Involvement of the hippocampus in chronic pain and depression

Tahmineh Mokhtari
CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China
Department of Psychology, University of Chinese Academy of Sciences, Beijing 100101, China

Yiheng Tu
Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA

Li Hu
CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China
Department of Psychology, University of Chinese Academy of Sciences, Beijing 100101, China

Follow this and additional works at: https://tsinghuauniversitypress.researchcommons.org/brain-science-advances

Recommended Citation
Tahmineh Mokhtari, Yiheng Tu, Li Hu. Involvement of the hippocampus in chronic pain and depression. Brain Science Advances 2019, 05(04): 288-298.
Involvement of the hippocampus in chronic pain and depression

Tahmineh Mokhtari1,2, Yiheng Tu3, Li Hu1,2 (✉)

1 CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China
2 Department of Psychology, University of Chinese Academy of Sciences, Beijing 100101, China
3 Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA

ARTICLE INFO
Received: 6 November, 2019
Revised: 8 December, 2019
Accepted: 15 December, 2019

© The authors 2019. This article is published with open access at journals.sagepub.com/home/BSA

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

KEYWORDS
depression, chronic pain, hippocampus, proinflammatory cytokines, brain-derived neurotrophic factor

ABSTRACT
Increases in depressive behaviors have been reported in patients experiencing chronic pain. In these patients, the symptoms of pain and depression commonly coexist, impairing their lives and challenging effective treatment. The hippocampus may play a role in both chronic pain and depression. A reduction in the volume of the hippocampus is related to reduced neurogenesis and neuroplasticity in cases of chronic pain and depression. Moreover, an increase of proinflammatory factors and a reduction of neurotrophic factors have been reported to modulate the hippocampal neurogenesis and neuroplasticity in chronic pain and depression. This review discusses the mechanisms underlying the depressive-like behavior accompanying chronic pain, emphasizing the structural and functional changes in the hippocampus. We also discuss the hypothesis that pro-inflammatory factors and neurotrophic factors expressed in the hippocampus may serve as a therapeutic target for comorbid chronic pain and depression.

1 Introduction
Pain, including both sensory and emotional—affective components, may protect organisms from either potential or real tissue damage. However, disruptive pain that exceeds its biologically useful function may develop from chronic pain that lasts from three to six months, or even longer [1]. Chronic pain, which is a significant cause of disability worldwide, causes both physical and psychological discomfort and raises huge medical costs [2, 3]. Due to differences in populations and inclusion criteria, the prevalence of chronic pain in different countries has been reported as ranging from 8% to 60%, and it seriously affects the working lives and the social and daily activities of people affected by it [4]. Chronic pain commonly coexists with major depressive disorder (MDD) [1]. Up to 80% of patients with chronic pain have comorbid depressive symptoms [5]. Moreover,
patients with chronic pain may also experience increased anxiety and deficits of both learning and memory [6]. Chronic pain may change a patient’s emotional state and induce depressive-like behaviors [7].

A literature suggests that, in a patient experiencing comorbid chronic pain and depression, the severity of pain is predictive of the time required for the remission of the patient’s depressive conditions following treatment [8]. Such findings indicate the existence of a mutual relationship between chronic pain and depression: depressive conditions may reduce the pain threshold, and painful conditions may contribute to depressed states [8]. In fact, pain is a major obstacle to achieve full remission during treatment for depression, and pain and depression may share the same neurobiological mechanisms [9].

Previous brain imaging studies have revealed the key brain regions involved in pain processing; these regions include the sensory areas (e.g., the primary somatosensory cortex, primary motor and supplementary motor cortices, secondary somatosensory cortex, insular cortex, anterior cingulate cortex, and thalamus), cognitive areas (e.g., the prefrontal and parietal cortices), and both memory and emotional areas (e.g., the amygdala and the hippocampus, and the subcortical structures of basal ganglia) [10–12].

In particular, the hippocampus, as one of the central components in the limbic system, has been found to exhibit abnormalities in cases of both chronic pain and depression [13, 14]. Reduced volume of the hippocampus has been found in patients experiencing chronic pain [15, 16] and depression [17]. The findings of a cross-species study involving both humans and animals indicate that abnormalities in the hippocampus, including reduced volume, neurogenesis, and synaptic plasticity, reflect certain functional abnormalities, such as negative affective states and emotions, associated with chronic pain [6]. Similarly, there have been reports of an association between the reduced volume of the hippocampus and the severity of depression [18, 19]. In addition, the reduced hippocampal volume, affected similarly by chronic pain and depression, has been found to be related to reduced neurogenesis and neuroplasticity in both human patients and rodent models [20]. This may represent a neuropathological mechanism underlying comorbid chronic pain and depression [21]. Moreover, inflammation is known to be an important modulator of the hippocampal neurogenesis. Both pain and depression are thought to be associated with inflammatory responses in the region of the hippocampus and can alter hippocampal neurogenesis [22–24]. The related pathophysiological mechanisms are summarized in Fig. 1.

