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评 述 迈向“发展群体神经科学”专辑

疼痛发展认知神经科学: 研究现状与未来趋势

张立波[1,2], 吕雪靖[1,2], 胡理[1,2*]

1. 中国科学院心理研究所心理健康重点实验室, 北京 100101;
2. 中国科学院大学心理学系, 北京 100049
* 联系人, E-mail: huli@psych.ac.cn

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摘要 疼痛认知神经科学在过去几十年间经历了高速发展, 但多数研究的对象局限于中青年成人, 对年龄差异的考虑不够充分. 为加深对儿童和老年人疼痛加工机制的理解并开发有针对性的疼痛治疗方法, 有必要弥补这一不足. 从毕生发展的角度看, 疼痛评估的准确性和治疗的有效性受特定年龄群体生理和心理特征的影响, 因而儿童和老年人的疼痛评估和治疗需要采取有针对性的方法, 不能简单推广基于中青年成人的研究成果. 未来的研究将更加强调新兴技术在疼痛毕生发展领域的应用, 采取多维度的整合性研究视角, 着力研发针对不同年龄群体的非成瘾性镇痛方法, 并大力推广开放的科学研究文化. 考虑到我国的研究现状、现实需求和独特优势, 建议我国未来在疼痛毕生发展领域致力于: (ⅰ) 开发可靠的疼痛特异性客观指标; (ⅱ) 建立大规模、多尺度的疼痛毕生发展数据库; (ⅲ) 探明年龄及心理因素对慢性疼痛发生、发展和维持的影响; (ⅳ) 开发针对不同年龄群体的高效非成瘾性疼痛治疗方法, 推动基础研究成果的临床转化.

关键词 疼痛评估, 疼痛治疗, 毕生发展, 未来趋势

自古以来, 疼痛就是一个人类不得不面对的健康难题. 对于个人而言, 疼痛带来的无尽痛苦可能引发抑郁症乃至自杀[1,2]. 对于整个社会而言, 慢性疼痛已成为一个重大公共卫生议题——患病率高达20%~50%[3~7], 每年给我国造成超过数千亿人民币的经济损失[8,9].

值得关注的是, 儿童和老年人的疼痛问题尤为严重: 一方面, 儿童疼痛因准确评估和临床试验的困难而经常被忽视[10]; 另一方面, 老年人的慢性疼痛患病率高达50%乃至80%[11~14]. 不幸的是, 多数疼痛研究招募的志愿者仅为中青年成人, 造成了对儿童和老年人疼痛的认识反而不足的局面. 儿童和老年人的生理、心理有其特点, 针对中青年成人的研究成果难以直接推广到这两个特殊群体. 国家统计局的资料(http://data.stats.gov.cn/easyquery.htm?cn=C01)显示, 截至2018年, 我国14岁以下的儿童和65岁以上的老年人已超过4.1亿人. 这一国情要求临床工作者和科研人员从发展的角度研究疼痛问题以切实保障我国整体国民健康.

为推动我国在疼痛毕生发展领域的进步, 本文从

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疼痛评估和疼痛治疗两个角度梳理儿童和老年人疼痛研究的现状, 并针对其中的不足和挑战, 提出本领域未来发展的展望和规划(图1).

1　毕生发展视角下的疼痛评估

疼痛的准确评估是疼痛研究和疼痛治疗的基础. 根据国际疼痛研究协会(International Association for the Study of Pain, IASP)于2020年更新的定义, 疼痛是“一种与实际或潜在的组织损伤相关的不愉快的感觉和情绪体验, 或与此类似的感觉和情绪体验”[15]. 就其本质而言, 疼痛是一种个体化的主观体验, 虽然与客观的组织损伤相关, 但却没有必然的联系. 考虑到这一特点, 目前的研究中疼痛主要通过主观评分进行测量[16]. 常见的疼痛主观评分量表包括数值评分量表(numerical rating scale, NRS)、视觉模拟量表(visual analog scale, VAS)、言语评分量表(verbal rating scale, VRS)和麦吉尔疼痛问卷(McGill Pain Questionnaire, MPQ)等[17,18]. 相关研究已证实, 它们都有良好的心理测量学性质, 信效度较高[17,18]. 然而, 准确报告自己的主观体验依赖于一定水平的认知和语言能力, 但年龄过小的儿童认知能力发育不完全, 而年龄过大的老年人认知能力衰退. 因此, 传统的主观报告法对评估这两个群体的疼痛而言存在一定的局限性.

