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针刺干预痛情绪的神经环路机制研究进展

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【摘　要】 痛情绪的发生发展与中枢神经环路结构和功能变化密切相关。针刺可有效缓解痛情绪，减轻与疼痛相关的焦虑、抑郁和痛厌恶记忆等负性情绪，其机制与针刺调节特定神经环路功能密切相关。本文对针刺干预的痛情绪相关环路进行梳理，总结出与焦虑相关的环路包括前喙扣带皮质→丘脑（$rACC^{Glu}$→Th）、前喙扣带皮质→中缝背核（$rACC^{Glu}$→DRN）、前喙扣带皮质→腹外侧导水管周围灰质（$rACC^{Glu}$→vlPAG）、基底外侧杏仁核→前喙扣带皮质（$BLA^{CaMK\,II}$→rACC）、中脑腹侧被盖区→伏隔核（VTA^{DA}→NAc）；与抑郁相关的环路为边缘下皮层→基底外侧杏仁核（$IL^{CaMK\,II\,\alpha+}$→BLA）；与痛厌恶记忆及奖赏相关的环路为边缘下皮层→伏隔核（IL^{Glu}→NAc）。其中，针刺可能通过抑制$rACC^{Glu}$→Th、$rACC^{Glu}$→vlPAG，激活$rACC^{Glu}$→DRN、$BLA^{CaMK\,II}$→rACC、VTA^{DA}→NAc环路发挥镇痛和抗焦虑的作用；通过抑制$IL^{CaMK\,II\,\alpha+}$→BLA环路发挥针刺的镇痛和抗抑郁作用；通过激活IL^{Glu}→NAc环路发挥针刺镇痛和调节痛厌恶记忆及奖赏的作用。这为针刺治疗痛情绪的神经环路机制研究和应用提供了参考依据。

【关键词】 痛情绪；神经环路；针刺；焦虑；抑郁；痛厌恶记忆

Research progress on neural circuit mechanisms of acupuncture intervention in pain-related emotions

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【ABSTRACT】 The occurrence and development of pain-related emotions are closely associated with structural and functional alterations in central neural circuits. Acupuncture can effectively alleviate pain-related emotions and reduce pain-associated negative emotions such as anxiety, depression and pain-aversive memory, and its mechanism is tightly correlated with the regulatory effect of acupuncture on the functions of specific neural circuits. This article sorts out the pain-related emotion-associated neural circuits modulated by acupuncture, and summarizes the relevant circuits as follows: the anxiety-related circuits include rostral anterior cingulate cortex glutamatergic neurons → thalamus ($rACC^{Glu}$→Th), rostral anterior cingulate cortex glutamatergic neurons → dorsal raphe nucleus ($rACC^{Glu}$→DRN), rostral anterior cingulate cortex glutamatergic neurons → ventrolateral periaqueductal gray ($rACC^{Glu}$→vlPAG), basolateral amygdala $CaMK\,II\alpha^{+}$neurons → rostral anterior cingulate cortex ($BLA^{CaMK\,II}$→rACC), and ventral tegmental area dopaminergic neurons → nucleus accumbens (VTA^{DA}→NAc); the depression-related circuit is infralimbic cortex $CaMK\,II\,\alpha^{+}$ neurons → basolateral amygdala ($IL^{CaMK\,II\,\alpha+}$→BLA); the circuit related to pain-aversive memory and reward is infralimbic cortex glutamatergic neurons → nucleus accumbens (IL^{Glu}→NAc). Among these, acupuncture may exert analgesic and anxiolytic effects by inhibiting the $rACC^{Glu}$→Th and $rACC^{Glu}$→vlPAG circuits, and activating the $rACC^{Glu}$→DRN, $BLA^{CaMK\,II}$→rACC and VTA^{DA}→NAc circuits; produce analgesic and antidepressant effects by suppressing the $IL^{CaMK\,II\,\alpha+}$→BLA circuit; and achieve analgesic effects as well as regulate pain-aversive memory and reward by activating the IL^{Glu}→NAc circuit. This review provides a reference for the research and application of neural circuit mechanisms underlying acupuncture treatment of pain-related emotions.

【KEYWORDS】 Pain-related emotions; Neural circuits; Acupuncture; Anxiety; Depression; Pain-aversive memory

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疼痛是一种与实际或潜在组织损伤相关或类似的令人不快的感觉和情绪体验[1]。疼痛作为一种主观性极强的多维体验，常伴随焦虑[2]、抑郁[3]、痛厌恶[4]等负性情绪，形成“痛情绪”的临床特征，严重影响患者生活质量和社会功能[5]。流行病学调查研究显示，约有20%～30%的慢性疼痛患者存在负面情感[6-7]，疼痛与情感相互影响，互为因果[8]。目前，药物和心理疗法是治疗痛情绪的主要方法[9-10]，但通常会伴有妄想、幻觉、思维和行为紊乱、感知障碍和不恰当的情绪等严重不良反应[11]。针刺在调控痛情绪方面展现出多层次、多维度的作用机制，既可提高痛阈缓解疼痛感知，又能改善焦虑、抑郁、厌恶等负性情绪状态，对由疼痛引发的情绪波动及认知功能变化均有积极的干预作用[12-14]。

