疼痛相关高频振荡信号: 进展与展望

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摘要 慢性疼痛不仅丧失了急性疼痛所具有的警示作用, 还严重危害患者的身心健康, 大幅增加家庭和社区的医疗成本. 慢性疼痛的有效治疗依赖于对疼痛的准确评估. 然而, 临床诊断中仍缺乏疼痛的客观评估方法, 大大增加了疼痛管理和镇痛效果评估的难度. 最近一系列电生理研究发现, 疼痛诱发的 γ 频带高频振荡信号和疼痛有密切关联, 能在一定程度上表征疼痛强度, 具体表现为: (1) 在短时疼痛情境下, 初级躯体感觉皮层 γ 振荡可特异性地编码疼痛的主观强度和疼痛敏感性的个体差异, 并能反映心理因素对疼痛的调节作用. (2) 在长时疼痛情境下, 前额叶 γ 振荡与主观疼痛评分显著相关. (3) 在慢性疼痛情境下, 前额区域 γ 振荡能反映不同类型慢性疼痛患者的自发疼痛强度. 然而, 目前研究仍存在 γ 振荡信噪比低、与其他神经振荡关系不明、产生机制复杂以及与疼痛的因果证据不足等问题. 未来研究有必要采用更加敏感和标准化的分析方法, 整合跨物种研究、神经调节等技术, 以系统、全面地阐明 γ 振荡在疼痛信息处理中的作用机制, 进而促进疼痛评估标准的客观化, 帮助改善疼痛管理现状.

关键词 疼痛, 疼痛评估, 疼痛管理, 高频振荡信号

疼痛(pain)是一种与实际或潜在的组织损伤相关的不愉悦体验^[1], 其生物学功能在于限制和避免伤害, 并促进躯体损伤的康复, 因此疼痛对个体生存具有重要意义. 然而, 当持续时间超过3个月, 或在损伤恢复后仍存在, 疼痛就转变成了慢性疼痛(chronic pain)^[2-4]. 作为一种疾病, 慢性疼痛不仅丧失了疼痛的警示作用, 更给患者和整个社会都造成了重大损失^[5]. 据统计, 慢性疼痛折磨着全球约五分之一的成年人^[6,7]; 仅在我国, 慢性疼痛每年造成的经济损失就高达数千亿人民币^[8,9].

在这一严峻局势下, 慢性疼痛治疗方法的开发刻不容缓. 疼痛的有效治疗依赖于对疼痛的准确评估和对疼痛加工机制的深入理解^[10]. 目前, 临床诊断中疼痛

评估主要采用主观评定方法, 即患者根据其疼痛体验口头报告疼痛程度, 或填写相应的疼痛问卷. 这一方法虽然考虑到了疼痛的主观性本质, 但也存在评定标准主观性过强、易受报告倾向性影响和难以应用到言语能力受损的特殊个体等局限性^[11,12]. 为克服主观评定法的局限性, 有必要开发客观、可靠、特异的疼痛评估方法. 利用伴随疼痛产生的电生理信号衡量疼痛水平, 或许是实现疼痛客观评估的有效途径^[13]. 在疼痛相关电生理信号中, 脑电(electroencephalogram, EEG)信号是一种较为理想的客观评估疼痛的生理指标. 它具有毫秒级的高时间分辨率和相对较低的数据采集成本, 并且直接反映了神经元电活动. 不仅如此, 大量研究证

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实, 神经系统中的神经振荡信号在协调不同神经环路的活动起着关键作用^[14]. 而且疼痛作为一种包含感觉分辨、情感动机和认知评价等多维信息构成的复杂主观体验^[15], 其多维信息的整合也依赖于神经振荡^[16,17]. 因此, 对疼痛脑电信号的研究既有助于开发客观的疼痛评估指标, 也有利于揭示疼痛的神经加工机制.

借助热刺激、激光刺激等多种伤害性刺激方式在实验室中诱发疼痛, 研究者已经分离了疼痛程度相关的脑电信号特征^[18~20]. 其中, 经典的信号包括时域上的N2、P2成分^[21], 以及时频域上8~12 Hz的 α 频带事件相关去同步化(α -band event-related desynchronization, α -ERD)^[22~24]和30~100 Hz的 γ 频带事件相关同步化(γ -band event-related synchronization, γ -ERS)^[25~27]. 然而, 以往研究发现, N2和P2受到刺激新异性(saliency: 新颖性和突显性)的影响^[24], 且不具有疼痛特异性^[28~30], α -ERD则无法反映疼痛程度的不同, 也不具备疼痛特异性^[31,32]. 因此, 这些脑电信号特征难以有效且特异地反映疼痛程度. 相反, 近年来, 越来越多的研究发现 γ -ERS似乎不受到刺激新异性的影响, 能够较好地衡量疼痛水平^[27,33~35](图1). 不仅如此, γ 频带的高频振荡信号既与健康被试的长时疼痛水平有关^[32,36~38](图2), 也与慢

性疼痛患者的自发疼痛水平有关^[39~42](图3). 由此可见, 疼痛诱发的 γ 频带高频振荡信号在客观评估疼痛和深入探究疼痛神经机制方面均有重大潜在价值.

为系统梳理 γ 频带高频振荡信号与疼痛的相互关系, 本文介绍了 γ 频带高频振荡信号的生理基础, 重点阐述 γ 频带高频振荡信号与短时疼痛、长时疼痛和慢性疼痛的关系, 指出目前的研究中尚待解决的关键性问题, 并提出可能的解决方案.