Here, we review the literature to discuss the interrelationship of chronic pain and depression, with a particular focus on the hippocampus as a potential common denominator for chronic pain and depressive-like behaviors. Knowledge of the associations between these two conditions in the hippocampus, linked through a common neuroanatomical pathway and structure and a common inflammatory neuromodulator, would help in the treatment and management of comorbid chronic pain and depression.

2 Comorbidity of pain and depression in chronic pain patients

Pain is an unpleasant sensory experience that is accompanied by affective components, including feelings of annoyance, anxiety, sadness, and depression. Pain is known to be a main risk factor for the development of depression in patients with chronic pain, and there has been considerable research into the close relationship between pain and depression [25].
A longitudinal 12-year cohort study reported a significant correlation between the onset of depression and the baseline, chronicity, and severity of pain [26]. Depression and anxiety in chronic pain patients are acknowledged as being pain-related disabilities [27], given that studies have shown that 30%–100% of patients with chronic pain are affected by depression; this prevalence is several times higher than that in the general population [28, 29]. Moreover, the severity of chronic pain may hinder treatment for depression. From 51.8% to 59.1% of depression patients have reported experiencing chronic pain [30, 31]. Before antidepressant treatment commenced, the presence and severity of baseline pain were able to predict negative outcomes after treatment [32].

Combined administration of available antidepressants and analgesics is recommended to treat these comorbid disorders, but the efficacy of treatment was not satisfactory [33]. In addition, a higher rate of functional interference has been identified in the comorbid occurrence of pain and depression. In a cross-sectional study, patients with MDD and chronic pain experienced more interference in daily living activities (2.1–4.6 times) than depressed patients who were free of pain did [34]. Recently, the administration of analgesic drugs, such as opioids and benzodiazepines, in antidepressant therapy has provided solid evidence confirming the link between depression and chronic pain [21]. Thus, analgesics are also used to ameliorate the depression-like behaviors caused by neuropathic pain [35, 36].

3 Altered hippocampal structure in patients with chronic pain and depression

Many studies have demonstrated hippocampal abnormalities in patients experiencing chronic pain. Reduced volume of the hippocampus has been reported in patients with different types of chronic pain, such as knee osteoarthritis [37], chronic back pain, and complex regional pain syndrome [6], and also in elderly nondemented patients with chronic pain [16]. The hippocampus is an important brain structure that plays a role in specific types of learning paradigms and is active primarily in the storage and retrieval of long-term explicit memories [38]. As a subjective...
sensation, pain also involves the cognitive integration of awareness with memory and emotional responses. The hippocampus can facilitate and process direct and indirect nociceptive inputs of pain [24]. The septohippocampal neurons receive direct nociceptive inputs from the spinal cord [39, 40], and the indirect inputs innervate the hippocampus via the spinothalamic and parabrachial ascending pathways [41]. In chronic pain, 70% of patients experience attention and memory deficits [42, 43], which are associated with disruption of attention affected by pain-related sensory inputs and the formation of working memory in the hippocampus [44, 45]. Furthermore, the hippocampal-related abnormalities, including the deficits in recognition [46] and short-term memory [47], have been reported in animal models of chronic pain [48]. Thus, changes in the hippocampus caused by chronic pain may also be associated with the chronic pain comorbidities of learning and memory deficits.

Cognitive impairments, such as anxiety and depression, have been reported often in patients experiencing chronic pain [49]. In human studies, patients with chronic pain have been shown to have higher scores in tests of anxiety and depressive symptoms, confirming the well-documented relationship between chronic pain and affective disorders [50, 51]. As with chronic pain, reduced volume of the hippocampus has been demonstrated in patients suffering from anxiety and depressive disorders [19], and it may regulate the depressive phenotype [52].

Therefore, the hippocampal abnormality may be a link between chronic pain and depression, indicating that depression and cognitive deficits in chronic pain disorders may be associated with changes in the hippocampus. Recent research findings show a significant correlation between changes in the hippocampus induced by chronic pain and anxiety-like behaviors that are normally related to the depressive condition [6].

4 Neurogenesis and neuroplasticity in the hippocampus following chronic pain and depression

Despite the comorbidity of chronic pain and depression having been shown to be related to reduced volume of the hippocampus, the underlying molecular mechanism remains unclear. Hippocampal abnormalities, including impaired neuroplasticity and enriched-environment neurogenesis, have been associated with a different mechanism in chronic pain conditions [53]. At least two specific anatomical regions, the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus in the hippocampus, have been reported to be involved in the neurogenesis of the adult mammalian brain [54, 55].

