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# 幼年期自闭症谱系障碍神经影像学病理研究进展

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## 摘　要

**自闭症谱系障碍(Autism spectrum disorder, ASD)是一种由遗传、免疫、环境等多因素共同作用导致的神经发育障碍疾病，其病因和神经病理机制尚不完全清楚。本文主要回顾了近年来ASD幼年患者或高风险幼儿特定脑区的形态结构、神经代谢以及不同尺度脑功能的神经影像学病理表现，以期促进神经影像学应用于ASD早期风险筛查和病理机制研究。**

## 关键词

**自闭症谱系障碍，神经影像学，幼年期，发育**

# Progress in Neuroimaging Pathology of Autism Spectrum Disorder during Childhood

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## Abstract

**Autism spectrum disorder (ASD) is a neurodevelopmental disorder caused by genetic, immune,**

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**environmental and other factors. The etiology and neuropathological mechanism of ASD are not fully understood. In this paper, we reviewed some neuroimaging pathological findings about morphological structure, neurometabolism and different scales of brain functions at specific brain regions in children with ASD or at a high risk of ASD in recent years, in order to promote the application of neuroimaging in the early risk screening and in the study of pathological mechanism of ASD.**

## Keywords

**Autism Spectrum Disorder, Neuroimaging, Childhood, Development**



## 1. 引言

自闭症谱系障碍(Autism spectrum disorder, ASD)又称孤独症，是一种可遗传的神经发育障碍疾病，主要表现为社会交往障碍、言语和非言语交流缺陷、兴趣狭隘和重复刻板行为等临床症状。孤独症患者对周围环境变化的适应能力较差，智力发展滞后且不均衡，在融入社会的过程中面临诸多挑战与困难。目前，在临床上多采用行为干预为主、药物治疗为辅(如利培酮 Risperidone)的系统化、个体化治疗措施[1] [2]。然而，由于 ASD 病因复杂，涉及神经、免疫、内分泌各个层面以及遗传、环境(如孕期重金属污染、药物误用、酒精暴露)等多个因素[3] [4] [5] [6]，单一的药物治疗难以对 ASD 的核心症状起到决定性的康复作用。

据近期筛查，我国 ASD 患病儿童的发病率约为 1%，与西方国家相当[7]。随着人们对 ASD 诊断标准的完善以及诊断工具的进步，预计 ASD 的诊断发病率将呈上升趋势。ASD 的诊断主要依据世界卫生组织出版的《精神与行为分类》(ICD-11) [8]、美国精神医学学会出版的《精神障碍诊断和统计手册》(DSM-5) [9]、以及中华医学会精神科分会出版的《中国精神障碍分类与诊断标准》(CCMD) [10]，对病患对象进行外在行为、内隐心理等多维度特征的综合评估。此外，由于 ASD 表型与 *Fmr1*、*MECP2*、*NLGN3/4*、*TSC1/2*、*DLX*、*PTEN* 等多个基因的突变有关[3]，基因检测技术可以用于 ASD 早期筛查及辅助诊断[11]。研究表明，早期诊断和早期干预对于减轻 ASD 患儿症状、尽量提高其脑功能水平、以及争取良好的预后非常重要[12] [13]。

随着医学影像技术的不断发展，关于 ASD 的神经影像学研究内容越来越丰富。神经影像学可以通过无创的方式，对 ASD 幼年患者或高风险儿童进行特定脑区的形态结构、生化代谢以及脑功能异常情况的长期监测，其监测结果将有助于揭示 ASD 的多维度病理机制，对早期诊断并及时缓解 ASD 的病情发展也将发挥重要的作用。本文回顾了近年来有关 ASD 早期诊断的神经影像学多维度病理研究，以期为 ASD 幼年患者得到及时、有效诊疗提供参考。

## 2. ASD 幼年患者大脑形态结构异常

对出生于 ASD 高风险家庭的幼儿采用结构磁共振成像(Structural Magnetic Resonance Imaging，sMRI)进行追踪研究，可发现其中一些 ASD 高风险幼儿的大脑存在早期过度发育的现象，表现为与正常对照组相比，高风险幼儿的皮层表面积增长较快，到 12 月龄时其大脑体积出现明显增大[14] [15]，其幼年期的