随着脑影像学和神经生物学技术的发展，多项研究显示[15-17]，针刺缓解疼痛改善相关的情绪症状，其作用机制可能与调节相关神经环路密切相关，针刺干预痛情绪神经环路的研究逐渐成为神经调控领域的热点。本文就针刺调节疼痛伴焦虑、抑郁、痛厌恶记忆及奖赏相关神经环路进行梳理总结，以期为针刺调节痛情绪神经环路机制的进一步研究提供理论基础和依据。

1 痛情绪神经环路损伤机制概述

疼痛不仅是单纯的感觉信号传递过程，更是一种与情绪密切交织的复杂神经行为状态[18]。慢性疼痛常伴随焦虑、抑郁等负性情绪反应，其本质是多个脑区之间神经环路功能异常的结果，即所谓的“痛情绪神经环路”受损[19-20]；主要涉及前喙扣带皮质（rACC）[21]、丘脑（Th）[22]、中缝背核（DRN）[23]、腹外侧中脑导水管周围灰质（vlPAG）[24]、基底外侧杏仁核（BLA）[16]、中脑腹侧被盖区（VTA）[25]、伏隔核（NAc）[26]、外侧缰核（LHb）[27]、边缘下皮层（IL）[28]、岛叶皮层（IC）[29]等中枢结构，这些区域共同参与对疼痛的感知、调节及其情绪反应的整合[4]。研究[30]表明，兴奋性谷氨酸（Glu）能系统过度激活，抑制性γ-氨基丁酸（GABA）能系统功能下降，导致脑区间信号传递失衡，引发神经网络的可塑性改变。功能连接的削弱或重塑被认为是痛觉敏感化与情绪障碍产生的核心机制之一[31]。因此，痛情绪神经环路的损伤不仅是慢性疼痛持续化的病理基础，也构成了疼痛与情绪障碍的重要神经机制[32-33]。而针刺对上述关键脑区及其连接网络具有调节作用，可能通过重塑相关神经环路的功能状态，发挥镇痛与情绪改善的双重效应，是针刺干预痛情绪的中枢作用机制，为临床治疗提供了潜在的神经调控靶点[34]。

2 针刺调节疼痛伴焦虑相关神经环路

2.1 前喙扣带皮质→丘脑（rACC^{Glu}→Th）

rACC位于胼胝体前方，是前扣带皮层的一部分，接收来自Th和脑干的传入信息，并与前额叶外侧皮质保持紧密的功能连接[35]。rACC是介导慢性疼痛负性情绪的关键结构，其中的Glu能神经元是诱发疼痛相关负面情绪的必要和充分条件[36-37]。Th是向大脑皮层传递伤害性感受信息的重要中转站[38]，在疼痛的上行传导和下行调控机制中均具有重要作用[39]。有研究[40]采用顺行示踪病毒识别来自rACC的Glu能神经元（rACC^{Glu}）投射核的输入区域，证明在接收rACC投射的从属核中，Th的腹前核/腹外侧核与疼痛认知和决策相关。

Shen等[41]向rACC内注射能特异性标记Glu能神经元的顺行示踪病毒，证实自rACC的Glu能神经元（rACC^{Glu}）可投射到Th，化学遗传学激活rACC向Th输出的Glu能神经元，可诱导大鼠产生焦虑样行为；化学遗传学抑制rACC向Th输出的Glu能神经元，可缓解完全弗氏佐剂（CFA）诱导的炎性痛大鼠的焦虑样行为。同时观察到电针“足三里”“三阴交”能有效减少CFA诱导的大鼠焦虑样行为，而化学遗传学激活rACC^{Glu}→Th神经环路有效阻断电针对CFA大鼠慢性疼痛诱导的焦虑样行为的影响，表明针刺可能通过抑制rACC^{Glu}→Th神经环路发挥对慢性疼痛伴焦虑样行为的治疗作用。

2.2 前喙扣带皮质→中缝背核（rACC^{Glu}→DRN）

DRN是位于中脑的神经核团，是中枢神经系统中最主要五羟色胺（5-HT）能神经元，通过广泛的投射参与调控疼痛感知和情绪反应[42]。有多项研究[15,17]采用病毒示踪技术证实DRN与ACC之间存在直接的神经纤维投射关系。

Xu等[17]将顺行示踪病毒注射到rACC，将逆行示踪病毒注射到DRN，观察到自rACC的Glu能神经元可投射到DRN的5-HT能神经元，rACC与DRN存在解剖学联系。化学遗传学激活rACC^{Glu}→DRN神经环路可缓解神经病理痛小鼠机械性异常性疼痛和焦虑样行为；化学遗传学抑制rACC^{Glu}→DRN神经环路并未诱导出正常小鼠机械性异常性疼痛和焦虑样行为。电针“足三里”“三阴交”可改善神经病理痛小鼠机械性异常疼痛及焦虑样行为，化学遗传学抑制rACC^{Glu}→DRN神经环路可阻断电

针的镇痛和抗焦虑作用；电针 $rACC^{Glu}$→DRN 神经环路的激活对机械性异常性疼痛和焦虑样行为没有产生协同效应。神经元的钙/钙调蛋白依赖性蛋白激酶Ⅱ（CaMKⅡ）作为兴奋性神经递质 Glu 信号转导的关键调控因子参与调节疼痛感知等过程[43-44]。Wu 等[15]采用顺行示踪病毒注射至前 rACC，逆行示踪病毒注射至 DRN，观察到 rACC 的 CaMKⅡ神经元可投射至 DRN 的 5-HT 能神经元；化学遗传学激活 $rACC^{CaMKⅡ}$→DRN^{5-HT} 神经环路可缓解由 CFA 诱导的焦虑样行为，而抑制该通路则加重焦虑样行为。电针刺激“足三里”“三阴交”可改善 CFA 诱导的焦虑样行为，而化学遗传学抑制 $rACC^{CaMKⅡ}$→DRN^{5-HT} 神经环路可阻断电针的抗焦虑作用。上述研究表明，针刺可能通过激活 $rACC^{Glu}$→DRN 神经环路发挥镇痛和抗焦虑的作用。