1 γ 频带高频振荡信号的生理基础

γ 频带高频振荡信号(简称为“ γ 振荡”)是一种常见的神经振荡信号, 频带范围通常为30~100 Hz, 可在不同哺乳动物的多个大脑区域中记录到^[43]. 就产生机制而言, 多项研究表明 γ 振荡是由抑制性中间神经元(inhibitory interneurons)与兴奋性锥体细胞(excitatory pyramidal cells)之间相互作用产生的^[44~48]. 从神经递质层面看, γ 振荡是分别由抑制性 γ -氨基丁酸能神经元(inhibitory GABAergic neurons)和兴奋性谷氨酸能神经元(excitatory glutamatergic neurons)之间相互作用产生的^[49,50]. 这种相互作用存在节律性, 使得细胞整体的兴奋性在每个周期内发生变化^[51]. 与此同时, 目前研究公认 γ 振荡是以节律抑制性突触后电位(inhibitory postsy-

图1 (网络版彩色)中央电极处(Cz) γ 频带高频振荡信号在个体内(a)和个体间(b)水平上均编码短时疼痛敏感性. γ -ERS: γ 频带事件相关同步化; Mag: 幅值; LT: 低疼试次; HT: 高疼试次; LS: 低疼被试; HP: 高疼被试. 改自文献^[35]

Figure 1 (Color online) Gamma band oscillations at the central electrode (Cz) encode pain sensitivity at both within-subject (a) and between-subject levels (b). γ -ERS: γ -band event-related synchronization; Mag: Magnitude; LT: Low pain trials; HT: High pain trials; LS: Low pain subjects; HP: High pain subjects. Adapted from Ref. ^[35]

图2 (网络版彩色)前额区域 γ 频带高频振荡信号编码长时疼痛强度。Tonic pain: 长时疼痛; scalp topography: 头皮地形图; gamma band oscillations: γ 频带高频振荡信号; pain intensity: 疼痛强度; stimulus intensity: 刺激强度; T value: 由线性混合模型所计算出的 T 值, 表征长时疼痛强度与脑响应信号之间的关系, 如 γ 频带高频振荡信号。改自文献[36]

Figure 2 (Color online) Gamma band oscillations in the prefrontal region correlate with continuous ratings of tonic pain. T value was calculated using the linear mixed model to estimate the relationship between tonic pain and brain responses, e.g., gamma band oscillations. Adapted from Ref. [36]

图3 (网络版彩色)前额区域 γ 频带高频振荡信号编码慢性背痛患者的自发疼痛强度。Chronic pain: 慢性疼痛; scalp topography: 头皮地形图; gamma band oscillations: γ 频带高频振荡信号; spontaneous pain: 自发疼痛; visual control: 视觉控制; T value: 由线性混合模型所计算出的 T 值, 表征自发疼痛强度与脑响应信号之间的关系, 如 γ 频带高频振荡信号。改自文献[41]

Figure 3 (Color online) Gamma band oscillations in the prefrontal region correlate with intensity ratings of spontaneous pain in chronic back pain patients. T value was calculated using the linear mixed model to estimate the relationship between spontaneous pain and brain responses, e.g., gamma band oscillations. Adapted from Ref. [41]

naptic potential, IPSP)为基础的振荡信号, 其抑制作用起源于小清蛋白型阳性篮状细胞(parvalbumin positive basket cell)[52,53]。

γ 振荡是脑中群体神经细胞放电的一种形式, 其生理功能尚不明确, 不同脑区 γ 振荡与感知觉、高级认知和慢波睡眠等多种生理、心理状态有关[46,49]。早期研究表明, 感官输入可以显著增强 γ 振荡[54], 而且这种信号增强的产生区域与刺激模式存在关联: 视觉刺激诱发 γ 振荡增强出现在初级视觉皮层(primary visual cortex, V1)[55], 而激光热痛刺激诱发 γ 振荡增强则在初级躯体感觉皮层(primary somatosensory cortex, S1)[25]。这使得研究 γ 振荡与某一特异性功能的关联必须考虑到 γ 振荡的产生区域。不过, 从宏观的信息加工角度看, γ 振荡的主要功能是促进大脑内部神经信号的交流通

讯[51,56]。现有假设认为, 这一功能可通过神经活动同步化(synchronization)产生的共享时间窗口[57,58], 或借助振荡峰值期间的相位(phase)编码[56,59]来实现。

2 γ 频带高频振荡信号与疼痛

根据持续时间的长短, 疼痛可分为短时疼痛、长时疼痛和慢性疼痛三大类。研究表明, γ 振荡与这三类疼痛均有密切关联(表1)。

2.1 γ 频带高频振荡信号与短时疼痛

Gross等人[25]首次证明了短时激光疼痛刺激会诱发源定位在S1的 γ 振荡, 而且这种振荡信号与疼痛的主观感知密切相关。他们的研究由两个实验组成, 实验一向被试的右手手背施加能量为600 mJ的激光刺激, 被

表1 γ 频带高频振荡信号与不同类型疼痛的关系

Table 1 The relationship between gamma band oscillations and different types of pain

疼痛类型	皮质区域	γ 频带高频振荡信号(Hz)
短时疼痛	初级躯体感觉皮层	60~95 ^[25] 、30~100 ^[27] 、70~90 ^[33] 、70~88 ^[35]
长时疼痛	前额皮层	30~100 ^[32,36,38] 、50~90 ^[37]
慢性疼痛	前额皮层	30~48 ^[40] 、60~90 ^[41] 、40~70 ^[42]

试则不需做任何反应,仅闭眼感受刺激.脑磁图(magnetoencephalogram, MEG)结果显示,在刺激呈现后100~300 ms时,对侧S1区域 γ 振荡(60~95 Hz)信号显著增强.实验二使用4个不同强度(150, 300, 450, 600 mJ)的激光刺激,被试需利用主观评分量表报告感受到的疼痛强度.结果显示, S1区 γ 振荡的信号强弱随激光刺激物理强度和被试主观疼痛强度的变化而变化,而且疼痛阈限处的刺激比阈限以下的刺激诱发更强的 γ 振荡.该研究刻画了S1区疼痛诱发高频振荡信号的时间空间特征,并揭示了S1区诱发 γ 振荡信号与刺激强度和疼痛感知之间的关系,引起了研究者对疼痛诱发高频振荡信号的重视^[27,33~35,60~63]