Adult hippocampal neurogenesis is associated with learning and memory [56], and findings suggest that reduced neurogenesis in the hippocampus region is involved in various neuropsychiatric disorders, including anxiety [57], depression [58], stress [59], and impaired contextual fear conditioning [60]. Importantly, research has shown that reduced neurogenesis in the adult hippocampus correlated with cognitive decline and mood alterations is associated with chronic pain [6, 53]. The neurogenic hypothesis of depression suggests that depression is caused by impaired adult hippocampal neurogenesis and that newly generated neurons in the adult brain play a key role in regulating mood and are associated with antidepressant efficacy [61]. Similarly, several preclinical studies [20, 62] have reported a correlation between persistent pain and either reduced hippocampal neurogenesis or a blunted response of hippocampal neural progenitor cells to proneurogenic stimuli [20, 62].

Based on findings related to the rate of neurogenesis, as quantified by counting the
number of bromodeoxyuridine (BrdU+)-positive cells (as a marker of neurogenesis) in the hippocampal dentate gyrus (DG), the number of BrdU-labeled cells remains unchanged following exposure to acute nociception (induced by formalin) [41]. However, a reduction in the number of BrdU+ cells in DG was recorded in animals exposed to prolonged nociception (via application of Complete Freund’s Adjuvant for 21 days to achieve hyperalgesia) [63]. In addition, impaired neurogenesis has been demonstrated in the depression-like behavior associated with peripheral neuropathy that persists following resolution of prolonged tactile hypersensitivity (at least three weeks) [64]. As these data demonstrated impaired neurogenesis in both chronic pain and depression, decreased neurogenesis may also contribute to the depression following chronic pain.

The phenomenon of neural plasticity, which refers to changes in neuronal synapses and pathways to adapt to new experiences in either healthy or damaged conditions [65], is known to be a fundamental characteristic observed in the development of chronic pain [66]. Studies using animal models have demonstrated that persistent peripheral nerve injury impairs long-term potentiation at CA3–CA1 synapses in the hippocampus, indicating reduced synaptic plasticity in the hippocampus following chronic pain [47]. According to the neuroplasticity hypothesis of MDD, the dysfunction of neural plasticity is a basic pathomechanism of the disorder [61]. Moreover, loss of volume of the hippocampus has been shown to be correlated with reduced neurogenesis and neuroplasticity following chronic pain-induced depression in both human patients and rodent models [21, 67]. To summarize, these findings have shown that reduced neural plasticity can occur in both depression and chronic pain. Depression-like behavior induced by chronic pain may be associated with reduced neural plasticity in the hippocampus.

5 Proinflammatory factors in the hippocampus following chronic pain and depression

There is mounting evidence that the immune system plays an important role in the etiology of chronic pain-induced depression [68]. Changes in the function and structure of the hippocampus have been suggested to be associated with increased proinflammatory cytokines in hippocampal tissue following nerve injury [47]. In particular, neuroinflammation of the hippocampus is key to the development of depressive and anxious disorders following chronic pain [69, 70]. Correlation between abnormal expression of cytokines in the hippocampus and chronic pain-like behavior has been demonstrated in animal models [23, 71]. Reduced proliferation and neurogenesis in the hippocampus, along with an increase in proinflammatory cytokines (CD86+) and a reduction in neuroprotective (CD163+) microglia/macrophages, indicates increased activity of microglia/macrophages, which may lead to the suppression of neurogenesis reported in chronic neuropathic pain [72]. Furthermore, the reduction in neurogenesis may be related to the increases in other hippocampal proinflammatory cytokines, such as TNF-α [47] and IL-1β [23, 71], following nerve injury.

TNF-α is an integral determinant/component of nociception involved at all neuroaxis levels contributing to the pathogenesis of chronic pain [73–75]. TNF-α has been shown to be essential to the cognitive experience of pain and chronic pain associated with mood changes [24]. Hippocampal noradrenergic neurotransmission, which plays an important role in the neurogenesis [76], could be dampened following elevated hippocampus
TNF-α levels due to the peripheral nerve injury in the sciatic nerve chronic constriction injury (CCI) model [77, 78]. In the absence of any peripheral injury, intracerebroventricular (ICV) microinfusion of TNF-α into the hippocampus induced chronic pain-like symptoms, indicating that the hippocampus was a site of the nociceptive action of TNF within the central nervous system [24]. Studies have revealed that increased levels of TNF-α in the brain activate the α2-adrenergic receptor (α2AR), thus inhibiting the release of norepinephrine in the hippocampus of animal models following chronic pain [77, 79]. This finding suggests that the administration of antidepressants, such as adrenergic drugs, in rodents reduced the animals’ sensitivity to pain by decreasing the production of TNF, thereby inducing the increased release of norepinephrine [80].