1.1　儿童疼痛评估

(1) 伤害性通路与疼痛调节系统的发育. 儿童——尤其是新生儿——的疼痛评估面临的第一个问题是: 他们是否可以感知到疼痛? 20世纪80年代以前, 新生儿能否感到疼痛曾引起巨大争论[19,20]. 结构是功能的基础, 疼痛的感知也必然建立在疼痛相关神经系统已基本发育成熟的基础之上. 因此, 神经系统发育不完

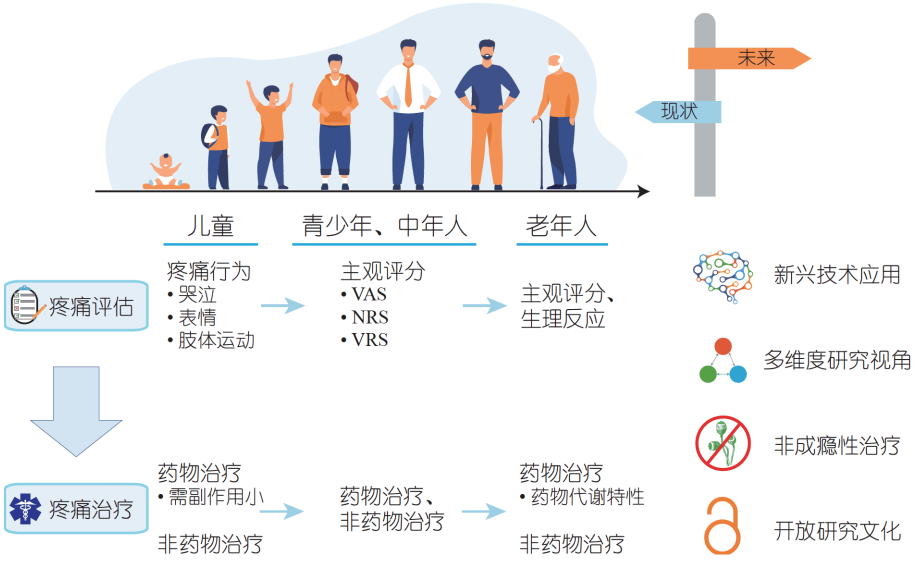

图 1　疼痛发展认知神经科学研究现状和未来展望. 疼痛评估和疼痛治疗方法受到不同年龄群体自身特点的影响. 婴幼儿认知能力受限, 疼痛评估更多依赖采用疼痛行为; 随着个体年龄的增长, 疼痛评估逐步依靠视觉模拟量表(visual analog scale, VAS)、数值评分量表(numerical rating scale, NRS)和言语评分量表(verbal rating scale, VRS)等主观报告; 老年人认知能力逐渐衰退, 疼痛评估时可辅以生理反应. 疼痛治疗可使用药物疗法和非药物疗法, 但儿童需选用副作用小的药物, 而老年人服药需注意其药物代谢特性的变化. 未来的研究将更注重应用新兴技术, 采取多维度研究视角, 开发非成瘾性疼痛治疗方案和推广开放的研究文化. (部分图片和图标改编自Freepik上pch.vector的作品和Pixabay上的作品)(网络版彩图)

Figure 1　The present and future of developmental cognitive neuroscience of pain. Developmental factors influence assessment and treatment of pain. Pain assessment in small children relies on pain behavior since they have limited cognitive capacities. As they grow, subjective pain reports become the major tool for measuring pain, for example, the visual analog scale (VAS), numerical rating scale (NRS), and verbal rating scale (VRS). Potential cognitive impairment in the elderly requires physiological responses as a supplement to pain reports. Pharmacological and non-pharmacological pain treatments work for people of different ages. However, children should be prescribed drugs with minimal side effects and the elderly's pharmacokinetics should be carefully considered. Future studies will exploit emerging innovative and advanced technologies, fully appreciate the multidimensional nature of pain, develop non-addictive pain treatment, and ensure transparency and openness in developmental pain research. (Some images and icons are adapted from the work of pch.vector from Freepik and works form Pixabay) (color online)

善的婴幼儿可能无法感知疼痛.

不过, 研究发现, 新生儿已经具备对伤害性信息进行感知和反应所需的生理结构[21~23]. 事实上, 疼痛相关神经结构在胎儿尚未出生就有了相当程度的发育: 怀孕8周时的胎儿就可以在脊髓层面对伤害性刺激做出脊髓反射, 第19周时脊髓背角就存在伤害性神经元, 第24~26周时丘脑传入神经就穿过皮质板(cortical plate), 并在29周时皮层第四层神经元形成功能型突触, 第35~37周时区分触觉和痛觉的神经环路就已出现[22,24,25].

