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儿童孤独症谱系障碍共病情绪症状的临床特征及神经环路机制的研究进展

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摘 要

孤独症谱系障碍是一种高共病率的神经发育障碍，以社交沟通障碍和重复刻板行为为核心症状。据统计，超过50%的ASD患者伴有焦虑、抑郁等情绪问题，导致临床表现复杂化、诊断困难及干预延迟，影响患者的社会功能与生活质量。目前，ASD共病情绪症状的机制尚未完全明确，治疗方案的疗效个体差异性大。因此，本文旨在梳理ASD共病焦虑与抑郁的临床表现特征，重点探讨其背后的神经环路机制，并综述现有及新兴的干预策略。旨在提倡早期甄别共病情绪障碍的ASD患者，并基于神经环路开发针对性的治疗策略，以期改善患者的整体生活质量。

关键词

孤独症谱系障碍，焦虑症状，抑郁症状，临床特征，神经环路

Emotional Comorbidity in Pediatric Autism Spectrum Disorder: A Review of Clinical Features and Neural Circuit Mechanisms

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by a high rate of comorbidity, with core symptoms including deficits in social communication and the presence of restricted, repetitive patterns of behavior. According to statistics, over 50% of individuals with ASD experience emotional problems including anxiety and depression, which leads to increased complexity in clinical presentation, diagnostic challenges, and delays in intervention, ultimately affecting patients' social functioning and quality of life. Currently, the underlying mechanisms of the comorbidity between ASD and emotional disorders remain incompletely understood, and treatment efficacy shows significant individual variability. Therefore, this review aims to systematically outline the clinical manifestations of ASD comorbid with anxiety and depression, with a focus on the underlying neural circuitry mechanisms, and to summarize existing and emerging intervention strategies. The goal is to advocate for the early identification of emotional comorbidities in ASD patients and to promote the development of targeted therapeutic strategies based on abnormalities in neural circuits, with the aim of improving their overall quality of life.

Keywords

Autism Spectrum Disorder, Anxiety Symptoms, Depressive Symptoms, Clinical Characteristics, Neural Circuits

1. 引言

孤独症谱系障碍(autism spectrum disorder, ASD)是一类通常起病于发育早期，以不同程度的社会交往与交流障碍、刻板行为和兴趣狭隘为主要特征的神经发育障碍。ASD 全球患病率高达 1%，我国为 0.7% [1] [2]。ASD 的共病率极高，70% 的 ASD 患者同时患有另一种精神疾病，50%有两种及以上，其中以注意力缺陷多动障碍、焦虑障碍、智力障碍常见[3] [4]。近年来，ASD 患者情绪失调症状逐渐受到重视，据统计，56.8%~85%的 ASD 患者存在情绪失调症状，其中 67%~79%的 ASD 患者表现为焦虑症状，42%~54%出现抑郁症状[5]。由于 ASD 个体存在表达性沟通困难，其情绪困扰常表现为外化行为问题(如易激惹、攻击、自伤)或内化问题(如社交退缩、刻板行为加剧)等非典型症状，加剧疾病严重程度。ASD 共病情绪症状加剧疾病治疗诊疗难度，甚至可能导致自伤、自杀等严重后果[6]。

ASD 共病情绪症状的干预主要遵循心理治疗为主、严重病例辅以药物治疗的原则[7]。然而，心理干预起效相对缓慢、对家庭时间和经济投入要求较高[8]。药物治疗则因个体差异性大以及体重增加、代谢异常等潜在不良反应，导致治疗依从性不佳，限制了其广泛应用[9]。这一困境揭示基于典型行为表型的治疗模式的局限性，凸显了深入探索其背后神经生物学机制的紧迫性。

综上所述，本文旨在系统梳理 ASD 共病焦虑与抑郁症状的临床表现特征，深入探讨其背后的神经环路机制，并综述神经调控等新兴干预策略的应用进展。期望通过整合临床表型与神经科学证据，为早期识别 ASD 患者的情绪问题、推动个体化精准治疗方案的制定提供理论依据。