IL-1β is another cytokine that is potentially overexpressed in supraspinal brain regions, particularly in the hippocampus, and that underlies the mechanism of behavioral and neurogenesis changes in neuropathic pain [22, 23]. Increased levels of neuronal IL-1β in the contralateral ventral hippocampus have been suggested to be linked with changes in astrocyte and microglial reactivity in the CCI model [81]. Moreover, IL-1β has been reported to reduce neurogenesis in the elderly [82], and it may play a similar role in neuropathic pain [22]. IL-1β knock-down in the hippocampus has also ameliorated lipopolysaccharide-induced depressive- and anxiety-like behaviors [83]. In the mouse model of spared nerve injury, the administration of the IL-1 receptor antagonist alleviates the effects of neuropathic pain on depression-like behaviors [69].

In addition, activation of the Nod-like receptor protein (NLRP) inflammasomes, which results in the direct maturation of caspase-1 and then induces production of the proinflammatory cytokines (IL-1β and IL-18), has been implicated in neuroinflammation-related diseases [84]. Recent findings have shown that hippocampal NLRP1 inflammasome activation contributes to the depression-like behaviors induced by neuropathic pain in rats [70]. Taken these findings together, we believe that the neuroinflammation in the hippocampal region may play a key role in pain-induced depressive behaviors.

### 6 Neurotrophic factors in the hippocampus following chronic pain and depression

Brain-derived neurotrophic factor (BDNF) expressed in neurons and in immune cells has been shown to be involved in neurogenesis, the formation of synaptic plasticity and memory [85, 86]. The receptor of BDNF is tropomyosin-related tyrosine kinase B (TrkB). TrkB has a critical role in signaling pathways associated with the function and development of the mammalian nervous system [87]. Abnormal expression of BDNF during either nociceptive or inflammatory processes has been reported [88]. Moreover, reduced expression of BDNF has been found in the hippocampus of animals exposed to painful stimuli [89]. BDNF has been reported to regulate both spinal and peripheral sensitivity in various animal models of chronic pain [90]. Moreover, BDNF has been shown to be a crucial signaling molecule between microglia and neurons, which represents an essential link in the transmission of neuropathic pain, and blocking this pathway may be a strategy for treating neuropathic pain [91]. In addition, reduced levels of serum BDNF have been found in patients with major depressive disorder, whereas successful antidepressant treatment increases the BDNF levels in these patients [92, 93]. By modulating synaptic plasticity throughout the peripheral and central pain circuits, BDNF may change pain sensitivity and, more importantly, the level of pain-induced
depression. Therefore, BDNF is a potential new therapeutic target for treating chronic pain-induced depression in the near future.

7 Conclusion

The data presented in this review show that chronic pain-induced depression may suppress adult neurogenesis in and synaptic plasticity of the hippocampus. Increases in the number of inflammatory factors and reductions in the number of neurotrophic factors in the hippocampal region may underlie the pathology of this condition. The development of new therapeutic strategies to both increase the neurotrophic factors, such as brain-derived neurotrophic factor, and inhibit the inflammation may attenuate depressive behaviors in patients with chronic pain and can be considered in future clinical studies.

Conflict of interests

The authors have declared that no competing interests exist.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 31671141, No. 31822025), the Informatization Special Project of Chinese Academy of Sciences (No. XXH13506-306), and the Scientific Foundation project of Institute of Psychology, Chinese Academy of Sciences (No. Y6CX021008).

References

[1] Boakye PA, Olechowski C, Rashiq S, et al. A critical review of neurobiological factors involved in the interactions between chronic pain, depression, and sleep disruption. Clin J Pain. 2016, 32(4): 327–336.

[2] Li XY, Hu L. The role of stress regulation on neural plasticity in pain chronification. Neural Plast. 2016, 2016: 6402942.

[3] Zhang L, Zhou LL, Ren QY, et al. Evaluating cortical alterations in patients with chronic back pain using neuroimaging techniques: recent advances and perspectives. Front Psychol. 2019, 10: 2527.

[4] Phillips CJ. The cost and burden of chronic pain. Rev Pain. 2009, 3(1): 2–5.

[5] Burke NN, Finn DP, Roche M. Neuroinflammatory mechanisms linking pain and depression. In Pain in Psychiatric Disorders. Finn DP, Leonard BE, Eds. Basel: Karger, 2015.

[6] Mutso AA, Radzicki D, Baliki MN, et al. Abnormalities in hippocampal functioning with persistent pain. J Neurosci. 2012, 32(17): 5747–5756.

[7] Torta RG, Munari J. Symptom cluster: Depression and pain. Surg Oncol. 2010, 19(3): 155–159.

