

· 综述 ·

事件相关电位区分单相双相抑郁及其疗效预测的研究进展

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【摘要】 双相抑郁在临床中常被误诊为单相抑郁,且误诊率较高,只有约20%的双相抑郁患者能在第1年被明确诊断,大部分患者需要首次发作后的7~10年才能被明确诊断。目前,对两者的鉴别仍然主要依靠临床相关症状和特征。现对事件相关电位在单相、双相抑郁的区别以及对其疗效预测方面进行综述,以找到能指导临床区分和预测两种疾病的客观指标。

【关键词】 单相抑郁; 双相抑郁; 事件相关电位; 疗效预测; 综述

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Research progress of event-related potential in distinguishing unipolar and bipolar depression and treatment outcome prediction

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【Abstract】 In clinical practice, bipolar depression is often misdiagnosed as unipolar depression, and the misdiagnosis rate is high. Only about 20% of bipolar depression patients can be definitive diagnosed in the first year, and most patients need 7 to 10 years to be diagnosed after the first episode. Now the differentiation between two affective disorders is still mainly based on clinical symptoms and characteristics. This paper reviews the difference between unipolar and bipolar depression and the prediction of its curative effect through event-related potential, hoping to find an objective index that can guide the clinical differentiation and prediction of the two diseases.

【Key words】 Unipolar depressive; Bipolar depressive; Event related potential; Treatment prediction; Review

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处于抑郁发作期的双相障碍容易被诊断为抑郁症,或称单相抑郁(unipolar depression, UD)。相关研究提示,抑郁发作在双相障碍病程中的比例为40%~50%,只有约20%的双相障碍患者能在接受治疗第1年内被诊断,而多数患者从发病到明确诊断通常长达7~10年,误诊率高达2/3,导致大部分双相抑郁(bipolar depression, BD)的患者病情未获缓解而延误^[1-3],并且BD患者可能存在更强的自杀观念和自杀行为,患者生活质量更差^[4-5]。

临床中,医生往往根据疾病当前的症状和症状

群选择相应的精神药物“对症”治疗,而忽略了UD与BD是两类特征相异的精神障碍。因而,导致抗抑郁药在BD的使用缺少循证证据及指南指导^[6]。研究显示,单用抗抑郁药物治疗BD通常无效,安慰剂效应高达39%,长久使用会诱发或导致患者转躁,病情恶化或加速复发^[7-8]。故在治疗BD时,使用抗抑郁药是“相对禁忌”,各种指南建议只对抑郁症状严重、既往使用有效的双相障碍抑郁发作患者在使用心境稳定剂的基础上联合使用抗抑郁药物,若患者具有混合发作特征、快速循环特征则应尽量避免

使用抗抑郁药物^[6,9]。

目前,临床中区分UD、BD主要是依据患者的临床相关表现及特征^[10],多年来探索区分UD、BD并指导临床治疗的相关生物学标志研究也从未停止,提出了可能区分UD、BD的生物标志物,包括生化、基因遗传、神经影像学、脑电生理等方面相关指标^[11-13],然而多数生物标志物因难以验证、特异性不高或操作可行性差,无法满足解决高误诊率并及早给予BD患者较为精准的治疗方案的需求。在UD、BD病因不明、机制不清的状况下,从相关生物学标志中寻找出相对简便易行、可及性良好、有效性尚佳的生物标志物成为了学界的重要关切。相较于纷繁复杂的众多生物学标志,事件相关电位(event related potentials, ERPs)在解决该问题中有许多值得临床借鉴的研究结果。因此,本文整理ERPs在区分UD、BD及其治疗疗效预测的相关研究,并对此进行综述。

一、基于不同指征区分UD、BD或指导治疗的相关研究

UD、BD临床表现难以区分,但BD存在以下特点,即双相障碍家族史,男性患者居多,伴多次抑郁发作史且抑郁症状严重,常伴睡眠障碍和童年创伤性事件,发病年龄小^[14]。青少年BD阈下躁狂症状更明显^[15]。长期随访研究发现,BD自杀倾向升高、抑郁情绪和快感缺失加重^[16]。目前,临床诊疗参差不齐,对BD过度诊断或诊断不足,仅凭经验或症状学、病史等信息难以从根本上区分UD、BD^[17]。

