激光诱发疼痛的神经电生理特征及其应用

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2014-09-09 收稿, 2014-09-22 接受, 2015-02-11 网络版发表

国家自然科学基金(31200856, 31471082)、重庆市自然科学基金(CQ CSTC)和中央高校基本科研业务费专项资金(SWU1409105)资助

摘要 疼痛是大脑编码和处理伤害性刺激, 避免潜在的或实际的组织损伤的一种保护功能. 人体内传导伤害性信息的神经纤维主要有A δ 和C纤维. 伤害性信息经过这两类纤维的传导和大脑结构的多重加工, 最终产生人体的一次快疼痛和二次慢疼痛. 较强烈的激光辐射热脉冲可选择性激活皮肤浅表层中的伤害性游离神经末梢, 诱发脑电(electroencephalography, EEG)活动的变化, 即激光诱发电位(laser-evoked potentials, LEPs). 至今, 研究者共挖掘出A δ -LEPs的6个稳定成分, 即时域上的A δ -N1, A δ -N2, A δ -P2, A δ -P4波, 时频域上神经振荡节律成分alpha频段的事件相关去同步化(event-related desynchronization, α -ERD)和gamma频段的事件相关同步化(event-related synchronization, γ -ERS). 与此同时, 研究者优化了C-LEPs提取的实验范式和参数, 获得了2个稳定成分, 即时域上的C-N2, C-P2波. 本文详述了LEPs相关的神经电生理特征及其认知功能. LEPs既能帮助我们探究伤害性感觉输入的外周和中枢加工机制, 在疼痛临床研究中具有重要价值, 也能为某些基础研究(如老龄化问题和社会认知等)提供新的手段.

关键词

疼痛
脑电
激光诱发电位
神经振荡信号

疼痛作为一种广泛存在于我们生活中的复杂主观感受, 国际疼痛研究协会(International Association for the Study of Pain, IASP)将其定义为“与组织损伤或潜在组织损伤相关的不愉快的主观感觉和情感体验”^[1]. 疼痛不仅会引起躯体的不适, 而且可能会引发一系列的情绪问题^[2], 导致人们认知功能的下降^[3], 严重影响着人们的生活质量. 疼痛涉及生理、社会和心理等多方面的因素, 这不仅表明疼痛的主观性和复杂性, 同时也说明疼痛研究具有很强的现实意义.

人体内传导伤害性信息的神经纤维主要有A δ 和C纤维, 然而它们的生理特征有很大不同. A δ 纤维有髓鞘, 直径约为1~5 μm , 传导速度约为5~30 m/s. C纤维无髓鞘, 直径约为0.2~1.5 μm , 传导速度约为0.5~2

m/s. 当对机体施加伤害性刺激后, A δ 纤维能快速传导神经冲动, 引起短暂、尖锐、似针刺的精确局部性疼痛, 即“一次疼痛(first pain)”^[4]; 随后, C纤维传递的伤害性信息引起一阵延迟的、类似烧灼的弥散性疼痛, 即“二次疼痛(second pain)”^[4]. 近年来, 脑电(electroencephalography, EEG)技术的发展和激光刺激器的应用为疼痛研究提供了一个新的视角. 激光刺激器产生的辐射热脉冲能选择性地激活皮肤浅表层中的A δ 和C纤维神经末梢, 神经冲动经复杂的神经通路的传导, 最终在大脑中产生激光诱发电位(laser-evoked potentials, LEPs). 波峰潜伏期与A δ 纤维传导速率相吻合的LEPs称为A δ -LEPs或晚期LEPs^[5], 与C纤维传导速率相吻合的LEPs称为C-LEPs或超晚期LEPs^[6]. 时域上, 典型的A δ -LEPs包

引用格式: 蔡敏敏, 郭晓丽, 唐丹丹, 等. 激光诱发疼痛的神经电生理特征及其应用. 科学通报, 2015, 60: 1150–1159

Cai M M, Guo X L, Tang D D, et al. Neural electrophysiological features of laser-evoked potentials and their applications (in Chinese). Chin Sci Bull, 2015, 60: 1150–1159, doi: 10.1360/N972014-01012