2. ASD 共病焦虑症状的临床特征及神经环路机制

2.1. ASD 共病焦虑症状的临床特征及影响因素

据统计，42%的 ASD 儿童青少年至少患有一种焦虑障碍[10]。其临床表现常具有非典型特征，主要与社交焦虑和特殊恐惧相关。社交焦虑多源于认知功能水平导致的社交沟通障碍，特殊恐惧则与感觉过敏相关[11]。社交沟通障碍易使 ASD 患者在人际互动中体验到挫败或误解，从而诱发社交焦虑，而焦虑情绪又会进一步强化其社交回避倾向，形成恶性循环[12]。社交沟通障碍程度与认知功能水平相关，高智力水平的 ASD 对自身社交困难有更高的意识，但缺乏有效应对策略[13]。因此，大龄 ASD 儿童总体焦虑水平和广泛性焦虑障碍发生率更高，而低龄 ASD 儿童则更多表现为分离焦虑和强迫症状[14]。ASD 儿童常存在感觉处理异常，难以过滤环境中的噪音、强光等刺激，易引发急性焦虑，表现为尖叫、冲动自伤等失控表现[15]。生理层面，ASD 患者的焦虑情绪不仅体现为紧张、担忧和烦躁，还常伴有自主神经系统功能紊乱，表现为心慌、胸闷、肌肉紧张及胃肠不适等躯体化症状。这些身体不适感会进一步降低患者的情绪耐受阈值，增加自我伤害或攻击性行为的发生风险[16]。此外，刻板重复行为(如摇晃身体、排列物品)的加剧，可被视为 ASD 患者应对焦虑的一种自我调节方式。通过这些行为，患者可能试图在感官超载或情绪压力下恢复控制感、缓解内在紧张[17]。因此，观察刻板行为的频率和强度变化，可作为评估其焦虑程度的重要行为指标[18]。

ASD 患者共病焦虑症状的临床表现与严重程度，受到性别、认知水平及核心症状严重程度等异质性因素的显著影响，塑造其情绪问题的独特性。在性别差异方面，与普通儿童群体相似，ASD 女性患儿也表现出更高的焦虑易感性[19]。动物模型研究进一步提示其潜在的神经机制，在携带 16p11.2 缺失的 ASD 模型雌鼠中，可观察到中央杏仁核神经元兴奋性增高，这为理解女性 ASD 个体焦虑风险增加的神经基础提供了线索[20]。另外，认知水平是影响焦虑症状表现特异性的重要影响因素。高功能 ASD 患儿通常具备一定的认知内省能力，其焦虑更多源于对自身社交困难的理解和对外界社会期待的觉察，表现为对社交失败的过度担忧和广泛性焦虑。其神经基础与前额叶–边缘系统环路的调控功能失代偿有关[21]。低功能 ASD 患儿由于语言和认知表达受限，其焦虑情绪往往通过行为外化表现出来，如冲动、攻击或刻板行为的加剧。其机制更侧重于杏仁核等情绪中枢的反应亢进及感觉整合异常[22]。因此，在临床评估与干预中，应充分考虑 ASD 的异质性特征，推动分层、分型的精准支持策略。

2.2. ASD 共病焦虑症状的神经环路机制

2.2.1. 杏仁核异常激活

杏仁核(Amygdala, AMY)作为情绪处理的关键脑区，其功能失调被普遍认为是焦虑症状发生的重要神经机制。研究显示，ASD 患者基底外侧杏仁核(Basolateral Amygdala, BLA)的激活程度与焦虑水平呈正相关，提示杏仁核过度活跃可能是构成焦虑症状的神经基础，进而干扰情绪调控与社交行为[23]。动物模型发现，Dip2a 基因敲除的 ASD 小鼠的 BLA 中 5-羟色胺水平降低，削弱了对小清蛋白(PV)阳性抑制性中间神经元的调节，进而降低对 BLA 锥体神经元的抑制性控制，最终表现为焦虑样行为[24]。

2.2.2. 前额叶–杏仁核的调控缺陷

磁共振功能成像(Functional magnetic resonance imaging, fMRI)研究显示，与不伴焦虑的 ASD 患者或健康对照组相比，共患焦虑的 ASD 患者其内侧前额叶皮质(Medial Prefrontal Fortex, mPFC)与杏仁核之间的功能连接显著降低，其中以皮层对边缘情绪的调控通路为主[25]。在 Shank3 突变小鼠中也证明，mPFC 向 BLA 的前馈抑制显著减弱，通过光遗传技术特异性激活该通路可有效改善焦虑样行为[26]。进一步研究发现，该环路中兴奋性和抑制性平衡失调，最终 GABA 能抑制功能下降，导致 pfc 对杏仁核的抑制调

控作用减弱，杏仁核持续性过度激活，表现为焦虑情绪与过度警觉[27]。另外，有研究发现前边缘皮层(Prelimbic Cortex, PL)-背侧纹状体(Dorsal Striatum, dSTR)的投射主要参与调控重复刻板行为，而 PL-杏仁核环路则参与焦虑样行为的产生[28]。前额叶不同投射分别调控 ASD 的不同行为维度，提示 ASD 共病焦虑症状具有明显的环路异质性。这一发现不仅深化了对 ASD 伴焦虑样表现的神经机制的理解，也为开发精准神经调控干预策略提供了理论依据。