额叶、顶叶、颞叶、右侧中央前回、两侧中央后回等皮质的体积都有明显增加[16] [17] [18] [19]。ASD 幼年患者皮层下的杏仁核、苍白球、壳核及伏隔核等脑区体积较小，额叶皮质厚度增加，颞叶皮质厚度减小[20]。这些幼年患者大脑皮质表面积和体积的增加可能与神经系统发育过程中的脑室周围祖细胞的分化异常有关，而皮质厚度的变化可能反映了神经细胞树突生长发育以及轴突髓鞘形成的异常。基于形态结构的表面形态测量学(Surface-based morphometry, SBM)对 ASD 的诊断准确性高于 80% [21]，可以为 ASD 的临床早期诊断提供一定的参考依据。

各脑区之间的通讯连接情况也是大脑形态结构检测的一个侧重点。采用弥散张量成像(Diffusion tensor imaging, DTI)可以非侵入性地观察和追踪脑白质纤维束的走向。DTI 研究发现，幼儿期 ASD 患者的胼胝体、弓状束、上纵状束、钩状束等多个脑区的神经纤维束各向异性分数(Fractional anisotropy, FA)降低[22]，表明 ASD 患者脑白质的组织化程度降低。这些研究结果提示，幼年 ASD 患者各脑区之间以及各脑区内部的神经信息通讯存在异常。

## 3. ASD 幼年患者脑内神经代谢紊乱

已有大量磁共振波谱(Magnetic resonance spectroscopy，MRS)研究表明，ASD 幼年患者特定脑区的神经递质系统代谢紊乱，导致神经元功能失调、数量减少、髓鞘丢失和轴突连接受损等不良后果，说明代谢紊乱可能是 ASD 病理发展过程中的一个重要机制[23]。由于谷氨酸能和 GABA 能神经递质系统对轴突发生、突触修饰以及神经元分化等神经发育过程具有重要调控作用，二者的代谢紊乱将使兴奋性和抑制性神经递质系统失去平衡，从而影响神经元活性和脑认知功能的正常发挥。MRS 检测发现，ASD 患者幼年时大脑皮层(如额叶)的谷氨酸[24]和 GABA [25] [26]神经递质含量明显减少；而到成年时，ASD 患者杏仁体-海马复合体的谷氨酸和肌酸含量明显增加[27]，初级视觉皮层、初级听觉皮层、运动皮层以及顶叶中的谷氨酸和 GABA 含量与正常对照相比无明显差异[28]。这些报道中，ASD 患者脑内谷氨酸和 GABA 含量的检测结果存在差异，推测与所检测的特定脑区以及患者的年龄不同有关。

在 MRS 对大脑代谢功能的研究中，N-乙酰天冬氨酸(NAA)、磷酸肌苷、胆碱和肌醇都是参与调控神经细胞代谢功能的重要化合物。MRS 检测发现，ASD 幼年患者额叶、丘脑、扣带回、小脑等脑区的 NAA 含量明显减少[24] [29] [30]。由于 NAA 与神经元数量及其代谢功能密切相关[31]，这些研究支持 ASD 幼年患者神经代谢功能异常的观点。此外，MRS 检测还发现磷酸肌苷、胆碱和肌醇在 ASD 幼年患者脑中呈广泛性减少[24] [29]，也同样提示 ASD 患者神经细胞的代谢功能受到损伤。随着现代物理化学技术的发展，有望进一步提升 MRS 对特定脑区目标化合物定量检测的灵敏度和准确度，这将有助于加深人们对 ASD 以及其它脑功能障碍病理机制的理解。

## 4. ASD 患者静息态和任务状脑功能异常

采用脑磁图(Magnetoencephalography, MEG)、功能磁共振成像(Functional magnetic resonance imaging，fMRI)和近红外光谱脑功能成像(Functional near-infrared spectroscopy, fNIRS)等神经影像学方法可以检测和评估在静息态或任务态的情况下，ASD 患者特定脑区的信息处理方式有何异常，从而根据患者具体病情有针对性的采取临床治疗措施。据报道，经 fMRI 检测进行 ASD 筛查的准确率为 80%，特异性为 66.7% [32] [33]，而 fNIRS 成功筛选 ASD 的灵敏度为 81.6%，特异性为 94.6% [18]。

应用 MEG 技术检测可揭示 ASD 幼年患者大脑具有特殊的信息处理方式，例如，ASD 儿童静息态的多个脑区对噪音输入的反应值(即相对熵)明显高于正常儿童，表明 ASD 儿童的静息态大脑具有较高的背景噪音，可能是 ASD 儿童认知功能损伤的机制之一[34] [35]。在处理认知灵活性相关的任务信息时，ASD 儿童的功率谱密度及多尺度熵等指标明显低于正常对照，反映出 ASD 儿童涉及大尺度神经网络的时间信

