and affective components of chronic pain remain unknown. Using a lesion approach in a murine model of neuropathic pain, we demonstrate that the ACC is critical in the anxiodepressive consequences of chronic pain, while conversely the pIC is only critical in mechanical allodynia. The repeated stimulation of the ACC by an optogenetic approach induces anxiodepressive behaviors in naïve animals, which further reinforces the essential role of this cortical region in mood disorders.

## METHODS AND MATERIALS

### Animals

The lesion experiments were conducted in adult male C57BL/6J mice (Charles River, L'Arbresle, France). Genetically modified mice expressing channelrhodopsin-2 and yellow fluorescent protein (Thy1-ChR2-YFP) in a subset of pyramidal neurons were used (29) for optogenetic studies (Supplement 1).

### Surgical Procedures

Chronic neuropathic pain was induced by placing a cuff around the right common sciatic nerve (4). Bilateral excitotoxic lesions of the ACC and the pIC by local injection of ibotenic acid were performed under stereotaxic surgery (see Supplement 1).

### Optogenetic Procedures

Animals were anesthetized (ketamine 17 mg/mL, xylazine 2.5 mg/mL, intraperitoneal 4 mL/kg) before being placed in a stereotaxic frame (David Kopf Instruments, Tujunga, California). Single glass fiber cannulas, 1.7 mm long with a diameter of 220 μm (MFC_220/250-0.66_1.7 mm_RM3_FLT, Doric Lenses, Quebec, Canada) were implanted in the left ACC. Coordinates derived from the Franklin and Paxinos atlas (30) were set to .7 mm anterior and .3 mm lateral to the Bregma. The cannula was lowered until 1.5 mm of optic fiber was inserted into the brain, covering the whole vertical span of the ACC.

After 3 to 7 days of recovery period, the ACC was stimulated with a blue light emitting diode (LED) with a peak wavelength of 463 nm (LEDFRJ-B_FC, Doric Lenses). From the LED, the light traveled through the fiber optic patch cable (MFP_240/250/2000-0.63_0.75m_FC_CM3) to the implant cannula. Light pulses were generated through a universal serial bus connected transistor-transistor logic pulse generator (OPTG_4, Doric Lenses) connected to a LED driver (LEDRV_2CH v.2, Doric Lenses). Transistor-transistor logic pulses were generated by open source software developed by Doric Lenses (USBTTL V1.9). Optical power was measured at the fiber tip using a photodetector (UNO, Gentec, Quebec, Canada).

Optogenetic stimulation took place on 4 consecutive days for 30 minutes. Stimulated animals received repetitive stimulation sequences of 10 seconds consisting of 8 seconds at 20 Hz with 40 milliseconds pulses and 2 seconds without stimulation (31). Light intensity was measured before implantation and was set between 4 mW and 5 mW. Control animals underwent the same implant procedures but the light was turned off during stimulation time.

### Electrophysiological Recordings

Patch-clamp recordings of the ACC pyramidal neurons were performed using acute slices prepared from 9- to 12-week-old Thy1-ChR2-YFP mice, the ACC being illuminated with the same system used for the in vivo experiments (Supplement 1).

### Pain- and Anxiodepressive-Related Behaviors

The mechanical threshold of hindpaw withdrawal was determined using von Frey filaments (Bioseb, Chaville, France) (4), while the spontaneous pain was evaluated using conditioned place preference in response to the intrathecal administration of the analgesic α2-adrenoceptor agonist clonidine (10 μg) (32) (Supplement 1).

For lesion studies, the novelty suppressed feeding (NSF), splash, and forced swimming tests (FST) were conducted 6, 7, and 8 weeks after the peripheral nerve injury, respectively. For the optogenetic studies, animals were tested with the NSF test 1 day after the last stimulation. Splash test and marble burying test were performed the fourth and the fifth days after the final stimulation (Supplement 1).

### Immunohistochemistry, Analysis, and Illustrations

For the lesion study, after the behavioral testing, the animals were perfused and NeuN immunostaining was performed. Lesions were indicated by neuronal cell loss localized bilaterally and extended from 1.18 to .14 mm from the bregma for the ACC lesion and from .38 to −1.22 mm from the bregma for the pIC lesion. Concerning the optogenetic study, after the completion of the behavioral tests, the animals were stimulated once with the same procedure as described before and

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