2.2.3. 右侧角回的功能异常

右侧角回(Right Angular Gyrus (RAG))是视、听等多种感觉信息整合和时间知觉处理的关键枢纽，其在 ASD 共病焦虑症状的神经机制中的作用日益受到关注[29]。日本金泽大学团队发现，焦虑情绪可能在右侧角回激活与感官过敏(Sensory Hyper-reactivity, SOR)之间扮演中介角色，形成“焦虑–时间知觉–感官过敏”的神经通路[30]。ASD 患者可能因时间知觉障碍，难以准确判断外界刺激的持续时间、节奏或顺序，这种“不可预测感”导致焦虑水平提升，焦虑状态进一步降低感觉刺激的处理阈值，形成恶性循环[31]。SOR 常见于 ASD 和焦虑障碍患者中，但其背后的神经关联模式可能存在差异[32]。在典型焦虑障碍中，SOR 可能与威胁相关脑网络(如杏仁核)的过度激活关联更紧密；而在 ASD 共病焦虑的个体中，SOR 则可能与包括右侧角回在内的感觉信息整合效率低下和时间处理网络的异常活动联系更为特异，说明右侧角回在 ASD 伴焦虑症状中的特有作用。

3. ASD 共病抑郁症状的临床特征及神经环路机制

3.1. ASD 共病抑郁症状的临床特征及影响因素

Meta 分析显示，ASD 患者终身抑郁障碍的患病率约为 14.4% [33]，显著高于一般人群。受 ASD 社交沟通障碍、刻板行为及感觉处理异常等特征的影响，其抑郁症状表现常不典型。在情绪行为层面，ASD 共病抑郁患儿常表现为持续性易怒、无明显诱因的情绪爆发(如哭闹、喊叫)以及极端社交退缩[34]。他们对微小挫折的耐受性降低，可因细微不如意而诱发强烈的情绪反应，这反映其情绪调节功能的严重受损[35]。ASD 患者的兴趣动力的减退表现为对原有特殊兴趣的彻底放弃，例如长时间独处，拒绝参与任何社交互动，甚至拒绝进食等基本生理需求[36]。此外，自伤行为(如撞头、咬手)及某些刻板行为显著加重，也是抑郁共病的重要行为标志。研究显示，自伤行为的严重程度与抑郁症状的严重程度可能存在正相关关系[37]。ASD 常存在由情绪引发的躯体不适，但 ASD 情感词汇量表达受限，难以准确描述头痛、胃痛等，常表现为捶打、抓挠自己。另有研究发现，睡眠障碍的恶化(如入睡困难、早醒或节律紊乱)也是 ASD 儿童抑郁发作的一个突出信号[38]。

研究显示，ASD 患者抑郁发生风险升高可能涉及多因素共同作用，包括性别、认知水平、临床亚型及社会心理因素等。研究发现女性 ASD 患者表现出更高的抑郁共病风险。性别差异源于神经内分泌系统与表观遗传调控的交互作用，其在情绪相关神经环路发育中扮演关键角色[39]。认知功能水平同样影响抑郁表现，高功能 ASD 患者对同伴排斥和社交失败具有更强的认知体验，其抑郁症状多表现为对社交挫折的过度反思和自我价值感低下[40]。低功能患者的抑郁与基本社交互动的缺失和日常活动受限相关，以攻击性、自我伤害等表达情绪困扰[41]。另外，临床亚型也与抑郁风险相关，如广泛性发育障碍未特指型(PDD-NOS)患者的抑郁发生率显著高于典型自闭症患者，提示不同症状谱系可能对应着差异化的神经发育轨迹[42]。

