·综述·

孤独症谱系障碍的结构磁共振成像研究进展*

寿小婧[1] 张 嵘[1,2]

孤独症谱系障碍(autism spectrum disorders,ASD)是一种以语言发育迟缓、社会交往障碍以及重复刻板行为为特征的广泛性发育障碍疾病[1]。近年来,孤独症的患病率也日趋上升,美国最新的调查结果显示,ASD在男孩中的患病率约为3.74%,在女孩中约为1.47%[2—3]。作为一种儿童期高发疾病,ASD的具体发病机制尚不明确,但已被公认是一种由遗传及环境因素共同作用的复杂神经精神疾病。ASD患者在幼儿时期已可被确诊,因此在胚胎(妊娠期前8周)及出生后(3岁以前)两个神经发育的关键时期很可能发生异常,导致大脑结构的异常和功能紊乱,进而致使孤独症的发生。

磁共振成像(magnetic resonance imaging,MRI)是一种在体无创性的成像技术手段,在神经科学以及心理学领域受到广泛应用。其在结构研究方面具有较高的对比灵敏度和空间分辨率,对人体没有电离辐射的损伤,对探究儿童及成人的大脑解剖结构普遍适用[4]。扩散张量成像(diffusion tensor imaging,DTI)对活体内水分子的扩散敏感,因此常用来探测白质纤维束的走行与完整性。

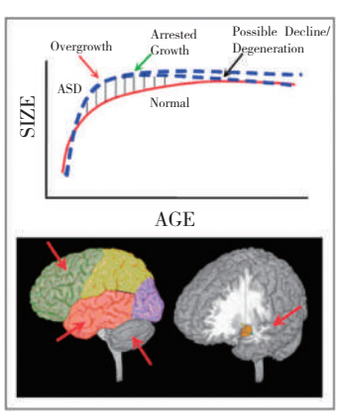
对于孤独症这种发育障碍性疾病,对其脑结构功能的研究是寻找病因的重要手段,笔者在PubMed、ScienceDirect Online、ProQuest、Springer、John Wiley、Cambridge Journals Online等数据库上搜索2007—2011年间关于孤独症谱系障碍的磁共振成像文章,检索的关键词包括"autism"、"autistic"、"Asperger"、"pervasive developmental disorder"、"magnetic resonance imaging"或"MRI"。对研究对象为ASD人群,设置有患病组及正常对照组,利用MRI进行扫描研究,内容涉及结构方面探究孤独症人群的发病机制的原创性研究性论文进行总结与梳理,具体内容如下:

1 全脑体积变化

在2—7岁的ASD幼儿/儿童中,无论男女,其颅内以及全脑体积相比于正常发育的幼儿/儿童都要增大[5]。Zeegers等[6]发现,这一年龄段的ASD幼儿/儿童的全脑体积与相匹配的发育迟缓(developmental delay, DD)组基本相似,不同的是其全脑体积与智力功能并没有显著的相关性。在学龄后的ASD儿童以及青少年中,全脑体积比正常人群相对偏大[7—8],或基本接近正常[9]。但是在成人青年中,ASD人群的这种显著性差异则消失[10—12]。

Courchesne等[13]在一篇综述中绘制出ASD人群全脑体积随年龄增长的发育变化图(图1),认为这一人群在发育的早期阶段大脑过度增长,在进入青春期以后生长速度减缓,因此与正常人群接近,随后可能进入比正常人加速的全脑体积的减小。在2011年一项年龄跨度为1—50岁的大样本研究中,Courchesne等[14]再次证明了这一观点。

图1 孤独症早期局部性过度生长



上图:孤独症早期大脑过度生长,随后生长阻滞
下图:孤独症早期局部生长的区域,包括额叶和颞叶皮质,小脑以及杏仁核。(Courchesne E, et al. Neuron, 2007)

2 语言中枢

布洛卡区(Broca's area):布洛卡区也是语言运动中枢,位于大脑皮质额下回(BA44/45),优势半球在左侧[15],它的主要功能是语言讯息的处理以及话语的产生。在ASD儿童的研究中,发现该区域的脑回化相对于正常发育儿童异常[16]。在青少年中,该语言区体积相比于正常对照组减少,并且异

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1 北京大学神经科学研究所,北京大学基础医学院神经生物学系,神经科学教育部重点实验室,卫生部神经科学重点实验室,北京,100191;
2 通讯作者
作者简介:寿小婧,女,博士研究生; 收稿日期:2012-10-09

常的右脑偏侧化更为常见[17]。DTI研究显示，额叶语言区通路的各向异性分数(fractional anisotropy, FA；FA值的减低可提示白质结构完整性的降低)广泛降低，且这种降低与语言及症状的严重程度评分有相关性[18—19]。运动语言区在发育中的结构异常，可能是ASD人群在发育过程中语言发育迟缓，以及语言发音不清等问题的生理基础。

威尔尼克区：威尔尼克区位于颞上回附近，区域内含有听觉性语言中枢，优势半球同样在左侧[15]，主要的功能是理解话语的意义。在ASD幼儿中，颞上区和颞极区域相对于正常发育幼儿异常增大[20]，这可能是某些ASD人群在发育早期语言发育超常的原因。但是在儿童到青少年，乃至成人的过程中，左侧的颞叶则呈现结构上的退化，如皮质变薄[21]，灰质减小[22—24]，白质密度的减小[21]，FA值的降低[25]等。另外在各年龄段的ASD人群中，都发现了颞上回偏侧化的翻转，即为右偏化[26—27]。这些结构上的异常可能解释了ASD人群对语言理解的障碍以及表达语句意义的障碍。