<https://engine.scichina.com/doi/10.1360/N972014-01012>

含了3个瞬时成分: A δ -N1, A δ -N2和A δ -P2^[7]. 最新研究发现了A δ -LEPs的第4个瞬时成分A δ -P4^[8]. 与A δ -LEPs相关的时频成分包括alpha频段的事件相关去同步化(event-related desynchronization, α -ERD)和gamma频段的事件相关同步化(event-related synchronization, γ -ERS)^[9~11]. 相对而言, 由于C-LEPs的信噪比很低, 除了提取出的C-N2和C-P2成分^[12]之外, 目前还没有研究发现其他稳定的C-LEPs成分. 这些LEPs成分的电生理特征均与疼痛知觉相关, 是疼痛研究与疼痛治疗效果评价的良好指标, 甚至在很多基础研究中也有广泛应用^[13~15].

1 A δ -LEPs的神经电生理特征

1.1 A δ -LEPs的时域特征

在时域上, A δ -LEPs主要包括4个瞬时成分, 即A δ -N1, A δ -N2, A δ -P2和A δ -P4. 如图1所示(来自文献[8]). 最早的成分是在刺激对侧的中心区域记录到的负波A δ -N1, 其波峰峰值较小, 并且提取较困难. 当刺激手背时, 其峰潜伏期大约为刺激后160 ms. 这一早期的单侧化响应可能起源于刺激的初级躯体感觉皮层(primary somatosensory cortex, SI)以及对侧盖岛叶皮层(operculoinsular cortex)的电生理活动^[16,17]. 有研究报道, A δ -N1除了编码疼痛的位置信息外, 也与疼痛强度编码有关^[18]. 特别需要指出的是, 由于诱发(evoked) A δ -N1的神经活动的幅值很小^[19,20], A δ -N1和A δ -N2在时空上有重叠^[21], 而且颞叶电极容易受到肌电影响, 所以A δ -N1信噪比非常低, 从而增加了提取这一早期成分的难度. Hu及其同事^[22]通过使用独立成分分析(independent component analysis, ICA)、小波滤波(wavelet filtering)和多重线性回归(multiple linear regression)等分析方法提升了A δ -N1的信噪比, 并推荐若将对侧中心电极重参考到Fz(C3/C4-Fz), 则可以更好地提取A δ -N1信号. A δ -N1之后是一对晚期的负-正复合波A δ -N2/P2, 峰值大约出现在刺激后200~350 ms, 且在头顶电极处的波峰幅值最大^[13,23]. 这一复合成分可能反映了双侧次级躯体感觉皮层(second somatosensory cortex, SII)、双侧脑岛(insula)以及前部/中部扣带回(anterior mid-cingulate cortex, ACC/MCC)等皮层的电生理活动^[16,17]. 研究发现, A δ -N2, A δ -P2的幅值与激光刺激强度、疼痛感知强度均具有显著的强相关^[15], 也有研

图1 (网络版彩色) A δ -LEPs的4个成分: A δ -N1, A δ -N2, A δ -P2和A δ -P4. (a) 刺激施加在右手背时, 在Cz电极点记录的A δ -N2和A δ -P2波形(以所有电极的平均值为参考). (b) 刺激施加在右手背时, 在其对侧(C3)中心电极点记录的A δ -N1和A δ -P4波形(以Fz作参考). 值得注意的是, A δ -N1和A δ -P4都在刺激对侧有更大的振幅. $N = 20$. 该图来自文献[8]

Figure 1 (Color online) Four typical components in A δ -LEPs: A δ -N1, A δ -N2, A δ -P2, and A δ -P4. (a) Time courses and scalp topographies of A δ -LEPs elicited by stimulation of the right hand. The A δ -N2 and A δ -P2 waves were optimally detected at electrode Cz (average reference). (b) Being stimulated at the right hand, the A δ -N1 and A δ -P4 waves were effectively detected at electrode C3 (Fz reference). Note that A δ -N1 and A δ -P4 waves were larger on the electrodes contralateral to the stimulated hand ($N = 20$, from Ref. [8])

究显示, A δ -N2和A δ -P2的潜伏期也与疼痛感知强度相关^[18], 这些都说明A δ -N2和A δ -P2可能是与疼痛感知相关的可靠电生理指标^[24].