2.3 前喙扣带皮质→腹外侧导水管周围灰质（$rACC^{Glu}$→vlPAG）

vlPAG 是神经系统中调节疼痛感受的关键部位，不仅传递疼痛感觉的上行通路，也是中枢神经系统疼痛下行调控系统中的一个关键核团[45]。vlPAG 对疼痛的调控具有细胞类型特异性和复杂性，有研究[46]通过化学遗传学方法观察到广泛激活 vlPAG 中的 Glu 能神经元可产生镇痛效应，但该区域也接受来自上游脑区的兴奋性投射并参与疼痛的易化。因此 vlPAG 与疼痛高度相关。除参与疼痛的调控外，vlPAG 还能双向调节焦虑样情绪[47]。

Zhu 等[24]在 rACC 中注射顺行示踪病毒，观察到自 rACC 的 Glu 能神经元（$rACC^{Glu}$）可投射到 vlPAG，并利用化学遗传学特异性激活 rACC 输出到 vlPAG 的 Glu 能神经元，可诱导小鼠产生痛觉过敏和焦虑样行为，化学遗传学抑制 rACC 输出到 vlPAG 的 Glu 能神经元，可减少神经病理性疼痛小鼠的痛觉和焦虑样症状，同时观察到电针“足三里”“三阴交”能显著减轻神经病理痛模型小鼠的痛觉过敏和焦虑样行为，化学遗传学激活 $rACC^{Glu}$→vlPAG 神经环路可阻断电针对神经病理痛小鼠的镇痛作用，但不影响慢性疼痛诱导的焦虑情绪。以上研究表明，针刺可能通过抑制 $rACC^{Glu}$→vlPAG 神经环路发挥对神经病理性疼痛的治疗作用。

2.4 基底外侧杏仁核→前喙扣带皮质（$BLA^{CaMKⅡ}$→rACC）

BLA 属于杏仁核的一部分，广泛表达 CaMKⅡ能神经元，在慢性疼痛过程中表现出高度的神经电生理活动[48-49]，是痛相关负性情绪产生的高级中枢[50-51]，且已有研究证实 rACC 与 BLA 之间存在相互投射[52]。研究[53]显示，rACC 的传入神经元主要来自 BLA，且 BLA 可接收来自 rACC 的调控信号，介导痛觉相关的负性情绪反应。CaMKⅡ广泛定位于神经元的突触后密度区，尤其在树突棘中高度富集[54]，是介导突触可塑性、学习与记忆的关键分子[55]。CaMKⅡ阳性神经元主要为兴奋性 Glu 能神经元[56]，在调节空间记忆[57]、认知情绪[58]及奖赏反应[59]中发挥重要作用，被视为神经环路调控和神经精神疾病研究的重要靶点。

CHEN 等[16]将顺行示踪病毒注射到 BLA，将逆行示踪病毒注射到 rACC，证实了 BLA 到 rACC 存在 CaMKⅡ神经元投射。化学遗传学抑制 $BLA^{CaMKⅡ}$→rACC 神经环路可诱导正常小鼠出现机械异常性疼痛和焦虑行为，化学遗传学激活 $BLA^{CaMKⅡ}$→rACC 神经环路可减轻神经病理痛小鼠机械异常性疼痛，改善焦虑样行为。电针“足三里”“三阴交”可减轻神经病理痛小鼠的机械性异常疼痛和焦虑样行为，抑制 $BLA^{CaMKⅡ}$→rACC 神经环路可阻断针刺的镇痛和抗焦虑作用。以上研究表明，针刺可减轻神经病理痛小鼠的机械异常性疼痛和焦虑样行为，可能是通过激活 $BLA^{CaMKⅡ}$→rACC 神经环路发挥镇痛和抗焦虑作用的。

2.5 中脑腹侧被盖区→伏隔核（VTA^{DA}→NAc）

VTA 位于黑质和红核之间，由多种类型神经元构成的核团[60]，其中包含约 65% 的多巴胺（DA）能神经元[61]。NAc 位于基底节与边缘系统的交界区域，NAc 是 VTA 的主要下游脑区，接受大量的兴奋性 Glu 能神经元传入，并从 VTA 接受 DA 能神经元传入，是调节动机、情绪处理和奖赏的关键脑区[62-63]。研究[64]显示，NAc 在慢性疼痛的维持及急性疼痛向慢性疼痛转化过程中具有重要的调控地位，VTA 中的 DA 能神经元及其相关神经环路在疼痛调制中发挥着关键作用[65]。有研究[63]证实，慢性神经病理性疼痛状态下，VTA 的 DA 神经元兴奋性增加，并通过向其投射靶区 NAc 释放脑源性神经营养因子（BDNF）参与调节慢性疼痛的发生发展。