然而,疼痛刺激具有较高的新异性,能吸引个体的注意,获得更多的认知加工.为排除新异性的混淆,Zhang等人^[27]使用相继施加3个间隔1 s但强度相同的疼痛刺激(triplets: S1-S2-S3)的方法减小疼痛刺激的新异性,从而考察 γ 振荡反映的是疼痛本身还是疼痛刺激的新异性^[24,64,65].结果显示,激光刺激在S1区诱发的 γ 振荡(30~100 Hz)不仅不受刺激重复的影响,还与被试的主观疼痛评分呈稳定的正相关关系,而且能够可靠预测被试的主观疼痛评分.该研究排除了刺激新异性这一混淆因素,进一步佐证了短时疼痛诱发的S1区 γ 振荡参与大脑疼痛加工过程,且能够直接反映人类的主观疼痛知觉.

进一步的研究发现, γ 振荡还反映了疼痛敏感性的个体差异.疼痛存在巨大的个体间和个体内差异:不同个体对同一疼痛事件的知觉体验不同,即便是同一个体在不同环境中的疼痛知觉的敏感性也会不同.Schulz等人^[33,66]发现,个体的疼痛敏感性变化能够反映在疼痛相关高频振荡信号中, γ 振荡能够反映个体内疼痛敏感性的变化,而基于8 Hz左右的疼痛诱发反应和 γ 振荡(70~90 Hz)能够以较高的准确性(83%)预测个体的疼痛敏感性.Hu和Iannetti^[35]采用跨物种研究的方法进一步证明了 γ 振荡能特异且可靠地编码个体内和个体间疼

痛敏感性.他们发现,所有由短时激光刺激诱发的EEG响应特征(N2、P2、LEPs、 α -ERD和 γ -ERS)均能较好地反映个体内的疼痛敏感性,但仅有 γ 振荡(60~85 Hz)能刻画个体间的疼痛敏感性(图1),且 γ 振荡无法预测个体对视觉、听觉和触觉刺激的感觉强度评分,这意味着 γ 振荡对感觉敏感性的预测具有一定的疼痛特异性.不仅如此,Hu和Iannetti^[35]还发现,这一结果具有跨物种一致性:只有 γ -ERS同时与Sprague-Dawley(SD)大鼠在个体内和个体间水平上的疼痛行为存在显著相关^[62],并且激光刺激诱发的 γ -ERS的空间地形图与听觉刺激诱发的 γ -ERS存在明显差异.

疼痛是一种主观的感觉和情绪体验,受到注意等心理因素的调节^[67].如果 γ 振荡反映的是主观的疼痛感知,那么它也应受到注意等心理因素的调节.注意对疼痛的影响分为两个方面:一是由疼痛刺激本身引起的自下而上的注意对疼痛的调节,二是个体主动发起的自上而下的注意对疼痛的调节^[68].相关研究证实, γ 振荡能够反映这两种注意对疼痛的调节作用.对于自上而下的注意效应,Hauck等人^[60]发现对疼痛刺激的定向注意能够增强感觉运动皮层(sensorimotor cortex)的 γ 振荡;对于自下而上的注意效应,Tiemann等人^[61]则发现疼痛刺激引起的注意力变化与 γ 振荡的变化密切相关.

γ 振荡与两种注意效应间关系的直接证据来自Hauck等人^[69],为分离自上而下的注意(空间注意)和自下而上的注意(刺激强度)对疼痛的影响,他们改进了先前的实验设计^[60]:在被试的食指和无名指上呈现等概率的激光热痛刺激,从而避免与刺激概率相关自下而上因素的混淆;同时要求被试闭眼感知激光刺激,但只对主试指定手指上的疼痛刺激进行高疼和低疼的分类,忽略另一根手指上的激光疼痛刺激.他们发现,两种注意效应对大脑低频、高频神经振荡反应存在不同影响.自上而下的空间注意效应会导致脑岛(insula)区域 α 振荡能量减少和 γ 振荡能量增加;自下而上的刺激强度注意效应则能同时调节 δ 、 α 、 β 和 γ 振荡的能量,但此时

的 γ 振荡能量变化出现扣带回(cingulate gyrus)和躯体感觉区域(somatosensory areas). 由此可见, 脑岛的 γ 振荡能够反映自上而下的注意效应, 而扣带回和感觉运动区的 γ 振荡则反映自下而上的注意效应. 因此, γ 振荡可能在疼痛相关信号传递、痛觉输入与痛觉体验整合中起着关键作用^[69].

不过, 在Hauck等人^[69]的研究中, 被试仅对关注的手指上的疼痛刺激进行强度评估和分类, 自上而下和自下而上两种注意效应可能存在一定的交互作用. Tie-mann等人^[34]分别使用刺激强度、安慰剂效应代表自下而上和自上而下的调节因素. 结果显示, γ 振荡对自下而上和自上而下的调节具有不同的敏感性: γ 振荡受刺激强度自下而上的调节, 但不受安慰剂效应自上而下的调节. 这一结果与Hauck等人^[69]的结果存在差异. 究其原因, 可能是因为两项研究中自上而下的调节因素存在差异: 安慰剂效应相对于空间注意涉及预期等更高级的认知加工.

总的来看, 现有证据表明, γ 振荡可编码短时疼痛的主观强度、个体差异, 并且反映心理因素对疼痛的调节作用, γ 振荡一定程度可作为短时疼痛的客观指标.