继早期的A δ -N1, 中晚期的A δ -N2和A δ -P2成分之后, 最新研究报道了一个新颖的晚期正成分, 即A δ -P4^[8]. 研究者把固定能量的伤害性热辐射刺激分别施加于被试的左右手背和左右脚背, 以诱发A δ -LEPs. 通过功能微状态分析(microstate analysis)、头皮地形图分析(scalp topography)和单试次估计(single-trial estimation), 研究者将A δ -LEPs可靠地分解为4个明显的功能微状态, 即A δ -N1, A δ -N2, A δ -P2和A δ -P4. 对应于手背和脚背的刺激, A δ -P4峰潜伏期分别约为390~410和430~450 ms. 为了提高A δ -P4的信噪比, 研究者采用了和提取A δ -N1相同的重参考方式(C3/C4-Fz). 与A δ -N1相同, 头皮和溯源结果均表明A δ -P4波主要产生于对侧SI的电生理活动, 显著区分于P3成分. 并且单试次A δ -P4和A δ -N1的潜伏期、

波幅都有很强的耦合性,对实验操作有相似的敏感性.这些结果均表明,A δ -P4和A δ -N1产生于相似的神经源,具备相似的神经功能.A δ -P4的发现意味着A δ -LEPs至少应该包含A δ -N1,A δ -N2,A δ -P2和A δ -P4四个主要成分.对A δ -P4的深入研究,有利于研究者全面理解大脑对伤害性刺激的响应机制.

然而,很多研究表明,A δ -LEPs受注意等多重因素的影响^[25],不能反映疼痛特异性的神经机制.Legrain等人^[26,27]采用CO₂激光伤害性刺激和oddball范式发现,与未被注意的刺激相比,当刺激得到注意加工时,A δ -N1,A δ -N2波幅更大,表明自上而下的注意机制能调节A δ -N1和A δ -N2波幅;A δ -P2的波幅受到刺激出现概率的调节,说明这一成分可能反映了自下而上的、刺激驱动的注意定向机制.另外,有研究发现诱发刺激的新异性(新颖性和突显性)是A δ -LEPs的主要决定性因素^[28-30].如当以1 s的固定时间间隔连续施加同一激光刺激(triplets: S1-S2-S3)时,相对于S1,S2和S3诱发的A δ -LEPs会显著减小,但知觉到的疼痛强度几乎不变.因为S2和S3在时间、空间和强度等多个维度都具有更高的可预测性,所以刺激的新颖性显著降低.Ronga等人^[29]通过操作刺激强度(低强度、中等强度、高强度)来检验刺激的新颖性和突显性对A δ -LEPs振幅的影响.结果发现,刺激的新颖性不足以决定A δ -LEPs的出现,刺激的突显性也对A δ -LEPs有重要影响.这与Mouraux和Iannetti^[28]的发现类似,即强烈的非伤害性感觉刺激也能诱发类似于A δ -N2/P2的顶顶电位(vertex potential),这一复合成分可能反映了与突显性相关的神经加工过程,而这一神经加工过程可能涉及监测感觉环境的改变^[31].因此,A δ -LEPs不能反映伤害性疼痛的特异性神经生理特征,而是反映了大脑对环境变化的监控和早期预警,从而实现对人体的有效保护.