魏夏利[66]在研究中观察到，慢性炎性痛大鼠 VTA^{DA}→NAc 活性降低，化学遗传学激活 VTA^{DA}→NAc 神经环路可减轻慢性炎性痛大鼠疼痛感受，改善负性情绪；而针刺可提高炎性痛大鼠痛阈，改善负性情绪，化学遗传学抑制 VTA^{DA}→NAc 神经环路可部分阻断电针对慢性疼痛及相关负性情绪的调节作用。以上结果表明，针刺可能通过激活 VTA^{DA}→

NAc神经环路发挥镇痛和调节负性情绪作用。

3 针刺调节疼痛伴抑郁相关神经环路-边缘下皮层→基底外侧杏仁核(IL$^{CaMK\,II\,\alpha+}$→BLA)

IL作为内侧前额叶皮层(mPFC)的关键组成部分参与情绪调节,在调控疼痛相关的情绪反应中发挥着重要作用[67],在慢性疼痛状态下,IL区域的灰质逐渐减少,表明IL区域与慢性疼痛之间存在紧密联系[68]。BLA对控制焦虑和抑郁样行为也至关重要,并参与慢性疼痛处理[69-70]。并有研究证实IL和BLA之间存在环路连接[71]。

Xie等[28]研究显示,神经病理痛小鼠出现机械异常疼痛和焦虑、抑郁样行为,且IL中Glu能神经元活性增加。将顺行示踪病毒AAV2/9-CaMKⅡα-EGFP注射入IL脑区,将逆行示踪病毒AAV2/R-CaMKⅡα-EGFP注射入BLA脑区,观察到自IL的Glu能神经元可投射到BLA,证实了IL$^{CaMK\,II\,\alpha+}$→BLA回路的解剖连接。化学遗传学激活IL$^{CaMK\,II\,\alpha+}$→BLA神经环路诱导神经病理痛小鼠出现抑郁样行为,但对机械性异常性疼痛和焦虑样行为无明显影响;化学遗传学抑制IL$^{CaMK\,II\,\alpha+}$→BLA神经环路可减轻神经病理痛小鼠的机械异常性疼痛和抑郁样行为。电针"足三里""三阴交"可有效缓解慢性疼痛及其伴随的抑郁样情绪,激活IL$^{CaMK\,II\,\alpha+}$→BLA环路可逆转电针对神经病理痛小鼠的镇痛抗抑郁效应。上述研究表明,针刺可减轻神经病理痛小鼠机械异常性疼痛,改善抑郁样行为,化学遗传学激活IL$^{CaMK\,II\,\alpha+}$→BLA神经环路可拮抗针刺的镇痛和抗抑郁作用。

4 针刺调节痛厌恶记忆及奖赏相关神经环路—边缘下皮层→伏隔核(IL^{Glu}→NAc)

前额皮质(PFC)中的Glu能神经元下行投射环路,是介导大脑皮层奖赏效应的关键神经环路[72]。其中mPFC中的IL与NAc之间存在密切的解剖和功能连接,主要通过Glu能神经元投射实现信号传递,在调节奖赏、动机、情绪及疼痛相关情绪行为中发挥着关键作用[73]。研究[74]表明,mPFC→NAc环路投射在调控疼痛相关情绪中发挥着重要作用,激活mPFC→NAc环路可有效缓解厌恶性疼痛行为。另有研究[75]显示,光遗传激活mPFC→NAc的投射可缓解与慢性神经性疼痛相关的感觉异常性疼痛和厌恶性学习。

刘会等[76]利用工具病毒及光遗传学技术证实,电针"足三里"可通过激活IL和NAc的兴奋性Glu能神经元而降低神经病理痛小鼠的热痛阈值,发挥镇痛效应,同时可改善小鼠的条件性位置偏爱,产生奖赏效应;光遗传学激活IL^{Glu}→NAc神经环路可发挥与电针同等的镇痛效应,表明电针可以通过对IL和NAc的兴奋性Glu能神经元的调节而产生镇痛作用。以上研究表明,针刺可能通过激活IL^{Glu}→NAc神经环路发挥镇痛和调节痛厌恶记忆及奖赏的作用。

5 小结

疼痛是一种复杂的生理与心理过程,患者在经历疼痛的同时常常伴随抑郁、焦虑、痛厌恶记忆等负性情绪,彼此相互作用、相互影响,加重患者的身心负担[39]。针灸治疗具有多维度、多层次和多靶点的整体调节特性,不仅能够有效缓解疼痛,还能显著改善与疼痛相关的焦虑、抑郁、厌恶等负性情绪[21]。本文从疼痛伴焦虑、抑郁、厌恶记忆及奖赏调节等多个维度,梳理了针刺干预所涉及的关键中枢结构和神经环路,认为疼痛与情绪密切相关,二者在中枢层面通过多个脑区交互形成复杂的神经网络。其中,针刺可通过抑制rACC^{Glu}→Th、rACC^{Glu}→vlPAG、IL$^{CaMK\,II\,\alpha+}$→BLA,激活rACC^{Glu}→DRN、BLA$^{CaMK\,II}$→rACC、VTA^{DA}→NAc、IL^{Glu}→NAc^{Glu}神经环路发挥镇痛和改善情绪的双重作用,展现出多维度、层次化的神经调控潜力。