2.2 γ 频带高频振荡信号与长时疼痛

由于锁时性较好, 短时伤害性刺激(phasic pain stimuli)在疼痛基础研究中应用非常广泛. 然而, 这种疼痛体验与日常生活中真实的疼痛体验和慢性疼痛均有较大差异. 为了模拟真实的疼痛体验, 进一步揭示 γ 振荡在真实疼痛情景中的作用, 研究者采用了更具生态效度的长时疼痛刺激. 长时疼痛持续时间在几分钟左右, 可通过接触式热刺激(thermal contact-heat stimuli)^[32,36]、肌肉注射高渗盐水(muscular injection of hypertonic saline)^[37]等方法诱发. 已有诸多研究结果支持 γ 振荡与长时疼痛强度存在密切关联.

例如, Peng等人^[32]设置睁眼休息、无痛分心、疼痛分心、疼痛注意4种实验条件, 考察了注意状态和5 min长时热痛刺激对神经振荡信号的影响. 结果显示, 长时热痛刺激使得刺激同侧头部中央区(C1、C3、CP1、CP3)和额叶-中央区(Fz、FC1、FC2和Cz)记录到的 γ 振荡(30~100 Hz)增强, 而且 γ 振荡增强与被试的主观疼痛评分增加存在显著正相关. 然而, γ 振荡并未受到分心任务的注意调节. 这些结果意味着, 在长时疼痛处理中, γ 振荡可能更多地表征自下而上的刺激加工^[32].

Schulz等人^[36]得到了类似的结果, 他们将热痛持续时间进一步延长至10 min, 并加入视觉控制条件和1 ms的短时激光热痛条件. 结果显示, 疼痛主观强度编码与客观刺激强度编码存在分离, 长时疼痛的主观评分仅与内侧前额叶(medial prefrontal cortex, mPFC)的 γ 振荡相关(图2), 但客观刺激强度却与感觉运动区域的 α 振荡和 β 振荡相关. 此外, 与短时疼痛不同的是, γ 振荡并未出现在感觉运动区域, 而是出现在内侧前额叶区域中. 这意味着长时疼痛加工与短时疼痛加工在脑内活动中存在差异. 这一差异可能反映了短时疼痛和长时疼痛的内在差异: 短时疼痛以感觉加工为主, 而长时疼痛的感知需要更多地依赖于背景、整合和情感评价加工^[36]. 进一步来看, 长时疼痛中疼痛强度编码且不存在空间特异性, 即左右手刺激不会造成内侧前额叶区域 γ 振荡对疼痛强度编码的偏侧化^[38].

总而言之, γ 振荡在长时疼痛中也可能具有疼痛感知编码的功能意义, 前额区域的 γ 振荡极有可能反映长时疼痛的大脑加工机制变化^[36-38].

2.3 γ 频带高频振荡信号与慢性疼痛

慢性疼痛作为一种病理状态, 严重影响大脑的疼痛加工过程, 但 γ 振荡仍与疼痛的大脑加工机制密切相关. 研究发现, 相对于健康对照组, 诸多慢性疼痛患者在前额区域表现出 γ 振荡信号增强. 例如纤维肌痛(fibromyalgia, FM)患者^[40]、慢性背痛(chronic back pain)患者^[41]、带状疱疹后神经痛(post-herpetic Neuralgia, PHN)患者^[42].

为了解FM患者静息态脑节律异常情况及其与临床疼痛症状的关系, Lim等人^[40]利用MEG记录了FM患者和健康对照组被试的在睁眼和闭眼时的静息态脑活动. 结果显示, FM患者在闭眼时 θ 、 β 振荡和 γ 振荡信号普遍增强, 同时 α 频带峰值频率也有所下降. 进一步来看, FM患者 β 、 γ 振荡增强集中在背外侧前额叶(dorso-lateral prefrontal cortex, DLPFC)和眶额皮层(orbitofrontal cortex, OFC), 这种 β 、 γ 振荡增强与FM患者的情感性疼痛评分存在较高相关性. May等人^[41]记录了慢性腰痛患者在自发疼痛条件和控制条件下各11 min的静息态脑电活动. 在自发疼痛条件下, 患者利用视觉评分量表实时评估疼痛的主观强度; 而在控制条件中, 患者只操纵评分装置以匹配屏幕上显示的评分. 结果显示, 患者的自发疼痛强度评分仅与前额区域 β 振荡和 γ 振荡之间存在正相关(图3). 由于感觉运动区域的 α 和 β

振荡与伤害性信息加工相关^[38,70], 但与患者的疼痛评分无显著相关, May等人^[41]认为这支持了慢性背痛患者的持续性疼痛和伤害性加工存在分离的观点, 即慢性疼痛患者在没有伤害性输入的情况也会感受到持续性的疼痛. 此外, Zhou等人^[42]的研究则进一步检验了 γ 振荡和带状疱疹后遗神经痛的关联. 他们发现, PHN患者前额等区域 γ 振荡(40~70 Hz)信号显著增强, 且与患者的主观疼痛评分、焦虑和抑郁量表得分呈显著正

相关.