1.2 A δ -LEPs的时频域特征

感觉、运动和认知加工不仅能诱发锁时锁相的事件相关电位(event-related potentials, ERPs)的变化,也能引起锁时非锁相的EEG神经振荡信号的调节.该调节包含了在特定频带范围内的瞬时EEG能量增强(ERS)和能量减少(ERD)^[32,33].ERS和ERD的功能意义取决于它们所出现的时间范围、空间位置和频谱特征^[34].如在alpha频带范围内(8~12 Hz)出现的ERD反映了大脑皮层的激活或去抑制化^[35].在gamma频带

范围内(30 Hz以上)出现的ERS可能反映了多个大脑皮层区域活动的整合^[36,37].为全面探讨A δ -LEPs的神经电生理特征,研究者不仅要研究伤害性激光刺激诱发的ERPs,也要研究其非锁相的振荡信息.

采用时频分析方法(time-frequency analysis),激光引发的EEG时域信号可转化为时频振荡图谱.A δ -LEPs的时频谱主要包含2个重要时频响应特征:短暂的高频ERS (gamma振荡, 100~300 ms, 30~100 Hz, γ -ERS)和其后持久的低频ERD(alpha振荡, ~500 ms, 8~12 Hz, α -ERD)^[9,10],如图2所示(来自文献[38]).

近期的研究表明,伤害性刺激引起人类SI产生gamma振荡活动^[9,10],该振荡的能量强度与主观疼痛强度呈显著正相关.然而,由于疼痛刺激的突显性特征会随主观疼痛强度的增强而增加,所以这些发现可能混淆了刺激突显性这一潜在因素^[39,40].为了澄清这一问题,Zhang等人^[41]使用4种激光刺激强度,以1 s的固定时间间隔向被试的手背施加3个同一能量的伤害性刺激(triplets: S1-S2-S3).虽然重复施加相同刺激会影响刺激的突显性特征,但不会影响其主观疼痛强度.结果发现,主观疼痛强度与刺激能量呈

图2 (网络版彩色) A δ -LEPs的时频谱. A δ -LEPs 主要包含2个重要时频锁时非锁相响应特征:短暂的高频ERS (gamma振荡, 100~300 ms, 60~80 Hz, γ -ERS)和其后持久的低频ERD (alpha振荡, 400~900 ms, 8~12 Hz, α -ERD). A δ -LEPs (100~400 ms, 1~10 Hz)对应于时域的N2-P2复合成分. $N = 96$. 该图采自文献[38]

Figure 2 (Color online) Time-frequency representations of A δ -LEPs. Time-frequency representations of A δ -LEPs contain two important non-phase-locked responses: a transient high-frequency ERS at gamma band (100~300 ms, 60~80 Hz, γ -ERS) and a long-lasting low-frequency ERD at alpha band (400~900 ms, 8~12 Hz, α -ERD). The low-frequency component (100~400 ms, 1~10 Hz, A δ -LEPs) represents the time-frequency representations of N2-P2 complex in the time domain ($N = 96$, from Ref. [38]).

正相关; SI所产生的gamma振荡(γ -ERS, 100~300 ms, 30~100 Hz)与主观疼痛强度呈显著正相关, 且不随刺激的重复而变化. 该研究证实, gamma振荡直接反映了大脑皮层的疼痛感知^[9,42].

α -ERD可分为2大类: 感觉相关 α -ERD(sensory-related α -ERD)和任务相关 α -ERD (task-related α -ERD). 前者与刺激模态(如视觉、听觉)有关, 后者与认知加工(如工作记忆)有关^[43~46]. 疼痛研究中, 研究者同时发现了感觉相关 α -ERD和任务相关 α -ERD^[11,32,47,48], 这表明疼痛知觉包含了感觉辨别成分和认知成分. Hu等人^[11]深入探讨了与疼痛知觉有关的 α -ERD的功能性特征. 研究发现, 在刺激后250~350 ms, α -ERD主要分布于刺激对侧中心电极, 可能反映了感觉运动皮层的有关活动; 在刺激后400~750 ms, α -ERD主要涉及后顶叶和枕叶处的电极, 可能反映了双侧枕叶皮层的有关活动. 另外, α -ERD还受到刺激前 α 频带神经振荡能量水平的影响. 这些结果表明, α -ERD与疼痛处理过程有密切联系, 涉及除感觉之外的更为复杂的心理操作. 该研究加深了我们对 α 振荡功能的理解, 对生理学和心理学痛觉研究都有重要的启发意义.