当涉及情绪、奖励和认知相关的任务时,BD患者的功能性磁共振成像(functional magnetic resonance imaging, fMRI)出现相应改变,包括前额叶皮层、前扣带回皮层、顶叶和颞叶功能的连接更强,背外侧前额叶皮层更薄,胼胝体前部和后扣带回完整性降低,但fMRI的相关研究样本获取困难、成像解析程序要求高,临床实施存在阻碍^[18]。IL-10、IL-4、硫代巴比妥酸反应物质可能用于区分UD、BD,但诊疗过程患者的应激反应、药物类型、烟酒及物质滥用等因素均会影响炎症因子和氧化应激水平,其稳定性难以保证^[19]。

BD经电休克治疗(electroconvulsive therapy, ECT)缓解率更高,症状缓解所需时间更短^[20],但由于社会因素,以有创治疗区分UD、BD难以被大众接受。

二、UD、BD的ERPs相关研究

脑电生理指标源于EEG,为再提取的波幅及潜伏

期。既往研究提示,UD患者左额叶皮质电活动减退以及右侧的额叶皮层电活动增强^[21]。ERPs为被试者接受某项刺激(视、听、触觉或奖赏任务等)所诱发的电生理指标,与被试者认知活动相关,常用于UD、BD临床研究的ERPs有视觉诱发电位(auditory evoked potentials, AEP)、听觉诱发电位(visual evoked potentials, VEP)、失匹配负波(mismatch negative, MMN)、错误相关负波(error-related negativity, ERN)、奖赏任务诱发电位等^[22-24]。

1. ERPs与UD: UD患者(未接受治疗)经悲伤面孔诱发的P300波幅最高,悲伤行为试验的有效反应时间较无效反应时间缩短,提示UD难以从负面刺激转移^[25]。刘纪猛等^[26]的研究发现,与健康对照比较,UD(未接受治疗)经高兴及中性面孔诱发的P300波幅下降,该结果与应激反应无关;UD无应激组悲伤面孔诱发的P300波幅降低,而患者经高兴、中性及悲伤面孔诱发的P300潜伏期均延长,提示应激事件可能影响抑郁发作期的情绪认知加工损害,而认知反应速度损害则相对稳定。UD的奖赏反应敏感性下降^[27]。Whitton等^[28]的研究发现,已停止治疗的缓解期UD患者的奖赏学习行为减少,奖赏反馈波幅降低,而其前扣带回皮质活动减少提示UD奖赏学习障碍持续存在,可能与奖赏反馈监测的神经加工过程(尤其是在前扣带皮层区域)相关。当UD患者自愿接受奖励时,其奖励正波(reward positivity, RewP)波幅下降,而被动接受状态则无波幅下降,但反馈晚期P300无相应变化,提示UD奖赏加工的损伤可能与患者自主选择的认知加工过程相关^[29]。MMN与被试者认知水平相关^[30]。Tseng等^[24]的荟萃分析发现,与健康对照相比,急性期UD患者的MMN波幅下降、潜伏期延长,而慢性UD患者的MMN无明显变化,UD疾病严重程度与MMN无相关性,提示MMN可能为UD的特征指标而非状态指标,该研究未限制治疗条件。Chen等^[31]的研究发现,已经接受治疗的UD患者,无论首发还是复发,其听觉诱发MMN波幅均较健康对照低,而患者组之间无显著差异,提示MMN波幅可能为UD的稳定生物指标。

2. ERPs与BD: 与健康对照相比,首发、未接受治疗的BD患者听觉诱发的MMN、P3a波幅和潜伏期异常可能与高级认知和功能水平损伤相关^[32]。Solé等^[33]的研究发现,经治疗达到缓解期的双相障碍存在认知功能损害,如注意力、记忆和执行功能、奖惩判断及评估能力。王心羽等^[34]发现,相较于健康对照,BD患者经“损失”范式诱发的N500波幅