此外, 胎儿的疼痛调节系统也有了一定程度的发育. 研究显示, 怀孕8~10周时, 胎儿的脊髓背角和背角神经节中就存在与疼痛加工和调节相关的P物质, 12~14周时则可检测到具有镇痛作用的内啡肽[26]. 这意味着新生儿的疼痛调节系统可能已经能够发挥部分作用. 疼痛调节系统可通过这些神经化学物质促进或抑制伤害性信息的传递, 从而调节疼痛感觉. 综合这两方面的神经发育情况, 新生儿至少具有感知和调节疼痛的生理基础.

(2) 疼痛评估方法. 虽然儿童已经具备疼痛感知的生理基础, 但由于认知能力的限制, 他们可能无法像成人一样准确描述所感受到的疼痛. 因此, 儿童的认知水平是影响儿童疼痛测量的关键因素. 儿童的年龄可以作为粗略判断他们能否完成疼痛主观评分量表的标准. 对于年龄较大的健康儿童, 主观报告是测量疼痛的最佳方法[27]. 具体而言, 无认知损伤的8岁以上儿童具备主观报告的能力, 可利用视觉模拟量表或疼痛形容词量表(如MPQ[28])评估自己的疼痛程度[29]; 6~7岁的儿童则可以使用疼痛面孔量表(faces pain scale, FPS)描述自己的疼痛水平[30]. 对于年龄更小、语言能力受限或认知能力受损的儿童, 主观报告法难以适用. 此时, 评估儿童疼痛更多地依赖疼痛行为和生理反应[31,32].

评估儿童疼痛的疼痛行为主要包括哭泣、面部表情和身体运动. 哭泣是评估婴儿疼痛的重要参考指标. 研究发现, 疼痛导致的哭泣和其他哭泣在声学特征上存在一些重要差异[33]. 应用机器学习方法区分疼痛和非疼痛哭泣的准确率可高达96.41%[34]. 一般而言, 结合哭泣的强度和时长将能更好地分辨疼痛哭泣和非痛哭泣.

面部表情是评估婴儿疼痛的另一个重要手段. 事实上, 面部表情出现在大多数常用的婴儿疼痛评定量表中[35], 面部表情与大脑活动的相关性也非常高[36]. 新生儿疼痛相关的面部表情编码可采用Grunau和Craig开发的新生儿面部运动编码系统(neonatal facial actions coding system, NFACS)[33]. 这一系统通过编码眉毛、眼睑、嘴唇、舌头、下巴等部位的运动模式来精确、细致地刻画表情的变化. 在经历疼痛时, 婴儿会有皱眉、眯眼、垂直或水平张大嘴、吐舌头、下巴颤抖等动作[33]. 不过, 婴儿的大脑发育水平似乎会影响面部表情和疼痛之间的关系: 孕期未满32周的早产儿对伤害性刺激的面部反应与对非伤害性的面部反应没有显著差别[37].

除了哭泣和面部表情以外, 遭遇疼痛时特定的肢体运动反应也可在一定程度上评估疼痛[38,39]. 通常来说, 新生儿对疼痛的肢体运动是弥漫性的; 出生6个月后则会表现出明确的退缩反应, 远离伤害性刺激源; 出生12个月后则会触摸受伤部位[29].

值得注意的是, 哭泣、面部表情和肢体运动等疼痛行为通常不是疼痛特异的, 因此利用它们评估疼痛存在较大的不确定性, 未必能真实反映疼痛程度[40]. 为增加评估的可靠性, 可将疼痛行为和心率、呼吸、血氧饱和度、出汗量、应激反应等生理指标相结合, 综合判断疼痛程度[29]. 近年来, 研究者们也开始尝试使用近红外成像(near-infrared spectroscopy, NIRS)、脑电图(electroencephalogram, EEG)和功能磁共振成像(functional magnetic resonance imaging, fMRI)等技术测量疼痛时的大脑反应, 从而评估婴儿疼痛[41,42]. NIRS研究发现, 机械性伤害刺激会提升28~36周的早产儿对侧躯体感觉皮层的氧合血红蛋白含量[43]; EEG研究结果显示, 婴儿头顶Cz电极的脑电活动会随着机械性伤害刺激强度的增加而增强[44], 而且镇痛药对该脑电活动能起到调节作用[45]; fMRI研究结果则显示, 婴儿接受机械性伤害刺激时的大脑激活模式与成人类似[46]. 虽然这些脑成像技术在评估疼痛领域的应用还相当初步, 它们是否能特异地反映疼痛也存在一些疑问[47~50], 但将这些技术和传统的疼痛行为和生理指标相结合, 将为准确评估疼痛提供新的思路.