2 C-LEPs的神经电生理特征

相对于A δ 纤维, C纤维的传导速率较慢(0.5~2 m/s)^[6]; 相对于A δ -LEPs, C-LEPs的峰潜伏期也较晚. 激光刺激手背时, C-LEPs峰潜伏期约为750~1150 ms^[32,49]. 在时域上, C-LEPs和A δ -LEPs有相似的形态、头皮分布和共同的起源^[50,51], 且均受到注意和激发状态的调节^[52~54]. 因此, C-LEPs在时域上可能也包括了C-N1, C-N2, C-P2和C-P4四种成分. 但由于C-LEPs的信噪比很低, 目前研究者只能清晰提取出C-LEPs成分中的C-N2/P2复合成分^[12], 即超晚期LEPs.

尽管前期研究提出了多种选择性激活C纤维的方法, 包括: (1) 选择性的阻滞A δ 纤维^[55], 如缺血性神经阻滞能有效并可逆的阻滞A δ 纤维; (2) 研究缺乏A δ 传入纤维的患者^[56], 如脱髓鞘性多发性神经病^[57]; (3) 因为相对于A δ 纤维, 皮肤中C纤维的分布密度更高, 所以采用极细的激光束(直径约为0.5 mm)可以更大程度地激活C纤维^[58,59]; (4) 由于C纤维游离神经末梢比A δ 纤维游离神经末梢的激活阈限更低, 所以有研究采用较低的刺激能量来选择性激活C纤维^[49,60]. 然而, 所有这些以孤立出C纤维为出发点的研究方式

都比较繁琐, 需要严格控制实验条件, 很难在临床上推广使用. 如用神经压迫法成功阻滞A δ 纤维需要持续对特定身体区域施压达60 min^[55]. 再比如Bragard等人^[58]为获得稳定的C-LEPs, 需要叠加平均600次实验刺激. 鉴于上述原因, 研究者需要开发一种简单可靠的C-LEPs提取方法.

Hu等人^[12]在其最新研究中明确提出了在A δ -LEPs存在的条件下提取C-LEPs的最优刺激参数和实验范式: 在一个小的皮肤区域内施加80次以上的多强度刺激, 如图3所示(来自文献[12]). 该方法简单可靠且无需选择性阻滞A δ 纤维. 通过对激光热刺激诱发的EEG响应实施波峰校准(peak alignment)和时频分解(time-frequency decomposition), 作者描述了C-LEPs的多重响应特征, 包括C-LEPs依赖于刺激能量和主观感知的特性. 当刺激能量大约达到个体的一次快疼阈限时, C-LEPs的信噪比最大; 当刺激能量从个体的感受阈限增加到一次快疼阈限时, 研究者就可刻画反映C纤维通路功能的刺激-响应曲线特

图3 (网络版彩色) LEPs的4个成分: A δ -N2, A δ -P2, C-N2和C-P2. 刺激左手背在Cz电极点(鼻尖参考)记录到的LEPs波形(aligned LEP waveforms, 峰值对齐)以及A δ -N2, A δ -P2, C-N2和C-P2的头皮地形图. 黑线代表所有被试的总平均波形, 其他的分别代表单个被试的平均波形. $N=34$. 该图来自文献[12]

Figure 3 (Color online) Four main components in LEPs: A δ -N2, A δ -P2, C-N2, and C-P2. Time courses of LEPs (Cz-nose), as well as scalp topographies of A δ -N2, A δ -P2, C-N2, and C-P2 waves, elicited by stimulation of the left hand (aligned LEP waveforms). Single-subject average waveforms are color-coded and superimposed, and the group average waveform is marked with black thick line ($N=34$, from Ref. [12])