虽然Lim等人^[40]、May等人^[41]和Zhou等人^[42]的研究发现来自不同类型的慢性疼痛患者, 但均显示前额区域 γ 振荡信号增强与患者自发疼痛评分存在显著相关. 这些研究结果不仅与慢性疼痛患者自发脑电活动的总体特征相吻合, 即功率谱(power spectrum)主峰向低频偏移, 额、顶枕电极位置功率谱反应增强^[70], 而且在一定程度上也符合功能磁共振成像(functional mag-

图 4 (网络版彩色)不同物种 γ 频带高频振荡信号的记录技术. (a) 脑电和脑磁技术常用于人类被试; (b) 皮层脑电和局部场电位技术常用于记录大鼠脑活动信号, 改自文献^[88]; (c) 光遗传和微电极记录技术(可记录局部场电位)常用于转基因小鼠, 改自文献^[82]. EEG: 脑电; MEG: 脑磁; LFP: 局部场电位; ECoG: 皮层脑电; PV-cre mouse: 阳性中间神经元表达有Cre蛋白的小鼠

Figure 4 (Color online) Techniques to record gamma band oscillations from different species. (a) EEG and MEG are normally used to collect signals from humans. (b) ECoG and LFP are normally used to collect signals from rats, adapted from Ref. ^[88]. (c) Microelectrode recording technique with optogenetics is normally used to collect signals from transgenic mice, adapted from Ref. ^[82]

netic resonance imaging, fMRI)的研究发现, fMRI相关研究显示, 相较于健康人, 慢性疼痛患者的前额皮层和边缘系统(limbic system)活动有所增加^[71,72]. 与此同时, 慢性疼痛动物模型中, 自发疼痛行为也伴随着海马——前额叶的活动改变^[73], 进一步证明了前额叶皮层与慢性疼痛的密切关系. 这些结果可能意味着, 长期疼痛使得慢性疼痛患者的疼痛加工从感觉维度更多转向了情绪和认知维度^[72,74,75].

鉴于 γ 振荡与慢性疼痛患者自发疼痛的关系, γ 振荡可能具有潜在的临床价值^[42]. 例如, 它或许可作为一个更客观的诊断工具^[76-78], 利用外部调节(如无创神经刺激)^[79]或内部调节(如神经反馈)^[80]的手段调节 γ 振荡或许能够缓解慢性疼痛.

3 研究展望

现有研究证据表明 γ 振荡在短时疼痛、长时疼痛和慢性疼痛的加工过程中都起着重要作用, 能在一定程度上反映主观疼痛的强弱. 不过, 目前仍存在诸多关键性问题亟待解答.

(1) γ 振荡的信噪比较低、受刺激特征变化的影响较大, 而且易受高频肌电伪迹的影响^[51], 对 γ 振荡的提取和相位的准确估计存在一定困难. 那么脑电研究中 γ 振荡的信号质量如何保证?

(2) 对于短时疼痛而言, S1区 γ 振荡具有疼痛特异性, 但是 γ 振荡与其他频率振荡信号以及与其他脑区振荡信号的关系仍不清楚. 那么S1区 γ 振荡是否足以作为疼痛的直接神经关联物?

(3) γ 振荡存在多种生理产生机制^[46,49], 虽然不同疼痛条件下(短时疼痛、长时疼痛和慢性疼痛)发现的 γ 振荡均与疼痛加工有关, 但是 γ 振荡的脑内源存在差异, 那么不同条件采集的 γ 振荡是否具有相同的功能意义?

(4) 现有研究揭示的多是 γ 振荡与疼痛的相关性, 虽

然已有研究表明健康被试刺激前 γ 振荡的能量大小对疼痛具有因果影响^[81], S1区 γ 振荡与小鼠的疼痛行为之间存在因果关系^[82], 但是在人类研究中 γ 振荡与疼痛的直接因果证据仍然缺乏, 那么通过调控 γ 振荡是否可以影响疼痛仍不清楚?

为解决以上4个问题, 未来可从4个方面入手开展研究.

(1) 采取更加敏感的测量方法^[83]和更加标准化的分析方法^[84], 提高 γ 振荡的信噪比、排除其他活动的潜在污染^[85]; 或者结合侵入性技术, 从人类(患者)和动物(大鼠、小鼠和猕猴)中获取更高质量的电生理数据.

(2) 考虑不同频率神经振荡信号之间的相互关系^[86,87], 在研究中对 γ 振荡与其他频率振荡信号以及与其他脑区振荡信号的关系和功能意义进行系统评估.

(3) 扩展现有电生理数据采集技术, 同时获取多个层面的电生理信息, 并与光遗传技术相结合, 以全面理解 γ 振荡的功能特性(图4). 例如, 在大鼠头部同时记录皮层脑电(electrocorticogram, ECoG)和局部场电位(local field potential, LFP)^[88].

(4) 关注刺激前大脑神经活动对疼痛感知的影响, 利用多种优势互补的研究技术, 在人类和动物身上对 γ 振荡的信号特征和功能相关性进行深入研究. 例如, 结合fMRI技术和EEG技术, 以较高的时空分辨率同时获取疼痛相关脑活动; 采用非侵入性大脑刺激技术(如经颅交流电刺激: transcranial alternating current stimulation, tACS)对高频振荡信号进行选择性的调制^[79], 在人类身上获取 γ 振荡和疼痛的因果关系证据^[89], 并发展为有效的神经调控镇痛技术.

从以上几方面入手, 对 γ 振荡和疼痛的关系进行全面、深入的研究, 将有助于揭示疼痛信息加工的神经机制和建立疼痛评估的客观标准, 为最终有效管理疼痛、消除患者痛苦和减轻社会负担奠定基础.

参考文献

- Merskey H, Bogduk N. Task force on taxonomy of the international association for the study of pain. In: Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definition of Pain Terms. 2nd ed. Seattle: IASP, 1994
- Treede R D, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. Pain, 2015, 156: 1003-1007
- Haxby J V, Connolly A C, Guntupalli J S. Decoding neural representational spaces using multivariate pattern analysis. *Annu Rev Neurosci*, 2014, 37: 435-456
- Von Korf M, Scher A I, Helmick C, et al. United states national pain strategy for population research: Concepts, definitions, and pilot data. *J Pain*, 2016, 17: 1068-1080
- Davis K D, Flor H, Greely H T, et al. Brain imaging tests for chronic pain: Medical, legal and ethical issues and recommendations. *Nat Rev Neurol*, 2017, 13: 624-638