整体上看, 疼痛行为和生理指标是疼痛评估的良好指标. 对于不适用主观报告法的儿童来说, 它们可能是评估疼痛的唯一方法; 对于可以获取主观报告的儿童来说, 整合主观报告和疼痛行为、生理指标, 发

挥它们各自的优势，将有助于更有效、更全面地评估儿童疼痛. 事实上，大量儿童疼痛评估量表都已经纳入了行为和生理反应，如早产儿疼痛量表(premature infant pain profile, PIPS)、新生儿疼痛分数(neonatal infant pain score)、新生儿疼痛与不适量表(neonatal pain and discomfort scale, NPDC)、COMFORT疼痛量表(COMFORT pain scale)、CRIES量表(CRIES scale)等[51~54].

1.2　老年人疼痛评估

(1) 疼痛评估方法. 儿童应用主观报告的困难在于认知能力发育不完全，而老年人的困难则在于认知能力衰退. 只要老年人认知能力没有明显衰退，能够理解评分量表的含义和明白无误地报告自己的感受，那么他们的疼痛就可利用NRS，VRS和MPQ等主观评分量表进行测量. 需要注意的是，老年人视觉能力的下降可能使得VAS的适用性不高[55]. 对于认知功能存在损伤的老年人而言，其认知损伤程度决定了是否可应用疼痛评估量表. 如果认知能力损伤程度相对较轻，NRS, VRS和MPQ等量表仍可使用, 但应确保老年人对量表使用方法的理解不存在任何错误，同时增大量表的文字字体，提高主试者给予指导语时的音量，以减小视听能力衰退对测量结果的干扰[55]. 如果认知功能衰退比较严重，疼痛的评估将主要依赖生理反应和行为观察记录[31].

(2) 疼痛敏感性. 研究者发现, 在利用以上疼痛评估工具测量老年人的疼痛时，老年人的疼痛敏感性可能与中青年成人有所不同. 疼痛敏感性的变化可通过疼痛阈限和耐痛阈限两个指标进行衡量. 疼痛阈限是刚好能引起疼痛感的刺激强度，而耐痛阈限则表示个体痛到无法忍受时的刺激强度.

就疼痛阈限而言，Sherman[56]的研究发现，50~80岁老年人的疼痛阈限比年轻人更高. 这一结论也得到了其他研究的证实[57,58]. 就耐痛阈限而言，研究结果则存在一些争议. 有的研究发现老年人耐痛阈限会升高[59]，也有研究发现老年人的耐痛阈限会有较大幅度的下降[60~62]，近期的一项元分析则得出了老年人耐痛阈限与年轻人之间没有显著差异的结论[57]. 疼痛刺激的类型等研究方法上的差异可能是导致这些结果不一致的原因[60,63]. 总的来看, 虽然不同研究的结果不甚相同, 但支持老年人耐痛阈限更低的研究占多数[64].

(3) 疼痛成因. 除了疼痛敏感性的变化外, 老年人的疼痛问题比年轻人更多，患慢性疼痛的概率远高于年轻人[4,6,7]. 生理结构和功能逐渐老化、其他疾病患病率增加和社会生活变化导致精神压力增大是老年人疼痛问题愈发严重的三大原因. 老年人生理结构和功能的老化体现在疼痛相关外周和中枢神经系统结构和功能的衰退. 在外周水平上，老年人的皮肤[65]和伤害性感受器[66]特性均发生了显著的变化：功能正常的有髓鞘伤害性Aδ纤维和无髓鞘伤害性C纤维密度日益减少[67~69]，同时受损的伤害性纤维的数目越积越多，导致外周神经传导速率降低[70~72]. 在中枢水平上，老年人内源性疼痛调控机制的镇痛效果逐渐减弱[60,62,73,74]，而且与疼痛调节有关的神经递质数量也越来越少[75].

老年人多发的基础疾病是其疼痛问题更为严重的另一成因. 相对于其他年龄群体, 老年人更易受到肌肉骨骼结构的退化、骨折、癌症、糖尿病、神经病变、营养不良、酒精滥用、呼吸和外周循环障碍、带状疱疹等问题的影响[76~83]. 不仅如此，老年人易患的疾病本身也和疼痛有着直接或间接的联系. 相关统计结果显示，患有可能导致疼痛的慢性疾病的老年人比率高达80%左右[84].