息组织能力低于正常对照，从而造成大脑执行功能的损伤[36]。青少年 ASD 患者在执行 NO-GO 任务时，主要招募额叶脑区，而正常对照组主要招募顶叶及颞叶脑区，提示青少年 ASD 患者具有非典型的有限抑制网络[37]。MEG 应用于研究 ASD 成年患者的报道较多，例如，ASD 成年患者的初级视觉皮层对具有社交信号属性的直接凝视缺乏足够的反应性[38]，颞叶、顶叶及额叶等脑区的源振幅与正常对照组相比存在明显差异[39]，海马脑区的动态信息存储效应值降低[40]，这些研究证明了 ASD 患者成年后存在弥散性的脑功能失调，其感知觉以及认知决策功能存在缺陷与神经信号异常编码有关。

功能磁共振成像(fMRI)主要应用于检测患者在任务态条件下的脑功能。fMRI 检测发现，ASD 幼儿在执行社交任务时，左侧中央后回激活增强，而右侧颞上回和右侧海马的激活程度相对较弱；在非社交任务中，ASD 幼儿右侧岛叶和左侧扣带回激活较多，右侧额中回激活较少[41]。对 1~8 岁幼年 ASD 患者与正常儿童的 fMRI 图像研究发现，ASD 患儿双侧顶叶下部、后扣带皮层、角回等不同功能区的连接较正常儿童弱[42]。青少年 ASD 患者在执行言语理解、听觉刺激、执行功能、视空间处理、情绪线索等任务时全脑或大尺度网络功能连接减低，相反某些特殊网络功能连接增强，不同尺度神经网络之间的功能活动水平高度不一致[43]。上述这些研究结果说明，ASD 对涉及视觉、听觉、语言、情绪、执行等多层次、多类型的脑功能都有影响。

采用近红外光谱脑功能成像(fNIRS)检测 4~6 月龄婴儿对人类社交活动影像、非社交性图像、人类语音及非人类声音的反应发现，与 ASD 低危儿童相比，后期确诊的 ASD 高危儿童大脑额下回和颞后区对社交性视觉刺激的反应降低，左侧颞叶对人类语音反应降低，对非人类声音反应增强[44]。另外，fNIRS 检测发现 ASD 患儿大脑半球间静息态功能连接减弱，双侧皮质局部功能连接减弱，氧合血红蛋白、还原血红蛋白波动幅度增强，可用于准确预测 ASD 的发病率[18]，说明该技术对 ASD 早期诊断具有良好的应用前景。

## 5. 小结及展望

ASD 是一种综合性的神经发育障碍疾病，临床症状表现复杂多样，且神经系统病变的个体差异较大，其病理机制还有待更深入的研究和探讨。目前得到较多认可的“脑连接失调假说”认为，ASD 高风险幼儿在早期发育阶段，其大脑的过度发育导致大脑神经纤维束的分支与修剪发生异常，从而引起中枢神经系统对网络信息处理加工的效能下降，最终表现出不良的症状[45]。本文分别阐述了幼年期 ASD 患者的神经影像学病理表现，主要包括脑内异常形态结构、神经代谢紊乱和异常脑功能三个方面的研究进展。由于发育关键期幼儿的中枢神经系统具有较强可塑性，在深入理解 ASD 病理机制的基础上，尽早采用无创、可重复和可连续监测的神经影像学技术进行 ASD 风险筛查，将有助于临床医生对 ASD 高风险幼儿及时采取干预措施，最终达到改善高风险幼儿预后的目的。

目前，有关幼年期 ASD 的神经影像学研究已有一定的成果，然而，无论是关于 ASD 幼年患者的脑结构还是脑功能研究，高敏感度和特异性强的 ASD 相关影像学技术指标仍有待进一步研发。从当前发展趋势来看，对 ASD 的研究需要整合不同学科的优势，从基因、细胞、神经环路及神经影像表型等多个不同层面开展多学科交叉研究，对研究结果进行多学科的交叉融合和相互验证，进一步研发多学科医学检测途径和诊疗手段。在神经影像学层面，也需要将多种先进技术交叉融合，如将精细的弥散成像技术(DSI)、功能磁共振与结构磁共振融合应用，将磁共振与基因技术相结合，以便更准确地解释疾病相关病理机制，提高特异性影像学技术指标在 ASD 临床诊断中的应用。

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