尽管近年来该领域取得了诸多进展,但目前的研究仍存在一定局限。(1)针刺对疼痛伴抑郁、痛厌恶记忆及奖赏的中枢环路机制研究较为单一局限,尚缺乏多环路、多脑区协同机制的系统研究;(2)多数研究聚焦于单一通路或局部脑区的作用,而对于针刺在全脑功能网络中的整体调节作用尚缺乏系统性描述,难以揭示其在复杂神经系统中真正的调控路径;(3)针刺参数(如取穴组合、刺激强度、频率和持续时间)对神经环路的影响尚未明晰,缺乏统一标准;(4)不同类型痛情绪(如焦虑主导型、抑郁主导型)是否存在特异性神经环路响应,也有待进一步分类探讨。未来的研究应结合功能磁共振成像(fMRI)、正电子发射断层扫描(PET)、弥散张量成像(DTI)等多模态影像学手段,建立多中心、动态化的神经网络调控模型,探索针刺对多环路、多脑区协同调节机制的全貌;并结合神经免疫、脑肠轴、代谢组等多系统整合研究思路,系统深入地揭示针刺调控痛情绪的神经环路机制研究。

利益冲突 所有作者声明不存在利益冲突。作者严兴科为

本刊编委,但未参与本文的审理。

参考文献

[1] RAJA S N, CARR D B, COHEN M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises [J]. Pain, 2020, 161(9): 1976-1982.

[2] WANG D, PAN X Y, ZHOU Y, et al. Lateral septum-lateral hypothalamus circuit dysfunction in comorbid pain and anxiety[J]. Mol Psychiatry, 2023, 28(3): 1090-1100.

[3] CHEN J, GAO Y, BAO S T, et al. Insula→Amygdala and Insula→Thalamus pathways are involved in comorbid chronic pain and depression-like behavior in mice [J]. J Neurosci, 2024, 44(15): e2062232024.

[4] MERCER LINDSAY N, CHEN C, GILAM G, et al. Brain circuits for pain and its treatment[J]. Sci Transl Med, 2021, 13(619): eabj7360.

[5] NAVRATILOVA E, MORIMURA K, XIE J Y, et al. Positive emotions and brain reward circuits in chronic pain[J]. J Comp Neurol, 2016, 524(8): 1646-1652.

[6] EDWARDS R R, DWORKIN R H, SULLIVAN M D, et al. The role of psychosocial processes in the development and maintenance of chronic pain[J]. J Pain, 2016, 17(9 Suppl): T70-T92.

[7] AHN H, WEAVER M, LYON D, et al. Depression and pain in Asian and white Americans with knee osteoarthritis[J]. J Pain, 2017, 18(10): 1229-1236.

[8] SHI Y, YAO S J, SHEN Z, et al. Effect of electroacupuncture on pain perception and pain-related affection: dissociation or interaction based on the anterior cingulate cortex and S1 [J]. Neural Plast, 2020, 2020: 8865096.

[9] YANG P, WANG T, HE Y J, et al. Research trends of acupuncture therapy for chronic pain-related depression or anxiety from 2003 to 2023: a bibliometric analysis[J]. J Pain Res, 2023, 16: 4301-4315.

[10] BUSHNELL M C, CEKO M, LOW L A. Cognitive and emotional control of pain and its disruption in chronic pain[J]. Nat Rev Neurosci, 2013, 14(7): 502-511.

[11] SHIN S W, LEE J S, ABDI S, et al. Antipsychotics for patients with pain[J]. Korean J Pain, 2019, 32(1): 3-11.

[12] PATIL S, SEN S, BRAL M, et al. The role of acupuncture in pain management[J]. Curr Pain Headache Rep, 2016, 20(4): 22.

[13] 卢宏玉, 王宝金, 马翠, 等. 针刺调节γ-氨基丁酸能系统改善痛情绪的机制研究进展[J]. 针刺研究, 2025, 50(9): 1095-1102.
LU H Y, WANG B J, MA C, et al. Mechanism research progress of acupuncture for ameliorating pain-related emotions through regulating GABAergic system (in Chinese) [J]. Acupuncture Research, 2025, 50(9): 1095-1102.

[14] 方剑乔, 邵晓梅. 针刺镇痛的新思路: 针灸参与疼痛多维度调节的可行性[J]. 针刺研究, 2017, 42(1): 85-89.
FANG J Q, SHAO X M. New trains of thoughts about acupuncture analgesia: acupuncture analgesia may involve multi-dimensional regulation of pain (in Chinese) [J]. Acupuncture Research, 2017, 42(1): 85-89.

[15] WU Z M, SHEN Z, XU Y L, et al. A neural circuit associated with anxiety-like behaviors induced by chronic inflammatory pain and the anxiolytic effects of electroacupuncture[J]. CNS Neurosci Ther, 2024, 30(4): e14520.

[16] CHEN Y R, TONG S Y, XU Y L, et al. Involvement of basolateral amygdala-rostral anterior cingulate cortex in mechanical allodynia and anxiety-like behaviors and potential mechanisms of electroacupuncture[J]. CNS Neurosci Ther, 2024, 30(9): e70035.

[17] XU Y L, ZHU X X, CHEN Y R, et al. Electroacupuncture alleviates mechanical allodynia and anxiety-like behaviors induced by chronic neuropathic pain *via* regulating rostral anterior cingulate cortex-dorsal raphe nucleus neural circuit[J]. CNS Neurosci Ther, 2023, 29(12): 4043-4058.

[18] APKARIAN A V, BUSHNELL M C, TREEDE R D, et al. Human brain mechanisms of pain perception and regulation in health and disease[J]. Eur J Pain, 2005, 9(4): 463-484.

[19] HASHMI J A, BALIKI M N, HUANG L J, et al. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits [J]. Brain, 2013, 136(Pt 9): 2751-2768.

