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MEETING ABSTRACT

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A prefrontal neuronal circuit for activating descending modulation of neuropathic pain

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Background: The medial prefrontal cortex (mPFC, homolog of the primate dlPFC) plays an important role in the cognitive and affective modulation of pain. Parvalbumin-expressing GABAergic interneurons (PVINs) in the mPFC are known to mediate an increased feed-forward inhibition of mPFC output after peripheral nerve injury. Conversely, inhibition of these PVINs consequently mediates analgesia in neuropathic pain. However, the cellular and molecular underpinnings of this phenomenon have remained unclear, and it is not known how the projections originating from the mPFC might modulate downstream targets in neuropathic states. The mPFC has been shown to exhibit reciprocal connections with the basolateral amygdala (BLA), a brain region that receives ascending sensory inputs from the spinal cord. Moreover, the mPFC sends projections to the ventrolateral periaqueductal gray (vlPAG) region which is known to be involved in descending pain modulation. We thus hypothesized that the observed alterations in mPFC function may originate from BLA inputs and that the processing of these inputs in the mPFC alters downstream pathways such as PAG projections.

Methods: We used optogenetics approaches, combined with patch-clamp electrophysiology, *in vivo* pharmacology and behavioral assessment to examine the role of specific glutamatergic BLA inputs into the mPFC and to elucidate the downstream brain circuitry that is involved in neuropathic pain.

Results: Our data show that peripheral nerve injury strengthens synaptic input from the BLA onto inhibitory interneurons located in layer 5 of the prelimbic mPFC, as a result of reduced expression of CB_1 receptors. Optogenetic inhibition of these inputs weakens feed forward inhibition to boost mPFC output, leading to analgesia. This effect is lost by ablation of mPFC–vlPAG projections, or by ablating projections from the vlPAG to the rostroventral medulla (RVM) and/or locus coeruleus (LC). Spinal administration of serotoneric and noradrenergic receptor antagonists blocks the analgesic effects mediated by optogenetic inhibition of BLA to mPFC inputs.

Discussion: Our data reveal that peripheral nerve injury leads to a selective augmentation of BLA inputs into GABAergic interneurons in the mPFC as a result of weakened endocannabinoid signaling. The selective enhancement of glutamatergic inputs onto PVINs results in an overall inhibition of layer 5 output towards the vlPAG. Within the vlPAG, the decreased input from mPFC causes reduced activity of glutamatergic neurons, and increased activity of GABAergic neurons. Altogether these alterations in the vlPAG result in a decrease in serotonergic and noradrenergic output from the RVM and LC to the spinal cord dorsal horn, respectively, thus leading to compromised descending modulation of ascending nociceptive transmission. Specific optogenetic inhibition of the BLA inputs into the mPFC weakens the feed-forward inhibition, thereby enhancing mPFC inputs into the vlPAG and its downstream targets including the RVM, LC and spinal cord, leading to analgesia. Our data presented here provide new insights into the understanding of the functional connectomics of the BLA–mPFC–PAG–spinal cord pathway, and establish a causal link between the dysregulation of this circuit and hypersensitive behavior during neuropathic pain.

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Keywords: neuropathic pain – neuronal circuit – prefrontal cortex – amygdala – periaqueductal gray – optogenetics – electrophysiology

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