·综述·

响度依赖性听觉诱发电位在情感障碍疾病中的应用进展

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【摘要】 中枢5-羟色胺功能活性与情感障碍疾病密切相关,而响度依赖性听觉诱发电位可反映中枢5-羟色胺功能的活性,为情感障碍疾病的诊断和疗效预测提供新的方法和依据。现将响度依赖性听觉诱发电位及其在抑郁症及双相情感障碍中的应用进行综述。

【关键词】 抑郁症; 双相情感障碍; 响度依赖性听觉诱发电位; 综述
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【**Abstract**】 The functional activity of central serotonin is closely related to affective disorders, and the loudness dependence of auditory evoked potentials can reflect the functional activity of central serotonin, which provides a new method and basis for the diagnosis and prediction of treatment response of affective disorders. The loudness dependence of auditory evoked potentials and its application in depression and bipolar disorder are reviewed in this paper.

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中枢5-羟色胺功能与情感障碍[1]、精神分裂症[2]、强迫症[3]、物质依赖[4]等精神疾病密切相关，响度依赖性听觉诱发电位(loudness dependence of auditory evoked potentials，LDAEP)与中枢5-羟色胺功能活性呈负相关[1]，作为5-羟色胺功能障碍的检测指标已广泛应用于临床和研究中，但其神经生物化学机制尚未完全阐明。现就LDAEP及其在抑郁症和双相情感障碍中的应用进行综述。

一、LDAEP及其影响因素

1. LDAEP：LDAEP是一种测量听觉皮层活动的方法，反映中枢神经信息处理过程的脑电图表型，是中枢神经递质活动的有效生物标志[5]。其实质是听觉诱发电位，N1为听觉刺激出现后50～150 ms的最大负向波，P2为听觉刺激出现后150～250 ms的最大正向波[6]，N1、P2常连续出现，将其称为N1/P2复合波。相比单独测量N1和P2的响度依赖性，N1/P2复合波的响度依赖性更加可靠[7]。将听觉刺激模态下振幅随刺激强度的变化称为LDAEP[5]。测量方法是在听觉模态下给予受试者5种不同强度的听觉刺激，通过皮层脑电记录仪测得5种不同刺激状态下的N1/P2(N1/P2计算为N1和P2振幅之差)值，对其进行线性回归分析，所得线性回归函数的斜率即代表LDAEP的值[6]。现有研究表明LDAEP与中枢5-羟色胺功能活性呈负相关，LDAEP值越高代表中枢5-羟色胺功能活性越低，反之亦然[8-9]。

2. LDAEP的影响因素：LDAEP可能不止受5-羟色胺功能活性的影响，其他中枢神经递质也可能对其有一定作用[10]。Juckel等[11]认为儿茶酚氧甲基转移酶(catechol-O-methyltransferase，COMT)调节多巴胺功能活性，促进多巴胺和5-羟色胺之间相互作用，通过间接调节5-羟色胺功能的方式影响LDAEP。关于脑源性神经营养因子(brain derived neurotrophic factor，BDNF)与LDAEP的研究认为BDNF参与5-羟色胺神经元的发育，血清BDNF的减少会导致中枢5-羟色胺功能活性减低，进一步影响LDAEP[12]。还有研究认为具有神经递质性质的气体NO也可能影响LDAEP[13]。Oliva等[14]使用快速增强5-羟色胺能和去甲肾上腺素能的药物后复测LDAEP，并未发现治疗前后有明显的变化，O'Neill等[15]的研究使用多巴胺和5-羟色胺快速耗竭剂5.5 h后重新测量LDAEP，也认为用药前后无明显变化，对这两项研究结果的解释是急性多巴胺和5-羟色胺的变化并未影响LDAEP，LDAEP可能是中枢神经递质长期调节的指标。Wyss等[16]的研究认为LDAEP与听觉皮层γ-氨基丁酸(gamma aminobutyric acid，GABA)或谷氨酸水平无关，但相关研究较少，需要更多研究探索GABA、谷氨酸等神经递质与LDAEP的关系。

