effect of pregabalin but rather effects applicable to specific subgroups of surgical models for better generalization of evidence and knowledge translation.

Fourth, regarding testing for publication bias, actually the Cochrane handbook recommends this when there are at least 10 studies in a meta-analysis. Essentially, tests for funnel plot asymmetry inform us whether there are significant differences between large and small study effects, and when all other explanatory factors (eg, clinical heterogeneity between studies) can be ruled out, publication bias becomes highly suspected. Sterne et al.[7] recommended preconditions for examining funnel plot asymmetry. We had stipulated these conditions in our protocol. We found either there were inadequate number of studies per meta-analysis, not much variability in sample sizes across studies, or heterogeneity in effect estimates between studies that did not seem to be related to study size. As such, we did not present nor undertake formal testing for publication bias.

Finally, although detailed protocols and rigorous methodology are essential for any meta-analysis to produce clinically reproducible results, any meta-analysis is also limited by the studies it includes. These systematic reviews should not only pool outcome data, they should in our opinion, also explore hypotheses and guide further clinical trials. Fu et al.[6] suggested that tests for heterogeneity alone should not guide lumping or splitting studies in a meta-analysis. They stated "*Ultimately the decision will be judged on whether combining the studies makes sense clinically, a criterion that is qualitative and perhaps subjective.*"

We thank Doleman et al. for their interest in our work. As perioperative multimodal analgesia evolves, accumulating experience and evidence needs to be analyzed so as to identify surgical procedures where pregabalin may benefit patients. Our systematic review may be an important first step in this direction.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Hippocampal neurogenesis: does it relieve or worsen chronic pain?

Letter To Editor:

Chronic pain is accompanied by cognitive impairment and emotional disorders, both of which are significantly modulated by adult hippocampal neurogenesis (AHN). But how neurogenesis affects pain remains unclear. With 3 different methods, Apkarian et al.[2] reported that downregulating AHN diminished or blocked chronic pain, whereas upregulating neurogenesis led to the opposite effect. These changes were independent of anxiety or depression, which modulated pain progression as well. This was the first direct evidence indicating the active role of neurogenesis in pain modulation.

However, these results were inconsistent with a number of previous findings. Environmental enrichment (EE), for example, promotes adult neurogenesis but benefits recovery from both chronic neuropathic and inflammatory pain.[18,20] In addition, several studies have reported the anxiolytic and cognition-improving effects of EE under pathological conditions.[4] Similar conclusions were reached in studies using brain derived neurotrophic factor (BDNF)-overexpression and GABA (B) receptor blockage in the hippocampus, both of which upregulated AHN and relieved pain.[7,17] The effects of many anxiolytic agents or antidepressants have been shown to be dependent on promoting hippocampal neurogenesis,[14,22] and some of them are recommended for clinical pain management.[8] Overall, these studies[4,6,7,13,16,17,19,21] indicate pain-relieving, cognition-improving, and anxiolytic effects of AHN, in sharp contrast to the conclusions reported by Apkarian et al.[2] Indeed, patients with more severe anxiety and depression, or less cognitive flexibility and memory capacities have been reported to suffer more from chronic pain.[3,13]

One may argue that the manipulations used in these previous studies, including studies if EE, BDNF-overexpression, GABA (B) receptor blockage, and anxiolytic agents or antidepressants, are not specific for neurogenesis and induce many other effects, such as antiinflammatory effects and endocrine changes. This supports the significance of the study by Apkarian et al.[2] Based on their findings, Apkarian et al. pointed out that "the role of AHN in postinjury pain is not dependent on the depressive effects of pain and more likely involves AHN-dependent memory formation processes." In other words, decreasing neurogenesis blocks the formation of pain-related memory, and prevents the development of chronic pain, as shown in their study.[2] However, previous studies reported significantly decreased AHN, 14 days after spared nerve injury surgery, a classical

rodent model of neuropathic pain,[16] which was not accompanied by any pain relief. Indeed, in consideration of findings from Apkarian et al.,[2] the only rational interpretation is that decreased neurogenesis acts as a self-protecting mechanism in painful animals. Paradoxically, mice were reported to require hippocampal neurogenesis for forgetting negative memories.[1] It is difficult to understand why decreased AHN in neuropathic animals promotes pain relief but prevents loss of negative memories, because chronic pain is undoubtedly a kind of negative memory that requires forgetting. Furthermore, a number of studies, inconsistent with the results of Apkarian et al.,[2] have reported anxiolytic effects of AHN under pathological conditions.[10,21]

Indeed, we would like to propose alternative explanations of the results reported by Apkarian et al.[2] Complete and reversible pain blocking by intracerebroventricular administration of antimitotic AraC could actually result from the nonspecific effects of AraC on glial cells, which significantly outnumbered newborn neurons. The surprisingly fast effects of AraC on pain behaviors[2] match with its immediate effects on glia more than newborn neurons, which usually take weeks to integrate into functional circuits.[6] Despite the lack of direct evidence for hippocampal glia in pain modulation, a large number of studies have confirmed the active role of glia at other sites, including the anterior cingulate cortex, which can be affected by intracerebroventricular administration of AraC in regulating the development of chronic pain.[11,12] Similarly, x-ray irradiation has been reported to reduce the proliferation of astrocytes, despite its wide acceptance as the most classical technique in neurogenesis research.[21] Nonspecificity is also present in the transgenic animals used in the study[2]: BMP4 and noggin are overexpressed not only in the brain, but in the peripheral nervous system as well. BMPs, for example, play a role in peripheral nerve fiber sprouting and neuronal-glial interactions,[9,15] both of which actively affect the development of chronic pain.[5,19]

In conclusion, the study by Apkarian et al.[2] raised an interesting question in pain research: how does AHN affect chronic pain? However, methods used in this study, similar to previous reports, were not sufficiently specific to draw convincing conclusions. More systematic and specific techniques are required to elucidate this question in the future.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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