3.2. ASD 共病抑郁症状的神经环路机制

3.2.1. 前额叶–杏仁核调控缺陷

目前，关于 ASD 伴抑郁症状的神经机制研究相对有限，现有证据主要集中在前额叶皮质、伏隔核和

海马等脑区。李影等对比 ASD 患儿的 fMRI，发现共病抑郁症状患者的感觉运动相关额叶区域及注意网络功能活动显著下降。该研究进一步发现，其右侧额中回(眶部)的局部一致性值与抑郁症状评分呈正相关，提示这些脑区的功能异常可能是 ASD 伴发抑郁情绪的特征性神经标志[43]。Ohtani 等采用功能性近红外光谱(Functional near-infrared spectroscopy, fNIRS)发现，伴抑郁症状的 ASD 患者右侧腹外侧前额叶皮层(Ventrolateral Prefrontal Cortex, VLPFC)的血流动力学反应弱于 ASD 无抑郁组[44]。神经环路连接方面，ASD 共患抑郁症状患者的 VLPFC 与杏仁核之间的功能连接显著降低，且连接强度与抑郁症状的严重程度呈负相关[45]。这一环路的连接性减弱，可能削弱前额叶对杏仁核等边缘系统情绪的自上而下调控能力，导致患者社交信息的处理能力受损及负性情绪调节困难。动物实验发现，该环路的正常功能依赖于多巴胺、5-羟色胺和 GABA 等多种神经递质系统的平衡。青少年期社会挫败应激导致成年动物内侧前额叶中 GABA 能抑制性突触传递持续减弱，表现为自发的抑制性突触后电流频率下降及 GABA 合成酶 GAD65 的 mRNA 表达降低[46]。进一步说明前额叶对杏仁核的抑制调控作用减弱，促使负性情绪过度表达，最终诱发抑郁样行为[47]。

3.2.2. 伏隔核功能障碍

伏隔核(Nucleus Accumbens, NAc)作为奖赏系统的核心枢纽，在动机形成和情感加工中扮演着关键角色，其多巴胺能信号传导的紊乱是 ASD 共病抑郁症状的病理生理机制。跨诊断研究发现，ASD 共病抑郁症状患者 NAc 的激活程度与个体的情感功能水平密切相关。该区域多巴胺释放不足，导致患者对社交奖赏的敏感性下降，表现为社交动机减退和快感缺失[48]。

3.2.3. 海马发育障碍

海马作为边缘系统的关键组成部分，在情绪调节、记忆整合和认知功能中发挥核心作用。研究表明，海马体的结构与功能异常可能是 ASD 与抑郁共病的重要神经病理基础之一[49]。ASD 患者海马区中突触后密度蛋白 95 和突触蛋白 I 等突触标志物的表达显著降低，细胞外基质蛋白酶 MMP9 的表达上调，提示突触可塑性受损[50]。类似的分子改变在抑郁症患者中也有报道，表明海马突触可塑性损伤可能是 ASD 与抑郁症状的共享机制[51]。结构神经影像学研究显示，ASD 患者与抑郁障碍患者均存在海马体积缩小和形态异常，导致社交记忆整合功能受损及负性情绪记忆消退障碍。进一步研究发现，学龄前 ASD 儿童的海马与前扣带皮层等脑区的功能连接降低，损伤社交信息加工和情绪调节能力，促进抑郁倾向的形成[52]。在 ASD 动物模型中，如 BTBR 小鼠、Shank3 突变小鼠和 Cntnap2 缺陷小鼠，均观察到海马神经元数量减少及神经炎症反应增强。此外，孕期母体免疫激活(MIA)模型显示，其子代海马出现炎症反应，并同时表现出自闭样和抑郁样行为。以上证据均提示海马神经炎症可能是连接 ASD 和抑郁共病的关键机制之一[53]。

4. 治疗策略

4.1. 行为干预及药物治疗

国内外权威指南均明确指出，ASD 共患情绪症状的干预，心理治疗是首选的一线治疗方案[54] [55]。改良版的认知行为疗法(Cognitive Behavioural Therapy, CBT)、虚拟现实暴露疗法(Virtual Reality Exposure Therapy, VRET)及社交技能训练(Social Skills Training, SST)均被证实可有效缓解 ASD 患者的焦虑症状[56]-[58]。通过帮助患者暴露刺激、识别并重构非理性认知与负面思维模式，学习更具适应性的情绪调节与行为应对策略。但心理治疗对患儿的认知水平有一定的要求，导致疗效的个体差异性大。另外，心理治疗周期长、开销大，也对养育者提出较高要求，一定程度上限制了该疗法在 ASD 群体中的可及性与长期依从性。目前，尚无任何药物经临床研究证实能直接改善 ASD 核心症状。英国精神药理学会(BAP)指