征. 该研究为评估小直径神经纤维的神经生理功能提供了重要的技术支持, 在基础研究和临床实践上都有重要的指导意义. 将来的研究或许可以通过改进算法来有效可靠地提取C-LEPs的其他子成分, 如可能存在的C-N1, C-P4, α -ERD或 γ -ERS, 并探讨其神经功能意义, 以使我们更深入地了解人类的疼痛, 尤其是二次慢疼的神经机制.

3 体感诱发电位(somatosensory-evoked potentials, SEPs)

值得一提的是, 人体皮肤中除了存在传导伤害性信息的A δ 和C神经纤维之外, 还存在着传导躯体感觉信息的大髓鞘A β 神经纤维^[19,20]. 其直径相对较大, 约为6~12 μ m, 传导速度约为35~75 m/s, 神经末梢的激活阈限很低. 低强度的躯体感觉刺激(如经皮电神经刺激, transcutaneous electrical nerve stimulation, TENS)能激活A β 神经纤维, 神经冲动经过复杂传导通路后最终在大脑皮层产生SEPs. 在时域上, SEPs主要包含了两阶段的复合成分: (1) 早期成分, 刺激上肢正中神经(median nerve)和下肢胫神经(tibial nerve)分别产生N20-P27-P45和P39-N50-P60, 其头皮地形图分布相似^[61,62], 可能起源于对侧SI^[19,63]; (2) 晚期成分, 刺激上肢正中神经产生的N120-P240^[64], 可能产生于双侧SII和ACC^[28,64-67]. 其中, 早期成分可能反映了大脑对躯体感觉信息的感知辨别加工, 晚期成分可能反映了大脑对躯体感觉刺激新异性(新颖性和突显性)的加工^[64].

临床上通常运用SEPs的早期成分检测躯体感觉通路的完整性, 但SEPs早期成分波幅很小, 信噪比低, 所以有研究者推荐, 要获得稳定可检测的SEPs波形, 需要叠加平均至少500个试次^[19]. 另外, 早期SEPs只能反映外周大直径A β 神经纤维、背柱、内侧丘系及其丘脑-皮质投射的通路功能^[20], 而晚期SEPs与高级认知加工有关^[68,69]. 这些特征便限制了SEPs的临床应用, 即只能用于检测躯体感觉通路(躯体感觉信息从外周感觉神经传递到大脑感觉区域)的完整性^[19,20,70]. 相比之下, LEPs的临床应用具有不可替代性.

4 LEPs的应用

4.1 基础应用

LEPs在基础研究中也具有广泛的应用价值. 例

如, 在老龄化研究中, 近期的一项研究^[71]采用红外线激光热刺激考察了老龄化对热感觉系统响应能力的影响. 通过对比老人和年轻人的热响应电位, 他们发现在温暖环境中, 老人的C-P2波幅显著小于年轻人的C-P2波幅. 这表明老龄化可能导致C纤维功能紊乱, 从而引起热敏性变化, 对温度变化的适应能力下降^[72,73]. 因此, 将来的研究可能运用A δ -LEPs和C-LEPs探讨与年龄相关的感知觉功能的变化.