- 6 Goldberg D S, McGee S J. Pain as a global public health priority. *BMC Public Health*, 2011, 11: 770
- 7 Rice A S C, Smith B H, Blyth F M. Pain and the global burden of disease. *Pain*, 2016, 157: 791–796
- 8 Yu S, Liu R, Zhao G, et al. The prevalence and burden of primary headaches in China: A population-based door-to-door survey. *Headache-J Head Face Pain*, 2012, 52: 582–591
- 9 Li J, Chen J, Qin Q, et al. Chronic pain and its association with obesity among older adults in China. *Arch Gerontol Geriatr*, 2018, 76: 12–18
- 10 Borsook D, Kalso E. Transforming pain medicine: Adapting to science and society. *Eur J Pain*, 2013, 17: 1109–1125
- 11 Giordano J, Abramson K, Boswell M V. Pain assessment: Subjectivity, objectivity, and the use of neurotechnology part one: Practical and ethical issues. *Pain Phys*, 2010, 13: 305–315
- 12 Li D, Puntillo K, Miaskowski C. A review of objective pain measures for use with critical care adult patients unable to self-report. *J Pain*, 2008, 9: 2–10
- 13 Hu L, Iannetti G D. Painful issues in pain prediction. *Trends Neurosci*, 2016, 39: 212–220
- 14 Nusbaum M P, Beenhakker M P. A small-systems approach to motor pattern generation. *Nature*, 2002, 417: 343–350
- 15 Loeser J D. Perspectives on pain. In: Turner P, Padgham C, Hedges A, eds. *Clinical Pharmacology & Therapeutics*. London: Palgrave Macmillan UK, 1980. 313–316
- 16 Siegel M, Donner T H, Engel A K. Spectral fingerprints of large-scale neuronal interactions. *Nat Rev Neurosci*, 2012, 13: 121–134
- 17 Ploner M, Sorg C, Gross J. Brain rhythms of pain. *Trends Cogn Sci*, 2017, 21: 100–110
- 18 Carmon A, Mor J, Goldberg J. Evoked cerebral responses to noxious thermal stimuli in humans. *Exp Brain Res*, 1976, 25: 103–107
- 19 Bromm B, Lorenz J. Neurophysiological evaluation of pain. *Electroencephalogr Clin Neurophysiol*, 1998, 107: 227–253
- 20 Treede R D, Lorenz J, Baumgärtner U. Clinical usefulness of laser-evoked potentials. *Neurophysiol Clin*, 2003, 33: 303–314
- 21 Iannetti G D, Zambreanu L, Cruccu G, et al. Operculoinsular cortex encodes pain intensity at the earliest stages of cortical processing as indicated by amplitude of laser-evoked potentials in humans. *Neuroscience*, 2005, 131: 199–208
- 22 Ploner M, Gross J, Timmermann L, et al. Pain suppresses spontaneous brain rhythms. *Cereb Cortex*, 2006, 16: 537–540
- 23 Mouraux A, Guérit J M, Plaghki L. Non-phase locked electroencephalogram (EEG) responses to CO₂ laser skin stimulations may reflect central interactions between A δ - and C-fibre afferent volleys. *Clin Neurophysiol*, 2003, 114: 710–722
- 24 Iannetti G D, Hughes N P, Lee M C, et al. Determinants of laser-evoked EEG responses: Pain perception or stimulus saliency? *J Neurophysiol*, 2008, 100: 815–828
- 25 Gross J, Schnitzler A, Timmermann L, et al. Gamma oscillations in human primary somatosensory cortex reflect pain perception. *PLoS Biol*, 2007, 5: e133
- 26 De Pascalis V, Cacace I. Pain perception, obstructive imagery and phase-ordered gamma oscillations. *Int J Psychophysiol*, 2005, 56: 157–169
- 27 Zhang Z G, Hu L, Hung Y S, et al. Gamma-band oscillations in the primary somatosensory cortex—A direct and obligatory correlate of subjective pain intensity. *J Neurosci*, 2012, 32: 7429–7438
- 28 Legrain V, Mancini F, Sambo C F, et al. Cognitive aspects of nociception and pain. Bridging neurophysiology with cognitive psychology. *Neurophysiol Clin*, 2012, 42: 325–336
- 29 Mouraux A, Iannetti G D. Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. *J Neurophysiol*, 2009, 101: 3258–3269
- 30 Legrain V, Perchet C, Garcia-Larrea L. Involuntary orienting of attention to nociceptive events: Neural and behavioral signatures. *J Neurophysiol*, 2009, 102: 2423–2434
- 31 Hu L, Peng W, Valentini E, et al. Functional features of nociceptive-induced suppression of alpha band electroencephalographic oscillations. *J Pain*, 2013, 14: 89–99
- 32 Peng W, Hu L, Zhang Z, et al. Changes of spontaneous oscillatory activity to tonic heat pain. *PLoS One*, 2014, 9: e91052
- 33 Schulz E, Zherdin A, Tiemann L, et al. Decoding an individual's sensitivity to pain from the multivariate analysis of EEG data. *Cereb Cortex*, 2012, 22: 1118–1123
- 34 Tiemann L, May E S, Postorino M, et al. Differential neurophysiological correlates of bottom-up and top-down modulations of pain. *Pain*, 2015, 156: 289–296
- 35 Hu L, Iannetti G D. Neural indicators of perceptual variability of pain across species. *Proc Natl Acad Sci USA*, 2019, 116: 1782–1791
- 36 Schulz E, May E S, Postorino M, et al. Prefrontal gamma oscillations encode tonic pain in humans. *Cereb Cortex*, 2015, 25: 4407–4414
- 37 Li L, Liu X, Cai C, et al. Changes of gamma-band oscillatory activity to tonic muscle pain. *Neurosci Lett*, 2016, 627: 126–131
- 38 Nickel M M, May E S, Tiemann L, et al. Brain oscillations differentially encode noxious stimulus intensity and pain intensity. *Neuroimage*, 2017, 148: 141–147
- 39 Li F, Xiang J, Wu T, et al. Abnormal resting-state brain activity in headache-free migraine patients: A magnetoencephalography study. *Clin Neurophysiol*, 2016, 127: 2855–2861