南建议，针对 ASD 共病的情绪、多动、睡眠紊乱等症状，可在充分评估风险效益比的基础上，审慎采用超说明书用药策略[59]。我国指南建议，对于 ASD 共病情绪症状的患者，应在规范诊疗流程下优先选用选择性 5-羟色胺再摄取抑制剂[60]。美国最新指南更细化：针对急性焦虑症状，推荐短期使用羟嗪、劳拉西泮或低剂量喹硫平；对于慢性焦虑，则首选米氮平、丁螺环酮等具有长期安全性的药物；共病抑郁症状时，度洛西汀与米氮平被视为一线选择[61]。另外，研究焦点正转向能直接调节 E/I 平衡的新型药物。例如，阿巴氯、N-乙酰半胱氨酸等通过调节 E/I 平衡，已在临床研究证实，能显著减轻 ASD 患者的情绪不稳症状[62] [63]。需要强调的是，上述药物的疗效存在显著的个体差异，且部分患者可能出现体重增加、代谢异常及镇静作用等不良反应，导致服药依从性差，影响预后。

4.2. 神经调控技术

神经调控技术作为一类非侵入性干预手段，具有作用路径直接、经济性良好及操作相对简便的特点。研究表明，在 ASD 共病情绪症状的神经机制中，以左侧背外侧前额叶皮层(Dorsolateral Prefrontal Cortex, DLPFC)与双侧杏仁核之间的功能连接异常为关键特征[64]。因此，DLPFC 成为神经调控技术干预的核心靶点，旨在通过调节前额叶－边缘环路的相互作用，改善情绪加工功能。重复经颅磁刺激(Repetitive Transcranial Magnetic Stimulation, rTMS)通过时变磁场在皮层诱导感应电流，调节神经元兴奋性。低频 rTMS (如 1 Hz)作用于 DLPFC，可增强 GABA 能中间神经元的抑制性功能，有助于改善 ASD 患者的情绪不稳症状[65]。初步临床研究显示，rTMS 干预后部分患者不仅行为症状减轻，杏仁核灰质体积与功能连接也有积极变化，提示可能诱发神经可塑性适应[66]。经颅直流电刺激(Transcranial Direct Current Stimulation, tDCS)利用恒定、低强度的直流电(通常为 1~2 mA)，以极性依赖的方式调节皮层兴奋性。一项针对右侧 DLPFC 的 tDCS 干预后，ASD 患者紧张症状减轻约 30% [67]。2025 年一项多中心随机双盲对照试验中，靶向 DLPFC 及前运动区的高精度 tDCS 也可改善 ASD 儿童的核心与情绪症状[68]。神经反馈训练通过让患者学习自我调节脑电活动，增强前额叶参与的情绪调控网络功能。有研究发现训练可优化 P300 等事件相关电位特征，提示提升情绪信息处理效率[69]。总体而言，非侵入性神经调控技术展现出良好的安全性和耐受性[70]。然而，目前证据等级仍较低，多数研究存在样本量小、对照设计不完善、缺乏长期疗效与个体化反应预测指标等问题。未来需开展更多方法学严谨的大样本研究，明确其临床应用价值与适用范围。

5. 讨论与展望

ASD 共病情绪症状加剧其临床表现的复杂性及严重程度，容易导致症状的重叠与识别困难，延误早期干预的关键时机。全球多国数据显示，从父母首次发现发育异常到最终获得 ASD 诊断之间存在 3 至 5 年的延迟[71]。另有研究发现，在 3 岁这一神经可塑性的关键窗口期前接受科学干预的 ASD 患儿，ASD 核心症状评估中表现更优，其未来融入主流教育环境的可能性也显著提高[72]。因此，早期识别 ASD 共病情绪症状的非典型临床表现，并实施针对性干预，对于阻断负面情绪对核心症状的叠加效应、改善长期预后具有决定性意义。

从神经机制层面剖析，ASD 共病情绪障碍有其独特的神经环路机制，主要包括负责威胁评估与情绪反应的杏仁核－前额叶环路功能连接减弱；介导动机与奖赏加工的纹状体系统反应低下；以及与情景记忆和语境理解相关的海马结构与功能异常。基于脑区病理生理异常开发的神经调控技术，具有特异性强、安全性高及疗效性好的特点，对 ASD 共病轻－中度情绪症状的治疗具有显著有效性及可行性。

当前，针对 ASD 共病情绪症状的治疗方案的疗效存在显著的个体差异，反映对共病背后的复杂神经生物学机制的研究尚不全面。未来研究应致力于利用多模态神经影像、遗传学及数字表型等技术，构建

从“行为症状”到“神经环路”再到“分子靶点”的精确映射关系，最终推动个体化精准治疗策略的发展。另外，鉴于 ASD 及其共病的高度异质性，多学科协作诊疗模式已成为临床实践的核心准则。通过整合发育行为儿科、儿童精神科、康复治疗及心理科学等多学科资源，创立“孤独症诊疗中心”模式为患儿提供一站式、个体化的精准服务，从而打破学科壁垒，优化诊疗路径。

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