更大,这可能与BD认知、情感冲突相关,提示双相障碍患者在“赌博”或决策方面过度的情感投入,从而引发了反应异常及情绪的失控,但研究并未控制治疗因素。Wada等^[35]的荟萃分析发现,相较于健康对照,处于发病期和稳定期的BD患者存在听觉和视觉诱发的P3a和P3b波幅降低、听觉P3b潜伏期延长,结果排除精神病史、诊断亚型(双相障碍I型和II型)、疾病所处阶段的影响,提示听觉或视觉诱发P300波幅可能为BD患者的性状标志而非状态标志,但研究未排除治疗对P300的影响。MMN被认为是BD中间效应的神经生理生物标志物,与谷氨酸能、N-甲基D-天冬氨酸受体等分子,前扣带皮层、海马等结构相关^[36]。Paris等^[37]的研究发现,相较于健康对照,正在接受治疗的BD患者其情感声音诱发的MMN波幅无明显差异,而潜伏期有所延长。但Shimano等^[38]的研究却发现,BD患者较健康对照音调诱发MMN波幅下降,且MMN波幅与疾病严重程度呈负相关,提示MMN与BD严重程度相关,该研究未限制治疗种类对结果的影响。

三、ERPs用于区分UD、BD

上述相关研究提示UD或BD的不同ERPs存在异常表现,可能与患者的高级认知功能、外界的情绪刺激、对奖赏判断和决定等因素相关,而UD、BD的ERPs异常存在区别。

Poyraz等^[39]的研究发现,健康被试者的听觉P300潜伏期与抑郁气质得分呈显著正相关,而与循环性气质得分呈显著负相关。P300反映被试者主动认知功能,可作为早期认知损害的指标之一^[40]。UD、BD患者的认知损害模式存在区别,UD为注意力转移障碍;而BD则为持续注意力损伤,其语言记忆、语言流畅性、注意力和执行功能受损更严重^[41]。作为内源性诱发电位,P300幅度和潜伏期取决于刺激携带的信息量,而非其物理特征^[42]。早期研究提示,与UD相比,双相障碍听觉诱发P3潜伏期显著延长,并且结果与年龄、药物因素等无关^[43]。一项荟萃分析发现,BD oddball诱发P300潜伏期较UD更长,差异持续至疾病缓解期,提示P300潜伏期可能反映BD更严重、更广泛的认知障碍^[44]。Barreiros等^[45]的研究发现,BD的CPz导联听觉P300波幅显著小于UD和健康对照,其P300波幅与临床因素如发病年龄、住院次数、末次缓解期长短、既往抑郁或既往躁狂发作次数、精神症状史、自杀观念及行为、疾病严重程度、目前及既往大部分药物治疗史无关。作为BD的性状标志,P300具有良好的稳定性^[35]。不同

诱发方式P300在UD、BD存在差异,可供临床参考以区分UD、BD。

Weinstock等^[46]的研究发现,与UD相比,BD的奖励反应、积极反刍、行为抑制和行为回避得分更高,且结果与疾病严重程度无关,提示BD存在更敏感的奖赏反应。Glazer等^[47]的研究发现,未服用任何药物的健康成人的基线诱发的RewP差异波(获益与非获益波幅差值)与轻躁狂易感性呈正相关,而与抑郁易感性呈负相关;随访第8个月,被试者经奖赏诱发的P3和晚期正电位(late positive potential, LPP)出现相同结果,提示RewP差异波可能预测首次就诊患者的UD和BD倾向。以上相关研究提示奖赏相关电位可能应用于UD、BD的临床鉴别。

Kim和Park^[48]的研究发现,与UD相比,双相障碍I型的听觉诱发MMN波幅显著降低。Kim等^[49]的研究发现,BD整体社会功能低于UD,且该指标与听觉诱发MMN波幅呈正相关,而与健康对照相比,仅发现BD的MMN波幅降低,提示MMN波幅并非BD特异性标志,而是与高级认知和心理社会功能相关的功能标志。但两个研究均未排除药物对MMN的影响,仍需进一步验证MMN区分UD、BD的作用。