另外, 伤害性刺激可作为惩罚刺激研究人际内疚(interpersonal guilt)等社会认知方面的问题^[74]. 再者, A δ -LEPs也可用于研究反应抑制^[75](重要的认知控制能力)和情绪^[76,77]对伤害性加工的调节作用. 特别地, Martini等人^[76]首次采用情绪面部表情图片考察了他人情绪冲突对旁观者A δ -LEPs的影响. 被试在观看面部表情图片(中性、高兴或疼痛)或注视点(控制条件)的同时接受激光疼痛刺激. 其中, 中性、高兴和疼痛3种面部表情图片和注视点分别在不同的block中呈现. 指导语告知被试, 中性、高兴或疼痛的面部表情是图片中的model在接受疼痛刺激时产生的. 研究者发现, 与控制条件相比, 被试观看高兴图片所引发的A δ -N2波幅显著更低; 并且该条件下的A δ -N2波幅与被试在述情障碍量表(Toronto Alexithymia Scale, TAS-20)的情绪识别子量表上得分成显著负相关. 这些发现表明, A δ -N2可能与个体监测他人的情绪冲突有关. 然而, 该研究可能至少存在以下局限: (1) 3种情绪图片和注视点的注意捕获程度不同, 这可能混淆实验结果; (2) 由于在认知研究领域中, 情绪冲突通常是通过一致条件和不一致条件的对比来量化, 所以, 本研究实际上并未发现情绪冲突效应; (3) 单独测量A δ -N2, A δ -P2波幅可能存在负走向的信号飘移问题. 尽管如此, 该研究将疼痛感知与高级认知控制功能结合起来, 从而拓宽了疼痛研究领域. 将来的研究可以采用A δ -LEPs探索高级的认知加工过程和疼痛感知的交互作用问题.

综上所述, 在方法学和理论上, 这些研究对疼痛相关的ERPs研究(社会认知、情绪等)都有一定指导意义.

4.2 临床应用

尽管研究者对于LEPs的神经生理学意义还存在着分歧, 但在生理学^[6]和病理生理学研究^[20]中, 它们已被广泛用于探讨伤害性传入信息的外周和中枢神

经处理过程。实际上, A δ -LEPs被认为是评估患者伤害性传导通路功能是否完善的最为有效的诊断工具^[20,78]; 而C-LEPs对于评估小直径纤维的神经功能有极其重要的应用价值。如A δ -LEPs可用于探索三叉神经痛、带状疱疹后神经痛和瓦伦堡氏综合征等疾病的病理生理学机制^[79,80]。三叉神经痛和带状疱疹后神经痛的患者常常缺失正常的A δ -LEPs; 而瓦伦堡氏综合征患者会同时缺乏A δ -LEPs和C-LEPs。这些LEPs的完全缺失、振幅减弱或峰潜伏期延迟, 可能预示着患者伤害性传导通路中的外周、脊柱或脑干的损伤。然而, Tinazzi等人^[81]发现, 颈肌张力障碍(cervical dystonia)患者(颈部肌肉疼痛)和正常被试的A δ -LEPs(N2-P2)波幅没有显著差别, 并且他们的疼痛评定分数也没有显著差异。这表明, 患者的伤害性传导通路功能是正常的, 并且他们的颈部肌肉疼痛与疼痛信息的中枢敏化无关。所以, 这些研究共同表明, A δ -LEPs能有效评估不同病患伤害性通路的完整性以及大脑对伤害性传入信息的处理过程。

由于某些病理上的疼痛发作或疼痛敏感性增强(痛觉过敏和异常性疼痛)会涉及LEPs的特征变化, 所以研究者可以根据LEPs的变化来评估疼痛感知的变化。例如, 与健康人相比, 纤维肌痛综合征(fibromyalgia syndrome)患者的热疼阈限更低、早期A δ -N1和晚期A δ -P2幅值都更大^[82,83]。A δ -N1幅值的增强可能由外周和脊髓敏化引起或是由伤害性感受的皮层或亚皮层抑制作用较少造成, 而A δ -P2幅值的增强可能反映了患者对伤害性刺激的关注和认知加工增加。

另外, LEPs也可用于实时监控镇痛药物或镇痛方式的临床疗效^[84-86], 甚至用于研究植物人和处于微意识状态患者的疼痛感受^[87]。例如, Lorenz等人^[84]考察了口服吗啡缓释片(oral sustained-release morphine)对慢性非恶性疼痛的治疗效果。他们发现, 吗啡治疗之后, A δ -N2/P2波幅明显减少, 疼痛阈限明显增加。这表明A δ -LEPs可以作为评估吗啡镇痛疗效的