LDAEP人口学影响因素的相关研究认为不同性别、年龄、婚姻状态、吸烟状况下的LDAEP也可能存在差异[17]，成年女性总体LDAEP值较高，不同性别之间LDAEP差异可能受体内激素水平的影响[18]。Jawinski等[19]的研究表明不吸烟人群LDAEP值明显高于吸烟和已戒烟的人群。目前关于LDAEP的研究尚缺乏一致性，除了可能的影响因素之外，还与评定的方法学有关，例如偶极子分析法和单电极分析法所覆盖的脑区不同，两种LDAEP评定结果可能存在差异[20]。另外，刺激强度分布范围、刺激方式、数据分析方法不同也可能对研究结果产生一定影响。

二、LDAEP在抑郁症中的研究

1. LDAEP与抑郁症症状特征的关系：LDAEP是否可作为抑郁症患者自杀风险的预测指标尚未定论。Uhl等[21]早期的研究认为自杀未遂的抑郁症患者LDAEP值处于较低水平。Graßnickel等[6]在后来的重复性研究中得到不同结果，他们认为有自杀未遂史的抑郁症患者LDAEP值高于无自杀未遂史的抑郁症患者。Kim和Park[22]的研究也认为高LDAEP值与抑郁症患者自杀想法和自杀企图相关。也有学者认为不典型抑郁症患者LDAEP值较典型抑郁症患者LDAEP值高，不典抑郁症患者中枢5-羟色胺功能活性低下与其自杀倾向相关[23]。目前较多研究倾向于高LDAEP值可作为抑郁症患者自杀的预测指标，不同研究结果可能是由于未严格限定研究对象所致，比如自杀意念、自杀未遂以及急性自杀未遂还是既往有过自杀未遂史都可能对试验结果产生影响。Uhl等[21]的研究对自杀未遂患者进行纵向随访研究，发现自杀未遂患者急性自杀后1周

内LDAEP不稳定，因此仍需要更大样本量以及更长期的随访研究探索，在将来更需要严格把握纳入、排除标准以及诊断准确性，还需考虑生物学、遗传、表观遗传的偏差[6]。更值得注意的是，5-羟色胺功能障碍并非自杀行为所特有，因此需要更多措施预测自杀行为[7]。

Kim等[24]的研究认为伴有注意缺陷多动障碍(attention deficit and hyperactivity disorder, ADHD)症状的抑郁症患者LDAEP显著低于不伴有ADHD症状的抑郁症患者，LDAEP可以鉴别成人抑郁症患者是否伴有ADHD症状，帮助医生为伴ADHD症状的患者提供相应的治疗。Park和Lee[25]探讨了有无双相情感障碍潜在可能抑郁症患者LDAEP的差异，研究结果表明LDAEP不能识别潜在的双相情感障碍患者，说明抑郁发作时二者中枢5-羟色胺功能活性没有差别。这项研究还认为抑郁症状的严重程度与5-羟色胺功能活性呈负相关，LDAEP可以用来评估抑郁症状的严重程度，但他们先前的研究认为LDAEP与抑郁严重程度无关[26]，这种差别可能取决于LDAEP的评定方法。有研究认为抑郁症状的严重程度与LDAEP显著相关，与皮质LDAEP不相关[27]。

2. LDAEP对抗抑郁药物疗效的预测作用：现有研究认为基线LDAEP值高的抑郁症患者使用5-羟色胺再摄取抑制剂(selective serotonin reuptake inhibitor, SSRI)类药物治疗效果好[8, 28]，而基线LDAEP值低的患者使用SSRI类药物疗效欠佳[9]。Park等[29]报道了1例基线LDAEP异常低的患者，这位患者使用SSRI类药物后总是出现恶心、呕吐、静坐不能、焦虑等不良反应，抑郁症状不仅没有得到改善反而加重，而停药后这些不良反应消失，继续使用SSRI类药物不良反应再次出现。停SSRI类药物改用噻奈普汀治疗21 d后患者的抑郁症状得到明显改善，提示中枢5-羟色胺功能过高的患者使用SSRI类药物不仅无效还可能导致一系列不良反应。Juckel等[28]早先的研究也得出相同的结论，对SSRI类药物反应良好的患者基线LDAEP值高，而对瑞波西汀反应良好的患者基线LDAEP值低。然而基线LDAEP值过高也存在一定风险，Lee等[30]报道了2例LDAEP值异常高的患者服用SSRI类药物后出现转躁的情况，这可能是由于持续、重度低下的5-羟色胺浓度导致中枢5-羟色胺受体敏感性升高，此时使用SSRI类药物使中枢5-羟色胺功能活性急剧升高，诱发躁狂。综上，基线LDAEP值在某一范围内增大治疗效果也随之增加，但基线LDAEP值异常高可能会诱发躁狂，异常低则预示SSRI疗效欠佳、出现不良反应的可能性较大。有关药物治疗前后LDAEP变化的研究结果并不一致，有学者认为健康人使用西酞普兰治疗后LDAEP值降低[31]，另有研究不支持SSRI类药物治疗前后LDAEP发生变化[32]。Park等[8]的研究结果表明治疗4周后的LDAEP与基线LDAEP相比未发生明显变化，分析其原因可能是4周的治疗时间太短，不足以使LDAEP发生变化。Lee等[9]对比基线与SSRI类药物治疗12周之后的LDAEP也未发生明显变化，认为治疗前后LDAEP保持稳定。不同研究结果的原因尚未明确，但现有研究大多数倾向于SSRI类药物治疗前后LDAEP无明显改变。关于LDAEP预测抗抑郁药物疗效的具体数值范围以及极高、极低LDAEP值的定义需在以后的研究中进行更多的探索。