ERPs区分UD、BD的研究方向各有侧重,如听觉或视觉诱发P300主要更多地与认知功能相关^[43-45],奖赏范式主要与行为激励和行为抑制相关^[46-47];而MMN与社会功能、前注意信息加工相关^[48-49]。单个ERPs范式区分UD、BD存在不足,多范式共同验证能取长补短,提高结果可靠性。BD需要多维度证据结合明确诊断,除症状学外,患者的个人史、家族史同样不可忽略,综合评估更能避免误诊。

四、ERPs预测UD、BD的治疗疗效

强度依赖性听觉诱发电位(the loudness dependence of the auditory evoked potentials, LDAEP)波幅与中枢5-HT能活性呈负相关,因此LDAEP可能预测锂盐和5-HT SSRI的疗效及不良反应,锂盐治疗有效者治疗前的LDAEP高于无效者,而异常升高LDAEP的UD患者接受SSRI治疗后转躁风险升高;相反,低LDAEP患者使用SSRI可能无效甚至出现严重的药物不良反应^[50]。

早期研究发现,舍曲林治疗有效、无效的抑郁症患者与健康对照治疗前和治疗12周后的P300波幅差异无统计学意义,治疗前后无效者的P300潜伏期显著延长,而有效者经治疗后P300潜伏期恢复至健康对照水平^[51];而国内类似的研究却提示,经舍

曲林治疗4周后UD患者的听觉P300波幅较治疗前显著上升^[52]。两者的研究差异可能与药物治疗剂量、随访时间不同有关。接受治疗的UD其P3a波幅与疾病严重程度呈负相关, P3a波幅下降程度与UD复发次数呈正相关^[31], P3a可能预测UD病情轻重和复发风险。

国内相关研究发现, 抗抑郁治疗前后患者P300波幅均低于健康对照, 提示患者可能存在持续的焦虑状态和功能障碍, 而F3电极P300波幅与症状严重程度呈负相关。但通过standardized low-resolution electromagnetic tomography (sLORETA)溯源分析却发现, 治疗后患者左顶上小叶和楔前叶的P300源激活与健康对照差异无统计学意义, 提示sLORETA结果可能预测抗抑郁药疗效^[53]。一项多中心的国际研究显示, 文拉法辛治疗无效的男性UD患者的听觉N1波幅明显小于有效者, 提示N1波幅可能预测抑郁症治疗效果, 但需考虑性别因素影响^[54]。

ERPs预测UD、BD或情感障碍疗效的相关研究存在一定进展, 如LDAEP、听觉P300、听觉N1以及通过sLORETA分析相关电位源激活治疗前后的改变, 可一定程度辅助预测药物疗效和不良反应。

五、总结与展望

回顾既往研究发现, 听觉和视觉诱发的P300和奖赏相关电位RewP与UD、BD存在特异性, 可辅助临床区分两者^[35, 43-45, 47]。MMN可能为UD的特征性指标, 而与BD的高级认知和心理社会功能相关性更高, 与其疾病特异性较低^[24, 48-49]。以5-HT能相关理论为基础, 结合临床案例亦提供了相关证据进行佐证, LDAEP预测如锂盐和SSRIs等药物疗效的临床应用值得探索和深入研究^[50]。听觉诱发N1波幅可预测男性抑郁患者对文拉法辛的疗效^[54]。

近年来, 关于UD及BD的生物学指标研究有所进展, 如横跨基因遗传、免疫相关的蛋白质研究、与药物反应的代谢产物和神经影像学等的交叉研究, 但暂未发现敏感性和特异性良好的生物标志物用于诊断或鉴别情绪障碍和预测治疗反应^[55-58]。

目前, ERPs对比研究多为UD与BD的比较, 而即使明确UD和BD, 双相障碍I型和II型的情绪注意损伤和ERPs异常也存在差异^[59]。此外, 大部分研究为横断面研究, 样本量较小, 存在生活事件、药物种类等影响因素, 导致研究结果缺乏一致性, 未来研究需扩大样本量, 明确研究亚型, 控制影响因素, 加入溯源分析研究相关脑区ERPs的激活状态, 全面地佐证既往研究结果, 并结合生化、神经影像、

基因遗传、临床表现等多维度共同预测UD、BD的诊疗及转归。

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