老年人不得不面对的生活事件也是他们疼痛问题高发的潜在原因. 步入生命晚期的同时, 老年人也面临着亲友死亡，退休后收入、社会地位、社会联系的丧失，孩子离家等重大负性事件的不断发生[77~79,85~88]. 此外，活动障碍、独立生活能力降低、住院和入住养老院等因素也可能加剧疼痛恶化或进一步持续.

2　毕生发展视角下的疼痛治疗

疼痛治疗方法可分为药物治疗与非药物治疗两大类. 与疼痛评估相同, 儿童和老年人的疼痛有效治疗也受其生理、心理特征影响. 中青年成人的疼痛治疗方法无法直接复制到这两个特殊群体身上.

2.1　儿童疼痛治疗

考虑到儿童的生理、心理特点，治疗儿童疼痛时需特别注意两方面的问题. 一是年龄较小的儿童语言能力有限，且易对治疗产生恐惧心理，因而治疗时需用易懂的语言进行更多的解释[89]；二是儿童更需要父母的安慰，这些安慰对缓解儿童疼痛有很大的作

用[89~92].

(1) 药物方法. 儿童的生理、心理都处在快速发育阶段. 使用药物治疗儿童的疼痛应充分考虑这一特点, 谨慎地选用副作用小的药物, 并搭配适宜的用药方式. 醋氨酚等非解热抗炎镇痛药副作用较小, 常用于缓解儿童疼痛. 解热抗炎镇痛药和非甾体类抗炎药(nonsteroidal anti-inflammatory drugs, NSAIDs)副作用较大, 不宜用于儿童. 前者虽无短期的副作用, 却有长期的不良影响, 后者则会影响胃、肾脏和血小板功能[89]. 有药物成瘾风险的阿片类药物应尽量避免给儿童使用[89,93]. 如果不得不使用阿片类药物, 应首先选用口服方式, 以避免儿童对针头的恐惧. 药物注射不可避免时, 则需给儿童解释清楚注射的必要性, 并采用转移注意力等方式减少儿童的恐惧. 除了这几类药物外, 镇静剂和抗抑郁药也有一定的镇痛作用, 但使用时需谨慎, 避免可能的副作用.

(2) 非药物方法. 治疗儿童疼痛常使用非药物方法[94]. 物理方法、行为方法和认知方法是三类常见的非药物疼痛治疗方法. 物理方法主要通过按摩、冷、热、针刺和电刺激等非药物物理刺激来缓解疼痛[95~97]. 儿童躯体对触觉刺激的感受性高于成人, 因而按摩的镇痛效果相对较好. 虽然不经常使用, 但有一些研究表明, 冷刺激、热刺激、针刺和电刺激等方法能够减缓疼痛[96~99].

行为方法通过躯体运动、生物反馈等身体活动或条件性学习等方式来缓解疼痛[100~104]. 儿童的心理特质促进了这些方法的疗效. 儿童活动倾向较强, 更享受以游戏形式进行的躯体活动, 因此身体活动缓解疼痛的可行性较高. 儿童的学习能力和学习热情则有助于开展生物反馈和条件性学习. 相关研究也已证实, 生物反馈对于缓解头痛和偏头痛有一定效果[105,106], 而条件性学习则可缓解短时疼痛和慢性疼痛[102,103].

认知方法通过调节个体的认知来缓解疼痛. 常见的认知方法包括分散注意力[107]、意象疗法[108]和音乐疗法[109,110]等. 儿童的心理特质同样影响这些方法的镇痛效果. 好奇心强的儿童适用于分散注意力[111], 丰富想象力的儿童更适宜使用意象疗法[89], 爱听音乐的儿童可用音乐疗法减轻疼痛[93,112,113].

2.2 老年人疼痛治疗

老年人的疼痛治疗有两个问题需要特别关注: 一是目前仍有许多老年人没有得到充分的疼痛治疗[114,115]; 二是对老年人疼痛的治疗经常忽视非生理因素对疼痛的影响[82].