[20] BALIKI M N, APKARIAN A V. Nociception, pain, negative moods, and behavior selection[J]. Neuron, 2015, 87(3): 474-491.

[21] 李丽, 马翠, 魏玉婷, 等. 针刺调节前扣带皮层功能改善痛情绪的研究进展[J]. 针刺研究, 2024, 49(10): 1092-1099.
LI L, MA C, WEI Y T, et al. Research progress of acupuncture in improving pain emotion by regulating functions of anterior cingulate cortex (in Chinese) [J]. Acupuncture Research, 2024, 49(10): 1092-1099.

[22] DENG J, CHEN L, LIU C C, et al. Distinct thalamo-subcortical circuits underlie painful behavior and depression-like behavior following nerve injury[J]. Adv Sci, 2024, 11(34): 2401855.

[23] ZHOU W J, JIN Y, MENG Q, et al. A neural circuit for comorbid depressive symptoms in chronic pain [J]. Nat Neurosci, 2019, 22(10): 1649-1658.

[24] ZHU X X, XU Y L, SHEN Z, et al. Rostral anterior cingulate cortex-ventrolateral periaqueductal gray circuit underlies electroacupuncture to alleviate hyperalgesia but not anxiety-like behaviors in mice with spared nerve injury [J]. Front Neurosci, 2022, 15: 757628.

[25] ZHANG L D, JI M H, SUN Y F, et al. VTA dopaminergic neurons involved in chronic spared nerve injury pain-induced depressive-like behavior [J]. Brain Res Bull, 2025, 222: 111261.

[26] YANG Y N, WEI X L, TIAN J, et al. Scalp electroacupuncture targeting the VTA(DA) neurons to relieve negative emotions and promote the alleviation of chronic pain [J]. Front Neurosci, 2023, 17: 1323727.

[27] CHEN T, LIU W B, ZHU S J, et al. Differential modulation of pain and associated anxiety by GABAergic neuronal circuits in the lateral habenula[J]. Proc Natl Acad Sci USA, 2024, 121(48): e2409443121.

[28] XIE Y P, SHEN Z, ZHU X X, et al. Infralimbic-basolateral amygdala circuit associated with depression-like not anxiety-like behaviors induced by chronic neuropathic pain and the antidepressant effects of electroacupuncture [J]. Brain Res Bull, 2024, 218: 111092.

[29] LU C B, YANG T, ZHAO H, et al. Insular cortex is critical for the perception, modulation, and chronification of pain[J]. Neurosci Bull, 2016, 32(2): 191-201.

[30] ZHU X, ZHOU W J, JIN Y, et al. A central amygdala input to the parafascicular nucleus controls comorbid pain in depression[J]. Cell Rep, 2019, 29(12): 3847-3858.e5.

[31] 翁春娇, 李文娟, 姚紫云, 等. 颈椎病慢性颈肩痛患者脑功能网络研究[J]. 磁共振成像, 2020, 11(7): 511-517.
WENG C J, LI W J, YAO Z Y, et al. A research of the resting state network in patients with chronic neck and shoulder pain of cervical spondylosis (in Chinese)[J]. Chinese Journal of Magnetic Resonance Imaging, 2020, 11(7): 511-517.

[32] ZHU X, TANG H D, DONG W Y, et al. Distinct thalamocortical circuits underlie allodynia induced by tissue injury and by depression-like states[J]. Nat Neurosci, 2021, 24(4): 542-553.

[33] 王笑珂, 舒晴. 慢性疼痛与负性情绪的神经交互机制及综合干预策略研究进展[J]. 中山大学学报(医学科学版), 2025, 46(2): 197-209.
WANG X K, SHU Q. The research progress on the neural interaction mechanisms and integrated intervention strategies of chronic pain and negative emotions (in Chinese) [J]. Journal of Sun Yat-sen University (Medical Sciences), 2025, 46(2): 197-209.

[34] SU N, CAI P P, DOU Z Q, et al. Brain nuclei and neural circuits in neuropathic pain and brain modulation mechanisms of acupuncture: a review on animal-based experimental research[J]. Front Neurosci, 2023, 17: 1243231.

[35] 陈丽梅, 李梦瑶, 黄颖欣, 等. 首发和复发抑郁症共病失眠的静息态脑功能网络特征初步比较研究[J]. 磁共振成像, 2025, 16(1): 89-94, 110.
CHEN L M, LI M Y, HUANG Y X, et al. A preliminary comparative study on the characteristics of resting-state brain functional networks in patients with comorbid insomnia in first-episode and recurrent depression (in Chinese) [J]. Chinese Journal of Magnetic Resonance Imaging, 2025, 16(1): 89-94, 110.

[36] GAO X Q, LIN J H, SUN L, et al. Activation of the N-methyl-D-aspartate receptor and calcium/calmodulin-dependent protein kinase Ⅱα signal in the rostral anterior cingulate cortex is involved in pain-related aversion in rats with peripheral nerve injury[J]. Behav Brain Res, 2023, 452: 114560.

[37] 肖思琦, 吴泽民, 沈醉, 等. 电针通过rACC谷氨酸能神经元缓解炎性痛伴发焦虑样行为[J]. 中国疼痛医学杂志, 2022, 28(7): 494-501.
XIAO S Q, WU Z M, SHEN Z, et al. Electroacupuncture alleviates the inflammatory pain-induced anxiety-like behaviors by glutamatergic neurons in rostral anterior cingulate cortex (in Chinese)[J]. Chinese Journal of Pain Medicine, 2022, 28(7): 494-501.