[8] von Korff M, Dworkin SF, Le Resche L, et al. An epidemiologic comparison of pain complaints. Pain. 1988, 32(2): 173–183.

[9] Delgado PL. Common pathways of depression and pain. J Clin Psychiatry. 2004, 65(12):16–19.

[10] Martucci KT, Mackey SC. Neuroimaging of pain: human evidence and clinical relevance of central nervous system processes and modulation. Anesthesiology. 2018, 128(6): 1241–1254.

[11] Brown JE, Chatterjee N, Younger J, et al. Towards a physiology-based measure of pain: patterns of human brain activity distinguish painful from non-painful thermal stimulation. PloS One. 2011, 6(9): e24124.

[12] Leknes S, Tracey I. A common neurobiology for pain and pleasure. Nat Rev Neurosci. 2008, 9(4): 314–320.

[13] Anand KS, Dhikav V. Hippocampus in health and disease: an overview. Ann Indian Acad Neurol. 2012, 15(4): 239–246.

[14] Yang S, Chang MC. Chronic pain: structural and functional changes in brain structures and associated negative affective states. Int J Mol Sci. 2019, 20(13): E3130.

[15] Vaculik MF, Noorani A, Hung PS, et al. Selective hippocampal subfield volume reductions in classic trigeminal neuralgia. Neuroimage Clin. 2019, 23: 101911.

[16] Zimmerman ME, Pan JW, Hetherington HP, et al. Hippocampal correlates of pain in healthy elderly adults: a pilot study. Neurology. 2009, 73(19): 1567–1570.
[17] Sawyer K, Corsentino E, Sachs-Ericsson N, et al. Depression, hippocampal volume changes, and cognitive decline in a clinical sample of older depressed outpatients and non-depressed controls. *Aging Ment Health*. 2012, **16**(6): 753–762.

[18] MacQueen GM, Yucel K, Taylor VH, et al. Posterior hippocampal volumes are associated with remission rates in patients with major depressive disorder. *Biol Psychiatry*. 2008, **64**(10): 880–883.

[19] Chan SW, Harmer CJ, Norbury R, et al. Hippocampal volume in vulnerability and resilience to depression. *J Affect Disord*. 2016, **189**: 199–202.

[20] Grilli M. Chronic pain and adult hippocampal neurogenesis: translational implications from preclinical studies. *J Pain Res*. 2017, **10**: 2281–2286.

[21] Sheng JY, Liu S, Wang YC, et al. The link between depression and chronic pain: neural mechanisms in the brain. *Neural Plast*. 2017, **2017**: 9724371.

[22] del Rey A, Apkarian AV, Martina M, et al. Chronic neuropathic pain-like behavior and brain-borne IL-1β. *Ann N Y Acad Sci*. 2012, **1262**: 101–107.

[23] del Rey A, Yau HJ, Randolf A, et al. Chronic neuropathic pain-like behavior correlates with IL-1β expression and disrupts cytokine interactions in the hippocampus. *Pain*. 2011, **152**(12): 2827–2835.

[24] Martuscello RT, Spengler RN, Bonoiu AC, et al. Increasing TNF levels solely in the rat hippocampus produces persistent pain-like symptoms. *Pain*. 2012, **153**(9): 1871–1882.

[25] Doan L, Manders T, Wang J. Neuroplasticity underlying the comorbidity of pain and depression. *Neural Plast*. 2015, **2015**: 504691.

[26] Hilderink PH, Burger H, Deeg DJ, et al. The temporal relation between pain and depression: results from the longitudinal aging study Amsterdam. *Psychosom Med*. 2012, **74**(9): 945–951.

[27] Lerman SF, Rudich Z, Brill S, et al. Longitudinal associations between depression, anxiety, pain, and pain-related disability in chronic pain patients. *Psychosom Med*. 2015, **77**(3): 333–341.

[28] Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry*. 2003, **60**(1): 39–47.

[29] Miller LR, Cano A. Comorbid chronic pain and depression: who is at risk? *J Pain*. 2009, **10**(6): 619–627.

[30] Águeda-Ortiz L, Failde I, Mico JA, et al. Pain as a symptom of depression: prevalence and clinical correlates in patients attending psychiatric clinics. *J Affect Disord*. 2011, **130**(1/2): 106–112.

[31] Lee P, Zhang MY, Hong JP, et al. Frequency of painful physical symptoms with major depressive disorder in Asia: relationship with disease severity and quality of life. *J Clin Psychiatry*. 2009, **70**(1): 83–91.

[32] Bair MJ, Robinson RL, Eckert GJ, et al. Impact of pain on depression treatment response in primary care. *Psychosom Med*. 2004, **66**(1): 17–22.