(1) 药物方法. 治疗老年人疼痛的药物主要包括NSAIDs、阿片类药物以及抗抑郁药等药物. NSIAIDs可用于治疗轻度或中度的疼痛, 与阿片类药物联用则可用于治疗重度疼痛. 不过, NSAIDs可能导致肾、胃肠道和心血管功能方面的副作用[116], 因此必须谨慎使用[76,117,118], 同时应避免其在体内过度积累. 在NSAIDs与利尿剂联用, 或治疗有肾脏功能障碍的老年人时, 尤其需要注意其过度积累可能导致的副作用[119].

阿片类药物主要用于治疗中等到严重程度的疼痛, 但鉴于其副作用在老年人群体中更加明显, 半衰期相对较短的其他药物可能是更好的选择[117]. 充分考虑老年人的特殊情况后仍需使用阿片类药物时, 应特别注意用药方式. 肌肉注射可能带来较大的副作用, 如短时间内体内药物含量急剧变化导致低通气和肺膨胀不全[120].

抗抑郁药、抗惊厥药、类固醇和安非他命等与NSAIDs或阿片类药物联用时只需要较少的剂量就能达到较好的镇痛效果, 但相应的副作用也可能更为明显[117]. 因此, 使用此类治疗方式需更为小心.

总的来说, 这些药物的使用必须建立在充分考虑老年人的药物代谢动力学性质变化的基础上. 健康问题和老化过程对老年人的药物代谢动力学特性有较大影响[117,121], 从而导致老年人更易发生与药物吸收有关的问题. 老化和一些疾病会导致肝、肾功能下降, 改变老年人的新陈代谢速率和肾清除率, 最终导致药物在体内的半衰期延长和浓度加大. 老年人肌肉质量下降会导致体内脂肪增加, 从而增加脂溶性药物累积的风险. 老年人更加缓慢的胃清空速率也增加了对胃的刺激.

(2) 非药物方法. 相比于药物治疗, 非药物方法的优势在于副作用较小, 基本没有成瘾的隐患. 物理、行为和认知等治疗方法也可用于治疗老年人的疼痛. 经皮神经电刺激(transcutaneous electrical nerve stimulation, TENS)是一种常见的疼痛物理疗法, 应用于老年人以缓解其疼痛已有几十年的历史[83]. 由于老年人感受性的变化, 应用TENS治疗老年人的疼痛可能需要使用更高的刺激强度[122]. 此外, 热疗和冷疗对缓解老年人的疼痛也有一定作用[123].

在行为疗法中，体育锻炼的镇痛效果认可度较高[82,83,101]. 除了锻炼身体机能、改善心血管功能外, 体育锻炼也有助于缓解疼痛引发的抑郁和焦虑情绪, 以及增加老年人的社会联系[123]. 尽管结果并不完全一致[124], 气功和太极等锻炼方法也对缓解老年人的疼痛有一定帮助[125,126]. 部分老年人对这些传统锻炼方式颇有兴趣, 这有利于他们坚持相应疗法.

认知行为疗法通过改变老年人疼痛相关的思维、情绪和行为来缓解疼痛[127]. 这一疗法镇痛的证据较为充分[116,127]. 考虑到老年人自身的特点, 这些方法配合个性化的监测和治疗可能会起到更好的效果.

3　未来发展预测与展望

认识疼痛、评估疼痛和缓解疼痛是疼痛毕生发展研究的核心. 从目前的研究发展趋势和研究文化变迁方向来看，未来研究将针对这几个核心议题，更加强调新兴技术方法在疼痛领域中的应用，从生理-心理-社会的整合性研究视角全面、深入地探究年龄因素在疼痛发展中的作用, 准确、客观地评估疼痛, 结合各年龄层的特性开发非成瘾性的高效疼痛治疗方法，同时加大研究文化的开放性，提升研究结果的可靠性和可信度.

3.1　新兴技术的应用

近年来，EEG、脑磁图(magnetoencephalography, MEG)、NIRS、fMRI等脑功能成像技术和机器学习算法在疼痛研究上的应用方兴未艾[50,128~132]. 借助这些新兴技术，研究者们致力于阐明疼痛加工的神经机制[133]，揭示编码疼痛及其个体差异的神经关联物(neural correlates)，并开发疼痛的客观测量指标[47,128,129,134]. 目前已有研究利用脑成像技术发现大脑激活模式和高频γ振荡等大脑活动可反映疼痛强度[129,132,135~137]. 不过, 这些研究依然以中青年成人为主要研究对象, 缺乏对儿童和老年人的足够关注, 但这两个群体恰恰是最需要疼痛客观评估指标的健康人群体. 事实上, NIRS, EEG和fMRI在测量幼儿的疼痛中已经有了一些应用[41,42], 但相关研究仍较为初步, 没有发现可广泛应用的疼痛测量指标. 未来的研究将更加注重开发新的疼痛客观指标，检验已有的疼痛神经关联物在儿童和老年人身上的适用性，以克服主观评分在这两个群体身上难以应用和准确性不足的问题.