有效指标。又如, Vassal等人^[85]将CO₂激光脉冲施加于健康被试的双脚脚背, 以此来考察TENS对A δ -LEPs和疼痛知觉的影响。他们发现, 当TENS和疼痛刺激施加于同一侧时, A δ -N1, A δ -N2/P2波幅明显减小, 被试的疼痛知觉阈限显著提高, 并且这一效应持续至少25 min。这表明, TENS能对疼痛加工和疼痛感知产生明显地相对持久抑制作用。因此, A δ -LEPs可用于评估TENS的临床镇痛疗效。另外, de Tommaso等人^[87]采用CO₂激光刺激检测了长时意识障碍患者(植物人和微意识状态患者)的疼痛知觉。结果显示, 两组病人都具有明显的A δ -N2和A δ -P2, 但是它们的峰潜伏期明显长于正常对照组。这表明长时意识障碍患者也可能具有疼痛感知和意识^[88]。因此, 该研究说明LEPs可用于意识障碍病人的诊断, 甚至有望用于评估其意识恢复治疗的疗效。

值得一提的是, 在临床疼痛的治疗方面, 安慰剂效应是影响疗效的重要因素之一^[89]。考虑到安慰剂效应主要由心理预期和经典条件化作用2种因素引起^[90-92], Colloca等人^[93]采用CO₂激光脉冲刺激考察了这2种因素对LEPs和主观疼痛评定的影响。结果显示, 预期和条件化作用都明显减少了A δ -N2/P2波幅, 并且在条件化作用下, A δ -N2/P2波幅减少得更多, 这和已有研究一致^[94,95]。更重要的是, 条件化作用也减少了被试的主观疼痛评定分数。这些发现表明, 被试先前疼痛经历(即学习)加强了安慰剂镇痛效应, 适当运用条件化作用可能使疼痛治疗取得更好的效果。同时, 本研究也表明A δ -LEPs能用于安慰剂镇痛的疗效评估。

基于所述, 大部分临床研究都以A δ -LEPs为指标考察疼痛通路功能的完整性以及疼痛加工过程。由于C-LEPs本身的信噪比很低, 提取相对困难, 所以对它的临床研究较少。将来的研究应该在澄清两类LEPs的神经生理学意义的基础上, 进一步探讨C-LEPs在临床应用方面的研究。

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Neural electrophysiological features of laser-evoked potentials and their applications

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Pain is related to the encoding and processing of afferent nociceptive information in the brain, and is a critical factor that allows humans and animals to learn to avoid potential or actual tissue injury. Being conducted by A δ fibers and C fibers, nociceptive signals are processed by multiple brain structures, and normally generate a double sensation: an initial pricking pain (first pain) and a prolonged burning sensation (second pain). Intense laser heat pulses can selectively excite nociceptive free nerve endings in superficial layers of the skin. Such stimuli can elicit changes in brain responses (laser-evoked potentials, LEPs) in the ongoing electroencephalograms (EEGs). Until now, six reliable components have been detected in A δ -LEPs: A δ -N1, A δ -N2, A δ -P2, and A δ -P4 waves in the time domain and alpha-band event-related desynchronization (α -ERD) and gamma-band event-related synchronization (γ -ERS) in the time-frequency domain. Meanwhile, by optimizing the experimental paradigm and parameters, two components of C-LEPs have been reliably detected: C-N2 and C-P2 waves in the time domain. The present paper reviewed the neural electrophysiological features of LEPs and their cognitive significance. LEPs can not only be used to investigate the peripheral and central processing of nociceptive sensory input, which is important in several clinical applications, but also be adopted in some basic research (e.g., the aging problem and social cognition) as a novel neurophysiological technique.

pain, electroencephalography (EEG), laser-evoked potentials (LEPs), neural oscillation

doi: 10.1360/N972014-01012