[33] Zhang GF, Wang J, Han JF, et al. Acute single dose of ketamine relieves mechanical allodynia and consequent depression-like behaviors in a rat model. *Neurosci Lett*. 2016, **631**: 7–12.

[34] Smith PD, Becker K, Roberts L, et al. Associations among pain, depression, and functional limitation in low-income, home-dwelling older adults: an analysis of baseline data from CAPABLE. *Geriatr Nurs*. 2016, **37**(5): 348–352.

[35] Wang J, Goffer Y, Xu D, et al. A single subanesthetic dose of ketamine relieves depression-like behaviors induced by neuropathic pain in rats. *Anesthesiology*. 2011, **115**(4): 812–821.

[36] Leitl MD, Onvani S, Bowers MS, et al. Pain-related depression of the mesolimbic dopamine system in rats: expression, blockade by analgesics, and role of endogenous κ-opioids. *Neuropsychopharmacology*. 2014, **39**(3): 614–624.

[37] Mao CP, Bai ZL, Zhang XN, et al. Abnormal subcortical brain morphology in patients with knee osteoarthritis: a cross-sectional study. *Front Aging Neurosci*. 2016, **8**: 3.

[38] Mansour AR, Farmer MA, Baliki MN, et al. Chronic pain: the role of learning and brain plasticity. *Restor Neurol Neurosci*. 2014, **32**(1): 129–139.

[39] Khanna S, Sinclair JG. Noxious stimuli produce prolonged changes in the CA1 region of the rat hippocampus. *Pain*. 1989, **39**(3): 337–343.

[40] Dutar P, Lamour Y, Jobert A. Activation of identified septo-hippocampal neurons by noxious peripheral stimulation. *Brain Res*. 1985, **328**(1): 15–21.

[41] Duric V, McCarson KE. Persistent pain produces stress-like alterations in hippocampal neurogenesis and gene expression. *J Pain*. 2006, **7**(8): 544–555.
[42] Dick BD, Rashiq S. Disruption of attention and working memory traces in individuals with chronic pain. *Anesth Analg.* 2007, 104(5): 1223–1229.
[43] Hart RP, Martelli MF, Zasler ND. Chronic pain and neuropsychological functioning. *Neuropsychol Rev.* 2000, 10(3): 131–149.
[44] Awh E, Vogel EK, Oh SH. Interactions between attention and working memory. *Neuroscience.* 2006, 139(1): 201–208.
[45] Eccleston C. Chronic pain and distraction: an experimental investigation into the role of sustained and shifting attention in the processing of chronic persistent pain. *Behav Res Ther.* 1995, 33(4): 391–405.
[46] Kodama D, Ono H, Tanabe M. Increased hippocampal glycine uptake and cognitive dysfunction after peripheral nerve injury. *Pain.* 2011, 152(4): 809–817.
[47] Ren WJ, Liu Y, Zhou LJ, et al. Peripheral nerve injury leads to working memory deficits and dysfunction of the hippocampus by upregulation of TNF-α in rodents. *Neuropsychopharmacology.* 2011, 36(5): 979–992.
[48] Preston AR, Eichenbaum H. Interplay of hippocampus and prefrontal cortex in memory. *Curr Biol.* 2013, 23(17): R764–R773.
[49] Hart RP, Wade JB, Martelli MF. Cognitive impairment in patients with chronic pain: the significance of stress. *Curr Pain Headache Rep.* 2003, 7(2): 116–126.
[50] Raftery MN, Sarma K, Murphy AW, et al. Chronic pain in the Republic of Ireland—community prevalence, psychosocial profile and predictors of pain-related disability: results from the Prevalence, Impact and Cost of Chronic Pain (PRIME) study, part 1. *Pain.* 2011, 152(5): 1096–1103.
[51] Gureje O, von Korff M, Simon GE, et al. Persistent pain and well-being: a world health organization study in primary care. *JAMA.* 1998, 280(2): 147–151.
[52] Malykhin NV, Carter R, Seres P, et al. Structural changes in the hippocampus in major depressive disorder: contributions of disease and treatment. *J Psychiatry Neurosci.* 2010, 35(5): 337–343.
[53] Terada M, Kuzumaki N, Hareyama N, et al. Suppression of enriched environment-induced neurogenesis in a rodent model of neuropathic pain. *Neurosci Lett.* 2008, 440(3): 314–318.
[54] Ijaz S, Mohammed I, Gholaminejad M, et al. Modulating pro-inflammatory cytokines, tissue damage magnitude, and motor deficit in spinal cord injury with subventricular zone-derived extracellular vesicles. *J Mol Neurosci.* 2020, 70(3): 458–466.
[55] Abbott LC, Nigussie F. Adult neurogenesis in the mammalian dentate gyrus. *Anat Histol Embryol.* 2020, 49(1): 3–16.
[56] Deng W, Aimeone JB, Gage FH. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nat Rev Neurosci.* 2010, 11(5): 339–350.
[57] Revest JM, Dupret D, Koehl M, et al. Adult hippocampal neurogenesis is involved in anxiety-related behaviors. *Mol Psychiatry.* 2009, 14(10): 959–967.
[58] Sahay A, Hen RN. Adult hippocampal neurogenesis in depression. *Nat Neurosci.* 2007, 10(9): 1110–1115.
[59] Dranovsky A, Hen R. Hippocampal neurogenesis: regulation by stress and antidepressants. *Biol Psychiatry.* 2006, 59(12): 1136–1143.
[60] Saxe MD, Battaglia F, Wang JW, et al. Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. *Proc Natl Acad Sci USA.* 2006, 103(46): 17501–17506.
[61] Liu W, Ge TT, Leng YS, et al. The role of neural plasticity in depression: from hippocampus to prefrontal cortex. *Neural Plast.* 2017, 2017: 6871089.
[62] Zheng J, Jiang YY, Xu LC, et al. Adult hippocampal neurogenesis along the dorsoventral axis contributes differentially to environmental enrichment combined with voluntary exercise in alleviating chronic inflammatory pain in mice. *J Neurosci.* 2017, 37(15): 4145–4157.
[63] Lempel AA, Coll L, Schinder AF, et al. Chronic pregabalin treatment decreases excitability of dentate gyrus and accelerates maturation of adult-born granule cells. *J Neurochem.* 2017, 140(2): 257–267.
[64] Dimitrov EL, Tsuda MC, Cameron HA, et al. Anxiety- and depression-like behavior and impaired neurogenesis evoked by peripheral neuropathy persist following resolution of prolonged tactile hypersensitivity. *J Neurosci.* 2014, 34(37): 12304–12312.
[65] Westlake KP, Byl NN. Neural plasticity and implications for hand rehabilitation after neurological insult. *J Hand Ther.* 2013, 26(2): 87–93.
[66] Fasick V, Spengler RN, Samankan S, et al. The hippocampus and TNF: Common links between chronic pain and depression. *Neurosci Biobehav Rev.* 2015, 53: 139–159.
[67] Apkarian AV, Mutso AA, Centeno MV, et al. Role of adult hippocampal neurogenesis in persistent pain. Pain. 2016, 157(2): 418–428.

