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Letter To Editor

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Letter To Editor

As academic scientists, we hope to be read, to have others adopt our ideas, and to see them taking on a life of their own, but it is an especially peculiar experience to see yourself cited in a critique questioning your own latest position. Examining chronic pain as a supraspinal learning process is a hallmark of our work, and we approach this as one might have any other learning experience: as a process of acquisition, maintenance, and extinction (or remission).² We strive to represent a consistent point of view, and seeing our own work turned against itself¹⁸ suggests that maybe something has been overlooked, has not been clearly articulated, or could at the very least use a modicum of clarifying discussion.

In Ref. 1, we attempted to demonstrate that adult hippocampal neurogenesis (AHN) is necessary for acquisition of persistent pain behavior in mice. The study is distinguished by how AHN was manipulated in healthy animals before nerve injury. Pharmacological, x-ray, and transgenic viral models reveal that inhibition of AHN prevents development of neuropathic or inflammatory pain behavior, whereas increasing AHN prolongs the latter. This supports the hypothesis that AHN is most likely necessary for acquisition of this behavior.

The role of the hippocampus in chronic pain must nevertheless be multifaceted. A rebuttal to this study¹⁸ draws attention to such complexity and questions the findings of Ref. 1 in part by pointing to our own previous work in which neuropathic-injury was associated with a decrease in AHN.¹³ However, a fundamental distinction between Ref. 1 and previous studies seems to have been missed—the latter address the consequence of the presence of persistent pain on the AHN, whereas the former addresses the converse: the consequence of AHN on pain acquisition. Acquisition of and remission from chronic pain are coincident with cortical reorganization,^{3,4,7,14} which is known to also occur with hippocampus-dependent learning and memory.^{6,8} Adult hippocampal neurogenesis stands as a candidate mechanism able to facilitate these processes, which may work through inducing sharp wave ripples in the hippocampus⁹ and driving distinct brain-wide cortical activity.^{10,15,17} Although further work is needed to link these phenomena, these studies paint a consistent picture where AHN is needed for acquisition of chronic pain, and is then downregulated, potentially impairing the brain's ability to recover.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

An alternative hypothesis proposed by Zheng et al. merits consideration, namely, that delayed or absent acquisition of chronic pain may be produced by affecting glial health. Two of the experimental methods of Ref. 1 (AraC infusion and bone morphogenesis protein/Noggin genetic manipulation) may have either reduced glial proliferation⁵ or modulated neuroglia interactions in the periphery.¹² In addition, a third experiment resulted in delayed allodynia after x-irradiation. X-irradiation is known to reduce the proliferation of all exposed cells days to weeks after exposure, and Zheng et al. specifically cite its effect on astrocytes. Two points should be emphasized here. First, each of the proposed glial confounds is different in nature, so disrupted AHN is the more parsimonious explanation for the observed changes in acquisition of chronic pain behavior. More importantly, nerve injury and behavioral testing was performed 6 months after x-irradiation. Although glia and neurons may have been affected in the short term, altered glial health cannot explain the results in Ref. 1 because the long-lasting effects of x-irradiation are shown to be neuron-specific.^{11,16}

The evidence brought forth in Ref. 1 argues that AHN is a necessary component for the acquisition of persistent pain, whereas Ref. 18 tacitly grants the necessity of hippocampal learning, but disagrees on the significance of AHN in particular. Confusion regarding differing roles for AHN in different phases of pain learning is partially to blame. We thank Zheng et al. for their constructive comments in this regard, which have allowed us an opportunity to further communicate and clarify these findings. We contend that the evidence is tenuous for glia supplanting AHN as the physiological basis underlying modulation of pain acquisition in our three AHN disruption models. The likelihood is low in the first place that 3 separate confounds would produce the same behavioral outcome across all 3 disruption models, and in the case of x-irradiation in particular, the likelihood of any kind of glial dysfunction is low given the waiting period between irradiation and surgery. Thus, we consider Ref. 1 as a first step toward establishing a causal role between AHN dependent hippocampal learning mechanisms and the development of chronic pain.

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