此外，也有越来越多的研究试图利用经颅交流电刺激(transcranial alternating current stimulation, tACS)、经颅直流电刺激(transcranial direct current stimulation, tDCS)、经颅磁刺激(transcranial magnetic stimulation, TMS)等神经调控技术揭示大脑活动在疼痛加工中的因果作用, 开发高效的镇痛方法[138~143]. 这些新技术、新方法深化了疼痛神经机制的研究，为进一步认识疼痛、治疗疼痛提供了重要工具. 未来疼痛毕生发展的研究将充分发挥这些技术的优势揭示疼痛加工的内在机制，并检验这些新兴技术对缓解儿童和老年人疼痛的长期效果.

3.2　多维度的研究视角

自20世纪六七十年代以来，研究者对于疼痛的理解逐渐从单一的生理现象转变为包含感知、情绪和认知等多个维度的复杂现象[144,145]. 疼痛感知和疼痛情绪在大脑层面的独立性已得到一些研究的证实[146,147]. 然而，目前疼痛毕生发展领域仍然强调疼痛感知维度的优势地位，对情绪和认知等其他疼痛维度的研究并不充分，疼痛治疗过程中也较少考虑这些维度. 未来的研究有必要从疼痛的多维度本质出发，重视对疼痛情绪和认知维度的测量，考察疼痛不同维度的生理机制、相互作用以及对疼痛体验的综合影响，并开发相应的整合性疼痛治疗方案.

3.3　非成瘾性的疼痛治疗方法

有效缓解疼痛是疼痛研究的终极目标. 服用镇痛药物是最常见的镇痛方法. 然而，镇痛药物——尤其是阿片类药物——有成瘾风险. 虽然相应药物的严格管控使得我国镇痛药物成瘾大规模爆发的可能性很低, 但其他国家和地区则不然. 近年来, 北美爆发了阿片危机，每天夺取上百人的宝贵生命(https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis), 每年造成785亿美元左右的经济损失[148]. 在这一背景下，研发没有成瘾隐患的新型药物和非药物镇痛方法是未来消除疼痛领域的研究重点和难点[149].

从毕生发展的角度来看，某些年龄群体的生理、心理特性使得开发针对他们的疼痛治疗方法面临着特殊的难题. 例如，儿童的镇痛药物开发存在极大的缺口. 近年来，美国食品药品监督管理局(U.S. Food and

Drug Administration, FDA)启动了儿科项目. 在这之前, 仅有20%的儿童用镇痛药物是经过FDA批准的(https://www.fda.gov/drugs/drug-information-consumers/drug-research-and-children). 形成这一局面的原因是多样的: 儿童镇痛药物研发时需考虑儿童自身的特点, 不能简单类比成人药物研究的方法和结果; 并且儿童镇痛药物研发面临独特的难题, 如儿童急速的身体发育致使不同年龄段儿童的疼痛问题异质性大, 年龄过小的儿童无法给予知情同意, 儿童安慰剂控制临床试验有伦理风险, 目前为止还缺乏许多儿童疼痛模型等[10]. 未来的研究将更加重视年龄因素对于疼痛治疗的影响, 针对不同的年龄群体的特性开发相应的疼痛治疗方法.

3.4 开放的科学研究文化

近年来, 心理学、神经科学、生物医学等多个领域爆发可重复性危机[150~153]. 大规模重复性研究发现, 许多研究——包括写入教科书的经典研究——的结果无法重复[150,154]. 低可重复性不仅损害科学研究的可信性, 还造成了巨大的经济损失. 据一些研究者的估计, 仅在美国, 每年不可重复的临床前研究造成的经济损失就高达280亿美元[155]. 可重复危机发生的重要原因之一是不开放、不透明的研究文化. 这一问题在疼痛领域也同样存在[156]. 大量疼痛研究不提供完整的样本量计算方法[157], 不报告疼痛强度、疼痛位置、疼痛测量方法等关键参数[158]. 注意到这些问题后, 疼痛研究领域逐渐改变了研究文化, 强调落实研究的预注册(preregistration)、研究数据和分析代码的分享、结果报告的标准化等加强研究开放性的关键举措[159]. *Pain*, *Journal of Headache and Pain*, *Molecular Pain*, *Regional Anesthesia and Pain Medicine*, *Clinical Journal of Pain*, *European Journal of Pain*等疼痛领域的重要期刊已采取措施增加研究的开放性. 未来疼痛毕生发展领域同样将推广开放的科学研究文化, 进一步提升研究结果的可靠性和可信度.