[68] Dellarole A, Morton P, Brambilla R, et al. Neuropathic pain-induced depressive-like behavior and hippocampal neurogenesis and plasticity are dependent on TNFRI signaling. Brain Behav Immun. 2014, 41: 65–81.

[69] Norman GJ, Karelina K, Zhang N, et al. Stress and IL-1beta contribute to the development of depressive-like behavior following peripheral nerve injury. Mol Psychiatry. 2010, 15(4): 404–414.

[70] Li Q, Liu SB, Zhu XC, et al. Hippocampal PKR/TLR4 inflammasome pathway is required for the depression-like behaviors in rats with neuropathic pain. Neuroscience. 2019, 412: 16–28.

[71] Al-Amin H, Sarkis R, Atweh S, et al. Chronic dicyclopinine or apomorphine and development of neuropathy in two animal models II: Effects on brain cytokines and neurotrophins. Exp Neurol. 2011, 228(1): 30–40.

[72] Egorova E, Starinets A, Tyrtysnnaia A, et al. Hippocampal neurogenesis in conditions of chronic stress induced by sciatic nerve injury in the rat. Cells Tissues Organs (Print). 2019, 207(1): 58–68.

[73] Schäfers M, Svensson CI, Sommer C, et al. Tumor necrosis factor-alpha induces mechanical allodynia after spinal nerve ligation by activation of p38 MAPK in primary sensory neurons. J Neurosci. 2003, 23(7): 2517–2521.

[74] Ohtori S, Takahashi K, Moriya H, et al. TNF-alpha and TNF-alpha receptor type 1 upregulation in glia and neurons after peripheral nerve injury: studies in murine DRG and spinal cord. Spine. 2004, 29(10): 1082–1088.

[75] Zelenka M, Schäfers M, Sommer C. Intraneuronal injection of interleukin-1beta and tumor necrosis factor-alpha into rat sciatic nerve at physiological doses induces signs of neuropathic pain. Pain. 2005, 116(3): 257–263.

[76] Berg DA, Belnoue L, Song HJ, et al. Neurotransmitter-mediated control of neurogenesis in the adult vertebrate brain. Development. 2013, 140(12): 2548–2561.

[77] Covey WC, Ignatowski TA, Knight PR, et al. Brain-derived TNFalpha: involvement in neuroplastic changes implicated in the conscious perception of persistent pain. Brain Res. 2000, 859(1): 113–122.