三、LDAEP在双相情感障碍中的研究

1. LDAEP与双相情感障碍症状特征的关系：Park等[26]早期的研究结果表明双相情感障碍患者的LDAEP值显著低于健康人群，双相躁狂与双相抑郁之间无显著差异。在其后来的研究中分析了双相情感障碍不同疾病状态下的LDAEP，结果显示双相缓解期LDAEP值最高，双相抑郁次之，双相躁狂最低，双相情感障碍患者的LDAEP与患者情绪状态密切相关。躁狂患者与精神分裂症患者的LDAEP相当，提示精神病性症状削弱了LDAEP，以后的研究中应考虑精神病性症状对试验结果的影响。Juckel等[33]的本研究中双相缓解期患者LDAEP值与健康人相当，随着双相障碍疾病状态不同，中枢神经递质活性发生了明显改变[33]。关于双相情感障碍LDAEP的研究较少，且现有研究样本量较小，需进一步扩大样本量证实现有结果。双相情感障碍纵向发展过程中，同一患者反复经历躁狂、抑郁、缓解等不同状态下LDAEP值的变化情况，LDAEP是否可作为双相情感障碍患者疾病变化的状态指标，以及双相缓解期是否可恢复到正常水平为今后的研究提供了新的思路[27]。另外，躁狂发作状态患者兴奋、易激惹等症状使LDAEP操作困难、数据准确性降低，可能也是双相情感障碍患者LDAEP相关研究较少的原因之一，这也是将来研究中需要解决的问题。

2. LDAEP对情绪稳定剂锂盐疗效的预测作用：锂盐具有良好的情绪稳定作用，并非所有患者对锂治疗反应良好。早期识别锂盐治疗效果反应良好的患者，可以有效避免因治疗效果不满意而延误病情，也可规避给患者带来不良反应的风险[33]。早期

Hegerl 等[34]的研究认为预防性锂盐治疗有效的患者基线 LDAEP 值高，中枢 5-羟色胺功能活性低与锂盐治疗反应良好有关。Juckel 等[33]对预防性锂盐治疗的患者进行了长达 3 年的随访，随访期间没有复发的患者被认为预防性治疗有效，复发的患者被认为预防性治疗无效。研究结果表明锂盐预防性治疗有效的患者基线 LDAEP 值明显高于无效患者，进一步证明 LDAEP 可作为锂盐疗效的预测指标。

四、展望

国外已有不少关于 LDAEP 与抑郁症、双相情感障碍的研究，但国内相关研究较少。LDAEP 具有操作简单、费用低廉、无创、可重复测量等诸多优点，有望成为辅助诊断精神类疾病的神经电生理指标。现有研究已表明 LDAEP 可作为 SSRI 类抗抑郁药以及锂盐疗效的预测因子，但未来仍需要更多研究证明其他神经递质与 LDAEP 的关系以及各种神经递质共同作用对 LDAEP 的影响，也需要更多的研究证明药物、酒精等其他混杂因素对 LDAEP 值的影响，未来关于 LDAEP 在药物治疗反应预测中具体数值指标变化也需要进一步研究，期待 LDAEP 发挥其在精神疾病诊断、疗效预测中的作用，为精神疾病诊断和治疗提供可量化的参考指标。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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