[38] LEPLUS A, ISAN P, BALOSSIER A, et al. Somatotopy of the sensory thalamus: inputs from directional deep brain stimulation in pain patients [J]. Ann Clin Transl Neurol, 2024, 11(6): 1502-1513.

[39] 马翠, 叶钰娟, 严兴科. 杏仁核介导的痛情绪神经环路研究进展[J]. 上海交通大学学报(医学版), 2023, 43(10): 1304-1310.
MA C, YE Y J, YAN X K. Research progress on the neural circuit of pain emotion mediated by amygdala (in Chinese)[J]. Journal of Shanghai Jiao Tong University (Medical Science), 2023, 43(10): 1304-1310.

[40] HOOKS B M, MAO T Y, GUTNISKY D A, et al. Organization of cortical and thalamic input to pyramidal neurons in mouse motor cortex[J]. J Neurosci, 2013, 33(2): 748-760.

[41] SHEN Z, ZHANG H Y, WU Z M, et al. Electroacupuncture alleviates chronic pain-induced anxiety disorders by regulating the rACC-thalamus circuitry[J]. Front Neurosci, 2021, 14: 615395.

[42] SOIZA-REILLY M, GOODFELLOW N M, LAMBE E K, et al. Enhanced 5-HT1A receptor-dependent feedback control over dorsal raphe serotonin neurons in the SERT knockout mouse[J]. Neuropharmacology, 2015, 89: 185-192.

[43] MONTES DE OCA BALDERAS P. Flux-independent NMDAR signaling: molecular mediators, cellular functions, and complexities[J]. Int J Mol Sci, 2018, 19(12): 3800.

[44] LV Z Y, XU X Q, SUN Z Y, et al. TRPV1 alleviates osteoarthritis by inhibiting M1 macrophage polarization *via* Ca^{2+}/CaMKⅡ/Nrf2 signaling pathway[J]. Cell Death Dis, 2021, 12(6): 504.

[45] 张秉宸, 马克涛, 罗淑. 中脑导水管周围灰质腹外侧区中γ-氨基丁酸受体在疼痛调节中作用的研究进展[J]. 中国疼痛医学杂志, 2023, 29(10): 759-765.
ZHANG B C, MA K T, LUO S. Research progress on the role of γ -aminobutyric acid receptor in pain regulation in ventrolateral gray matter around aqueduct of midbrain (in Chinese)[J]. Chinese Journal of Pain Medicine, 2023, 29(10): 759-765.

[46] SAMINENI V K, GRAJALES-REYES J G, COPITS B A, et al. Divergent modulation of nociception by glutamatergic and GABAergic neuronal subpopulations in the periaqueductal gray[J]. eNeuro, 2017, 4(2): ENEURO.0129-ENEURO.0116.2017.

[47] TOVOTE P, ESPOSITO M S, BOTTA P, et al. Midbrain circuits for defensive behaviour [J]. Nature, 2016, 534(7606): 206-212.

[48] MAZZITELLI M, MARSHALL K, PHAM A, et al. Optogenetic manipulations of amygdala neurons modulate spinal nociceptive processing and behavior under normal conditions and in an arthritis pain model[J]. Front Pharmacol, 2021, 12: 668337.

[49] 林鸿, 石天乐, 张玉秋, 等. 基底外侧杏仁核小胶质细胞参与单关节炎小鼠痛觉敏化和痛相关厌恶行为[J]. 复旦学报(医学版), 2024, 51(3): 285-294.
LIN H, SHI T L, ZHANG Y Q, et al. Contribution of microglia in the basolateral amygdala to pain hypersensitivity and pain-related aversion in mouse model of monoarthritis (in Chinese)[J]. Fudan University Journal of Medical Sciences, 2024, 51(3): 285-294.

[50] CORDER G, AHANONU B, GREWE B F, et al. An amygdalar neural ensemble that encodes the unpleasantness of pain[J]. Science, 2019, 363(6424): 276-281.

[51] DUAN K Z, GU Q H, PETRALIA R S, et al. Mitophagy in the basolateral amygdala mediates increased anxiety induced by aversive social experience[J]. Neuron, 2021, 109(23): 3793-3809.e8.

[52] KITAMURA T, OGAWA S K, ROY D S, et al. Engrams and circuits crucial for systems consolidation of a memory[J]. Science, 2017, 356(6333): 73-78.

[53] MA X Y, YU W, YAO P A, et al. Afferent and efferent projections of the rostral anterior cingulate cortex in young and middle-aged mice[J]. Front Aging Neurosci, 2022, 14: 960868.

[54] LISMAN J, SCHULMAN H, CLINE H. The molecular basis of CaMKⅡ function in synaptic and behavioural memory[J]. Nat Rev Neurosci, 2002, 3(3): 175-190.

[55] COULTRAP S J, BAYER K U. CaMKⅡ regulation in information processing and storage[J]. Trends Neurosci, 2012, 35(10): 607-618.

[56] WANG H, ARDILES A O, YANG S, et al. Metabotropic glutamate receptors induce a form of LTP controlled by translation and arc signaling in the hippocampus[J]. J Neurosci, 2016, 36(5): 1723-1729.

[57] HE T, LI N Q, SHI P B, et al. Electroacupuncture alleviates spatial memory deficits in METH withdrawal mice by enhancing astrocyte-mediated glutamate clearance in the dCA1[J]. Addict Biol, 2022, 27(1): e13068.