[78] Ignatowski TA, Covey WC, Knight PR, et al. Brain-derived TNFalpha mediates neuropathic pain. Brain Res. 1999, 841(1/2): 70–77.

[79] Starke K. Regulation of noradrenaline release by presynaptic receptor systems. Rev Physiol Biochem Pharmacol. 1977, 77: 1–124.

[80] Ignatowski TA, Sud R, Reynolds JL, et al. The dissipation of neuropathic pain paradoxically involves the presence of tumor necrosis factor-alpha (TNF). Neuropharmacology. 2005, 48(3): 448–460.

[81] Fiore NT, Austin PJ. Glial-cytokine-neuronal adaptations in the ventral hippocampus of rats with affective behavioral changes following peripheral nerve injury. Neuroscience. 2018, 390: 119–140.

[82] Kuzumaki N, Ikegami D, Imai S, et al. Enhanced IL-1beta production in response to the activation of hippocampal glial cells impairs neurogenesis in aged mice. Synapse. 2010, 64(9): 721–728.

[83] Li MM, Li CL, Yu HJ, et al. Lentivirus-mediated interleukin-1β (IL-1β) knock-down in the hippocampus alleviates lipopolysaccharide (LPS)-induced memory deficits and anxiety- and depression-like behaviors in mice. J Neuroinflammation. 2017, 14(1): 190.

[84] Song LM, Pei L, Yao SL, et al. NLRP3 inflammasome in neurological diseases, from functions to therapies. Front Cell Neurosci. 2017, 11: 63.

[85] Mokhtari T, Akbari M, Malek F, et al. Improvement of memory and learning by intracerebroventricular microinjection of T3 in rat model of ischemic brain stroke mediated by upregulation of BDNF and GDNF in CA1 hippocampal region. Daru. 2017, 25(1): 4.

[86] Nuseir KQ, Altarifi AY, Tasslaq A, et al. Early and late anti noiceptive effects of sucrose on neonatal inflammatory pain in rats: Comparison to a non-steroidal anti-inflammatory drug. Physiol Behav. 2019, 206: 37–42.

[87] Eftekhar S, Mehrabi S, Soleimani M, et al. BDNF modifies hippocampal KCC2 and NKCC1 expression in a temporal lobe epilepsy model. Acta Neurobiol Exp (Wars). 2014, 74(3): 276–287.

[88] Merighi A, Salio C, Ghirri A, et al. BDNF as a pain modulator. Prog Neurobiol. 2008, 85(3): 297–317.

[89] Sosanya NM, Garza TH, Stacey W, et al. Involvement of brain-derived neurotrophic factor (BDNF) in chronic intermittent stress-induced enhanced mechanical allodynia in a rat model of burn pain. BMC Neurosci.
[90] Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009, **10**(9): 895–926.

[91] Coull JA, Beggs S, Boudreau D, et al. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. *Nature*. 2005, **438**(7070): 1017–1021.

[92] Boulle F, van den Hove DL, Jakob SB, et al. Epigenetic regulation of the BDNF gene: implications for psychiatric disorders. *Mol Psychiatry*. 2012, **17**(6): 584–596.

[93] Karege F, Perret G, Bondolfi G, et al. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res*. 2002, **109**(2): 143–148.

Tahmineh Mokhtari received her Ph.D. degree in Anatomical Sciences from School of Medicine, Tehran University of Sciences, Tehran, Iran (2017), and now she is working as CAS-TWAS Fellowship at Institute of Psychology, Chinese Academy of Sciences, Beijing, China. Currently, she is working on the neurobiology of pain and its relationship with depression. She has published several papers with a focus on cellular and molecular mechanisms in the pathogenesis of neurodegenerative disorders. E-mail: mokhtari.tmn@mails.ucas.ac.cn

Yiheng Tu received his Ph.D. degree from the University of Hong Kong in 2016 and then completed his postdoctoral training in Massachusetts General Hospital and Harvard Medical School. Now he is an Instructor at Harvard Medical School and a faculty member at Massachusetts General Hospital. He has published many papers on high-quality journals, including *Neurology*, *PNAS*, *Journal of Neuroscience*. His current research interests focus on developing biomarkers of neuropsychiatric disorders using machine learning and neuroimaging techniques. E-mail: yihengtu@gmail.com

Li Hu received his Ph.D. degree in Biomedical Engineering from the University of Hong Kong, Hong Kong, China (2010). He is now a professor in Institute of Psychology, Chinese Academy of Sciences, Beijing, China. He has published many papers on high-quality journals, including *PNAS*, *Trends in Neurosciences*, *Journal of Neuroscience*. His current research interests focus on the psychophysiological mechanism of pain and the development of non-pharmacological analgesic strategies. E-mail: huli@psych.ac.cn