- 40 Lim M, Kim J S, Kim D J, et al. Increased low- and high-frequency oscillatory activity in the prefrontal cortex of fibromyalgia patients. *Front Hum Neurosci*, 2016, 10: 111
- 41 May E S, Nickel M M, Ta Dinh S, et al. Prefrontal gamma oscillations reflect ongoing pain intensity in chronic back pain patients. *Hum Brain Mapp*, 2018, 40: 293–305
- 42 Zhou R, Wang J, Qi W, et al. Elevated resting state gamma oscillatory activities in electroencephalogram of patients with post-herpetic neuralgia. *Front Neurosci*, 2018, 12: 750
- 43 Buzsáki G, Logothetis N, Singer W. Scaling brain size, keeping timing: Evolutionary preservation of brain rhythms. *Neuron*, 2013, 80: 751–764
- 44 Bragin A, Jando G, Nadasdy Z, et al. Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat. *J Neurosci*, 1995, 15: 47–60
- 45 Whittington M A, Traub R D, Jefferys J G R. Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation. *Nature*, 1995, 373: 612–615
- 46 Whittington M A, Cunningham M O, LeBeau F E N, et al. Multiple origins of the cortical gamma rhythm. *Devel Neurobiol*, 2011, 71: 92–106
- 47 Bartos M, Vida I, Jonas P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nat Rev Neurosci*, 2007, 8: 45–56
- 48 Buzsáki G, Wang X J. Mechanisms of gamma oscillations. *Annu Rev Neurosci*, 2012, 35: 203–225
- 49 Bosman C A, Lansink C S, Pennartz C M A. Functions of gamma-band synchronization in cognition: From single circuits to functional diversity across cortical and subcortical systems. *Eur J Neurosci*, 2014, 39: 1982–1999
- 50 Cardin J A. Snapshots of the brain in action: Local circuit operations through the lens of oscillations. *J Neurosci*, 2016, 36: 10496–10504
- 51 Ray S, Maunsell J H R. Do gamma oscillations play a role in cerebral cortex? *Trends Cogn Sci*, 2015, 19: 78–85
- 52 Cardin J A, Carlén M, Meletis K, et al. Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature*, 2009, 459: 663–667
- 53 Sohal V S, Zhang F, Yizhar O, et al. Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature*, 2009, 459: 698–702
- 54 Adrian E. Olfactory reactions in the brain of the hedgehog. *J Physiol*, 1942, 100: 459–473
- 55 Jefferys J G R, Traub R D, Whittington M A. Neuronal networks for induced ‘40 Hz’ rhythms. *Trends Neurosci*, 1996, 19: 202–208
- 56 Fries P. Rhythms for cognition: Communication through coherence. *Neuron*, 2015, 88: 220–235
- 57 Fries P. A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends Cogn Sci*, 2005, 9: 474–480
- 58 Fries P. Neuronal gamma-band synchronization as a fundamental process in cortical computation. *Annu Rev Neurosci*, 2009, 32: 209–224
- 59 Fries P, Nikolić D, Singer W. The gamma cycle. *Trends Neurosci*, 2007, 30: 309–316
- 60 Hauck M, Lorenz J, Engel A K. Attention to painful stimulation enhances gamma-band activity and synchronization in human sensorimotor cortex. *J Neurosci*, 2007, 27: 9270–9277
- 61 Tiemann L, Schulz E, Gross J, et al. Gamma oscillations as a neuronal correlate of the attentional effects of pain. *Pain*, 2010, 150: 302–308
- 62 Peng W, Xia X, Yi M, et al. Brain oscillations reflecting pain-related behavior in freely moving rats. *Pain*, 2018, 159: 106–118
- 63 Tiemann L, Hohn V D, Ta Dinh S, et al. Distinct patterns of brain activity mediate perceptual and motor and autonomic responses to noxious stimuli. *Nat Commun*, 2018, 9: 4487
- 64 Iannetti G D, Mouraux A. From the neuromatrix to the pain matrix (and back). *Exp Brain Res*, 2010, 205: 1–12
- 65 Legrain V, Iannetti G D, Plaghki L, et al. The pain matrix reloaded. *Prog Neurobiol*, 2011, 93: 111–124
- 66 Schulz E, Tiemann L, Schuster T, et al. Neurophysiological coding of traits and states in the perception of pain. *Cereb Cortex*, 2011, 21: 2408–2414
- 67 Wiech K, Ploner M, Tracey I. Neurocognitive aspects of pain perception. *Trends Cogn Sci*, 2008, 12: 306–313
- 68 Legrain V, Damme S V, Eccleston C, et al. A neurocognitive model of attention to pain: Behavioral and neuroimaging evidence. *Pain*, 2009, 144: 230–232
- 69 Hauck M, Domnick C, Lorenz J, et al. Top-down and bottom-up modulation of pain-induced oscillations. *Front Hum Neurosci*, 2015, 9: 375
- 70 Pinheiro E S S, de Queirós F C, Montoya P, et al. Electroencephalographic patterns in chronic pain: A systematic review of the literature. *PLoS One*, 2016, 11: e0149085
- 71 Rauschecker J P, May E S, Maudoux A, et al. Frontostriatal gating of tinnitus and chronic pain. *Trends Cogn Sci*, 2015, 19: 567–578
- 72 Kuner R, Flor H. Structural plasticity and reorganisation in chronic pain. *Nat Rev Neurosci*, 2016, 18: 20–30
- 73 Ma L, Yue L, Zhang Y, et al. Spontaneous pain disrupts ventral hippocampal ca1-infralimbic cortex connectivity and modulates pain progression in rats with peripheral inflammation. *Cell Rep*, 2019, 29: 1579–1593.e6
- 74 Hashmi J A, Baliki M N, Huang L, et al. Shape shifting pain: Chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain*, 2013, 136: 2751–2768
- 75 Baliki M N, Apkarian A V. Nociception, pain, negative moods, and behavior selection. *Neuron*, 2015, 87: 474–491
- 76 Uhlhaas P J, Singer W. Neural synchrony in brain disorders: Relevance for cognitive dysfunctions and pathophysiology. *Neuron*, 2006, 52: 155–168