[58] WEI N X, GUO Z, YE R, et al. A systematic review of the pain-related emotional and cognitive impairments in chronic inflammatory pain induced by CFA injection and its mechanism[J]. IBRO Neurosci Rep, 2025, 18: 414-431.

[59] EBRAHIMI M N, BANAZADEH M, ALITANEH Z, et al. The distribution of neurotransmitters in the brain circuitry: Mesolimbic pathway and addiction[J]. Physiol Behav, 2024, 284: 114639.

[60] 赵炜楠, 胡苏皖, 翟晓静, 等. 中脑多巴胺奖赏系统与疼痛调控[J]. 中国疼痛医学杂志, 2021, 27(1): 20-30.
ZHAO W N, HU S W, ZHAI X J, et al. Dopamine reward system in midbrain and pain regulation (in Chinese)[J]. Chinese Journal of Pain Medicine, 2021, 27(1): 20-30.

[61] TAN K R, YVON C, TURIAULT M, et al. GABA neurons of the VTA drive conditioned place aversion[J]. Neuron, 2012, 73(6): 1173-1183.

[62] 韦东方, 周瑜, 潘翔宇, 等. 丘脑-边缘系统参与急性疼痛慢性化的研究进展[J]. 中国疼痛医学杂志, 2024, 30(2): 85-93.
WEI D F, ZHOU Y, PAN X Y, et al. The research progress on the involvement of the thalamic limbic system in the chronicity of acute pain (in Chinese)[J]. Chinese Journal of Pain Medicine, 2024, 30(2): 85-93.

[63] 刘风雨. 中脑奖赏环路中的BDNF参与慢性神经病理性疼痛的发病机制[J]. 中国疼痛医学杂志, 2017, 23(9): 647.
LIU F Y. BDNF in the midbrain reward circuit participates in the pathogenesis of chronic neuropathic pain (in Chinese)[J]. Chinese Journal of Pain Medicine, 2017, 23(9): 647.

[64] MAKARY M M, POLOSECKI P, CECCHI G A, et al. Loss of nucleus accumbens low-frequency fluctuations is a signature of chronic pain[J]. Proc Natl Acad Sci USA, 2020, 117(18): 10015-10023.

[65] SONG Q, WEI A Q, XU H D, et al. An ACC-VTA-ACC positive-feedback loop mediates the persistence of neuropathic pain and emotional consequences[J]. Nat Neurosci, 2024, 27(2): 272-285.

[66] 魏夏利. 调神电针通过调控VTA^{DA}-NAc环路改善负性情绪缓解慢性疼痛的机制研究[D]. 武汉: 武汉体育学院, 2024.
WEI X L. Mechanism of Shen-Shen electroacupuncture in alleviating negative emotions and chronic pain by modulating the VTA^{DA}-NAc circuit (in Chinese)[D]. Wuhan: Wuhan Sports University, 2024.

[67] VIANA M C, LIM C C W, GARCIA PEREIRA F, et al. Previous mental disorders and subsequent onset of chronic back or neck pain: findings from 19 countries[J]. J Pain, 2018, 19(1): 99-110.

[68] FITZGERALD J M, KLUMPP H, LANGENECKER S, et al. Transdiagnostic neural correlates of volitional emotion regulation in anxiety and depression[J]. Depress Anxiety, 2019, 36(5): 453-464.

[69] LI Z, WANG J, CHEN L, et al. Basolateral amygdala lesion inhibits the development of pain chronicity in neuropathic pain rats[J]. PLoS One, 2013, 8(8): e70921.

[70] SENO M D J, ASSIS D V, GOUVEIA F, et al. The critical role of amygdala subnuclei in nociceptive and depressive-like behaviors in peripheral neuropathy[J]. Sci Rep, 2018, 8(1): 13608.

[71] CHEN Y H, WU J L, HU N Y, et al. Distinct projections from the infralimbic cortex exert opposing effects in modulating anxiety and fear[J]. J Clin Invest, 2021, 131(14): e145692.

[72] 刘胜. 针刺镇痛研究新视角: 疼痛缓解的奖赏效应和脑奖赏环路[J]. 针刺研究, 2022, 47(3): 268-273.
LIU S. New perspective of acupuncture analgesia: reward of chronic pain relief and related brain reward circuits (in Chinese)[J]. Acupuncture Research, 2022, 47(3): 268-273.

[73] CARLEZON W A, THOMAS M J. Biological substrates of reward and aversion: a nucleus accumbens activity hypothesis[J]. Neuropharmacology, 2009, 56: 122-132.

[74] MARTINEZ E, LIN H H, ZHOU H C, et al. Corticostriatal regulation of acute pain[J]. Front Cell Neurosci, 2017, 11: 146.

[75] LEE M, MANDERS T R, EBERLE S E, et al. Activation of corticostriatal circuitry relieves chronic neuropathic pain[J]. J Neurosci, 2015, 35(13): 5247-5259.

[76] 刘会. 前额皮层-伏隔核神经环路在针刺缓解慢性痛奖赏效应中的作用[D]. 上海: 上海中医药大学, 2020.
LIU H. The role of the prefrontal cortex-nucleus accumbens circuit in the analgesic reward effect of acupuncture in chronic pain (in Chinese)[D]. Shanghai: Shanghai University of Traditional Chinese Medicine, 2020.

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