4 国内发展分析与未来规划

我国整体科技水平不断提升, 已成为一个科技大国, 但在人类疼痛毕生发展领域的研究仍较为落后. 总的来看, 我国在疼痛毕生发展领域存在以下两个重要不足: 一是相关研究起步晚, 积累不足, 基础研究相对薄弱; 二是现有研究较为零散, 缺乏系统性、大规模的研究.

不过, 在我国开展疼痛毕生发展研究也有着得天独厚的优势. 首先, 我国人口总数超过14亿, 位列世界第一, 这为收集大规模、多尺度的疼痛毕生发展数据, 全面、系统刻画疼痛毕生发展曲线提供了数据基础. 其次, 我国对阿片类药物管制严格, 镇痛药物成瘾的人数少、概率低, 这提高了数据的可靠性. 最后, 我国传统医学中关于镇痛的理论和方法提供了丰富的疼痛治疗潜在资源. 针刺在镇痛和治疗慢性疼痛方面已取得了很好的效果[160,161], 而其他有镇痛潜力的方法则尚待发掘和研究.

根据本领域的发展前景, 结合我国的研究现状、现实需求和独特优势, 我国未来疼痛毕生发展领域可重点关注以下科学问题.

(1) 阐明疼痛认知神经加工机制, 开发可靠的疼痛特异性客观指标. 综合利用神经影像技术和生理信号采集系统, 从生物电信号、大脑血氧信号等复杂生物信号中挖掘疼痛特异性客观指标是解决部分儿童和老年人难以适用主观评分量表问题的根本出路.

(2) 建立疼痛毕生发展数据库, 刻画疼痛毕生发展曲线. 充分利用我国人口基础大的优势, 采集大规模、多尺度的疼痛毕生发展数据, 建立相应疼痛数据库, 最终刻画疼痛毕生发展曲线, 揭示大脑发育与疼痛变化的内在联系, 明确发展因素在疼痛感知和疼痛调节中的关键作用.

(3) 探明年龄因素及心理因素对慢性疼痛发展的影响. 慢性疼痛的高患病率和难治愈性给患者、家属和整个社会都造成了沉重的负担. 阐明年龄和心理因素在慢性疼痛的发生、发展和维持过程中所起的具体作用, 有助于加深对慢性疼痛病理机制的认识, 促进研发相应的疼痛治疗方法.

(4) 研发针对不同年龄群体的非成瘾性镇痛方法, 积极推动基础研究成果的临床转化. 全面考虑各年龄群体的生理和心理特征对不同镇痛方法镇痛效果的影响, 大力开展疼痛转化研究, 推进基础研究成果的临床转化, 为不同年龄群体开发有针对性的非成瘾性疼痛治疗方法, 将有效减轻疼痛问题给患者、家属和整个社会带来的健康和经济负担, 有力保障全体国民的身体和心理健康.

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Developmental cognitive neuroscience of pain: present and future

ZHANG LiBo[1,2], LU XueJing[1,2] & HU Li[1,2]

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 100049, China

Past several decades have witnessed a booming research field of cognitive neuroscience of pain, yet the majority of such studies include young adult participants only, largely ignoring the age differences. The field needs to fill the gap and provide more comprehensive understanding on how pain is processed in the brain of the young and the elderly, and how pain can be successfully managed for different age groups. Importantly, the developmental perspective gives the invaluable insight that psychological and physiological characteristics of different age groups influence the validity of pain assessment and the efficacy of pain treatment, thus necessitating different pain measures and treatments for children, adolescents, adults, and the elderly. Future studies will exploit emerging innovative and advanced technologies, fully appreciate the multidimensional nature of pain, develop age-specific non-addictive pain treatment, and ensure transparency and openness in developmental pain research. Considering the current situation of the field in our country, we shall focus on four promising research projects in the future: (i) to develop reliable and valid objective pain measures; (ii) to establish a large-scale and comprehensive database on pain development; (iii) to untangle the role of age and psychological factors in the development and maintenance of chronic pain; (iv) to develop effective and safe pain management strategies for different age groups and promote clinical translation of basic research.

pain assessment, pain treatment, lifespan development, future directions

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