3 运动中枢

3.1 大脑皮质运动区

背侧前额叶：背侧前额叶参与管理动物行为的高级执行功能[15]，即决定该做什么，不该做什么。在ASD人群中背外侧前额叶灰质体积的增加结果不一致[28—30]，可能与研究对象的亚群与年龄不一致相关；比较一致的结果是该结构白质的体积减小[28]，FA值降低，并且FA值与ASD的社交障碍呈负相关[31]。这可能就解释了ASD儿童的自我控制能力差，以及对指令的依从性差等问题。

主运动皮质区(primary motor cortex)：也称初级运动皮质区，位于中央前回，其功能是发出运动控制指令以及为运动参数编码[15]。在ASD儿童的研究中，该区灰质减少[20, 32]，白质的体积显著增加[33]，密度增加[34]；在运动操作评估(physical and neurologic examination of subtle signs, PANESS；用来评估躯体和神经系统的检查的细微体征，评分越高运动能力越差)中，ASD儿童的PANESS评分与双侧半球主运动皮质区的白质体积成正比，而在正常发育儿童中则成反比。这提示了该区域神经细胞的减少以及神经纤维的过度生长可能是ASD儿童运动障碍的原因之一。

3.2 小脑

小脑(cerebellum)是中枢神经系统中最大的运动结构；其中蚓部(内侧区)和蚓旁部(中间区)对进行中的肢体运动起重要的适时调节作用，小脑半球(外侧部)参与随意运动的计划和编程，提高精确程度[15]。在ASD儿童中，小脑的白质增大，灰质减少[5]，蚓部体积整体减小[23,35—37]；小脑体积与智商没有关联，但是与操作智商(PIQ)呈显著的正相关[38]。DTI研究显示小脑上脚、中脚和下脚均有不同程度的纤维束损害[39]。这些证据为ASD患儿发育早期的运动平衡障碍以及精细动作缺陷提供了解剖结构基础。另外在ASD不同的亚群间，小脑的灰质密度也存在差异，如高功能的ASD患儿双侧小脑的灰质密度相对于正常儿童增加，而低功能的ASD患儿双侧的小脑灰质密度减少[40]。提示高功能ASD儿童可能通过灰质密度的增加从而代偿结构上的缺陷。ASD人群小脑缺陷不仅存在于生长发育时期，并会一直延至成人阶段[12,22,41—42]。

4 情绪中枢

扣带前回(anterior cingulate cortex，ACC)：位于大脑内侧面，对情绪认知起关键作用[15]。在ASD儿童的研究中，ACC白质体积较正常儿童明显减小[43]，白质的密度[34]及完整性均降低[31]；在一项纵向研究中，发现在青春期ASD男孩的白质发育异常缓慢，而ACC皮质则过度生长[44]。在成人的功能及结构的研究中，ACC白质的FA值减低，并且功能激活异常[45]。这些结构的异常，都被认为与ASD人群的社交障碍，交流缺陷以及重复刻板行为有关。

前额叶(prefrontal cortex，PFC)：大脑的前额叶是执行功能重要的物质基础，负责对各种具体的认知加工过程进行控制和协调，是大脑最高级的认知活动[15]。在ASD幼儿中，PFC的体积较正常发育儿童明显增大[20]；而在儿童到成人阶段，该区域的皮质体积较正常人群显著减小[29,46—47]，白质的FA值降低[31,48]，密度减小[46]。相关性分析显示，PFC皮质的减少与孤独症症状的严重程度显著相关；白质结构的FA值与社交障碍呈负相关。

杏仁核：位于大脑颞叶内侧，其与情绪有以下3方面关系：对情绪状态的表达极为重要；对于认知其他动物表达的情绪很重要；对于情绪的学习不可或缺[15]。ASD 幼儿及儿童的杏仁核相比于正常发育组显著增大[20,49—52]；在一项2—4岁的纵向研究中，杏仁核的体积随时间增长，而生长率则与正常幼儿基本平行[51]，说明ASD人群杏仁核的异常可能在胚胎发育和出生后已经存在。在4岁时，杏仁核体积的大小已经显示出与注意力的相关性[51]。杏仁核的体积在幼儿和儿童中都与ASD临床症状和社交障碍的严重程度显著相关[29,50]。青少年和成人中，杏仁核的体积与正常人群相比没有差异[53]或相对减小[54—55]，年龄和社会焦虑与杏仁核的体积有显著关联，杏仁核越小焦虑程度越高且患者年龄更小[53]，这和儿童时期正好相反。

5 小结

从整个谱系层面来看，ASD人群存在发育早期的全脑过度生长，尤其是涉及认知、语言、情感以及运动的额叶、颞叶、杏仁核，以及小脑区域，但是白质纤维束及胼胝体结构的研究显示，联系纤维的结构完整性受到广泛的损害，并且这些

结构异常已被证明与ASD的核心症状有所关联,说明这些早期发育的结构异常可能是其功能障碍的结构基础。

另外,对于脑结构而言,正常人群本身就存在性别差异;而在ASD中,亚群复杂,亚群间的表型不一致,个体差异大,在神经结构及功能方面的变化更是千差万别。因此对于日后的研究,控制因素要尤其注意。在选择被试时,主要的匹配参数为年龄,性别;对于研究结构大小尺寸,一般对头围、颅内体积以及全脑体积进行匹配校正;对于研究半球偏侧性优势,通常对被试的用手偏好进行匹配。这样,采集的数据才能客观准确地反映患者脑结构的真实情况。

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