- 77 Uhlhaas P J, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci*, 2010, 11: 100–113
- 78 Uhlhaas P J, Singer W. Neuronal dynamics and neuropsychiatric disorders: Toward a translational paradigm for dysfunctional large-scale networks. *Neuron*, 2012, 75: 963–980
- 79 Polania R, Nitsche M A, Ruff C C. Studying and modifying brain function with non-invasive brain stimulation. *Nat Neurosci*, 2018, 21: 174–187
- 80 Sitaram R, Ros T, Stoessel L, et al. Closed-loop brain training: The science of neurofeedback. *Nat Rev Neurosci*, 2017, 18: 86–100
- 81 Tu Y, Zhang Z, Tan A, et al. Alpha and gamma oscillation amplitudes synergistically predict the perception of forthcoming nociceptive stimuli. *Hum Brain Mapp*, 2016, 37: 501–514
- 82 Tan L L, Oswald M J, Hehl C, et al. Gamma oscillations in somatosensory cortex recruit prefrontal and descending serotonergic pathways in aversion and nociception. *Nat Commun*, 2019, 10: 983
- 83 Brunet N, Vinck M, Bosman C A, et al. Gamma or no gamma, that is the question. *Trends Cogn Sci*, 2014, 18: 507–509
- 84 Hu L, Xiao P, Zhang Z G, et al. Single-trial time-frequency analysis of electrocortical signals: Baseline correction and beyond. *Neuroimage*, 2014, 84: 876–887
- 85 Hipp J F, Siegel M. Dissociating neuronal gamma-band activity from cranial and ocular muscle activity in EEG. *Front Hum Neurosci*, 2013, 7: 338
- 86 Canolty R T, Knight R T. The functional role of cross-frequency coupling. *Trends Cogn Sci*, 2010, 14: 506–515
- 87 Samiee S, Baillet S. Time-resolved phase-amplitude coupling in neural oscillations. *Neuroimage*, 2017, 159: 270–279
- 88 Yue L P, Zhang F R, Lu X J, et al. Simultaneous recordings of cortical local field potentials and electrocorticograms in response to nociceptive laser stimuli from freely moving rats. *J Vis Exp*, 2019, 143: e58686
- 89 Hohn V D, May E S, Ploner M. From correlation towards causality. *Pain Rep*, 2019, 4: e723

Summary for “疼痛相关高频振荡信号: 进展与展望”

Pain-related gamma band oscillations: Progress and prospect

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Pain is vital for survival as it signals bodily threats and promotes recovery from tissue damage. Chronic pain, however, is considered maladaptive since it provides no apparent protective or recuperative benefits. Currently, approximately 20% of adults around the world suffer from chronic pain, which seriously affects their quality of life. Besides, the extent of the chronic pain problem poses a significant economic burden for both patients and the whole society (in China, the annual cost of pain exceeds \$100 billion). Unfortunately, most of the patients had not received adequate treatment for their pain. Therefore, effective treatment of chronic pain is highly needed, which necessitates reliable and valid pain assessment. Since pain is a subjective first-person experience, self-report using a visual analog scale or a numeric rating scale is the gold standard to determine the intensity of pain in clinical practice. However, self-report of pain is well known to be easily contaminated with reporting biases, and could not be used in some vulnerable populations, e.g., infants and patients with disorders of consciousness. As a result, the lack of an accurate assessment of pain could lead to an inadequate or suboptimal treatment of pain in these vulnerable populations. To solve this issue, it would be necessary to explore the possibility of assessing pain objectively using neural indicators that could complement the self-report of pain. Recent studies showed that pain-induced gamma band oscillations are one of the most promising biomarkers of the perceived intensity of both stimulus-evoked and spontaneous pain across different populations. First, being elicited by nociceptive stimuli, gamma band oscillations in the primary somatosensory cortex encode subjective pain perception reliably and selectively: Reliably, because they consistently reflect pain at both within-subject and between-subject levels; selectively, because they always track the intensity of pain, even when saliency of nociceptive stimuli is modulated. Second, gamma band oscillations in the prefrontal cortex encode selectively subjective ratings of tonic pain. Third, gamma band oscillations in the prefrontal area are positively correlated with subjective ratings of ongoing pain in chronic pain patients. All these findings demonstrated that gamma band oscillations could be identified as an objective neural indicator of pain perception, which could be useful for the assessment of pain in the future. However, the neural origin and neural mechanisms of pain-induced gamma band oscillations are largely unknown due to a series of technical issues, e.g., the low signal-to-noise ratio of gamma band oscillations, the low spatial resolution of the sampling techniques to record gamma band oscillations, and the intrinsic limitation of correlation analysis in current studies (unable to reveal causal relationship). To achieve a better understanding of the functional significance of pain-induced gamma band oscillations, novel analytical strategies are required to process neural responses that are collected using advanced experimental techniques on different species. With these efforts, we will understand better the neural mechanisms of pain-induced gamma band oscillations, which will increase the accuracy of the diagnosis of pain and the prediction of treatment outcome in various clinical conditions. In addition, the development of approaches to modulate pain-induced gamma band oscillations, e.g., via transcranial alternating current stimulation coupled with neurofeedback, could provide a promising avenue for effective pain treatment in the future.

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