

注意缺陷多动障碍儿童执行功能性别差异及机制研究进展

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摘要: 儿童注意缺陷多动障碍(ADHD)在发病率、症状及预后方面均有显著的性别差异, ADHD 儿童认知障碍的主要特征之一是执行功能(EF)损害。本文通过对近年来 ADHD 儿童 EF 的性别差异及机制的相关研究进行梳理, 发现 ADHD 儿童的 EF 存在显著性别差异, 主要体现在抑制控制、认知灵活性、热 EF 上, 但研究结果不尽相同; 对 EF 性别差异的机制知之甚少, 主要局限在脑功能区的差异方面, 如初级运动皮层、内侧眶额皮层、基底节、杏仁核(正/负功能连接), 及额-小脑回路等, 少有更深层次的研究。

关键词: 注意缺陷多动障碍; 执行功能; 性别差异

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Progress in gender differences and mechanisms of executive function in children with attention-deficit/hyperactivity disorder

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Abstract: Children with attention-deficit/hyperactivity disorder (ADHD) have significant gender differences in incidence rate, symptoms and prognosis. One of the main characteristics of ADHD children's cognitive impairment is executive function (EF) impairment. This article reviews the research on gender differences and mechanisms of ADHD children's EF in recent years, and finds that there are significant gender differences in ADHD children's EF, mainly reflected in inhibitory control, cognitive flexibility, hot EF. But the research results are different. Little is known about the mechanism of gender differences in EF, which is mainly limited to the differences in brain functional areas, such as the primary motor cortex, medial orbitofrontal cortex, basal ganglia, amygdala (positive/negative functional connection), and frontal cerebellar circuit, and there is little in-depth research.

Keywords: attention-deficit/hyperactivity disorder; executive function; gender difference

注意缺陷多动障碍(attention-deficit/hyperactivity disorder, ADHD)是儿童时期最常见的神经发育性障碍之一, 主要表现为与发育年龄不相符的注意力缺陷、活动过多、冲动和控制力差, 不仅影响学习, 甚至可出现人际障碍、品行障碍及情绪障碍等问题。这些障碍不仅限于儿童期, 还可延续至青少年甚至成年期, 对个人、家庭和社会均产生一定的负面影响^[1-3], 因此加强 ADHD 发病机制等方面的研究, 对促进其防治具有重要意义。ADHD 在发病率、症状及预后等诸多方面均存在显著的性别差异^[4-7]。ADHD 儿童认知障碍的主要特征之一是执行功能(executive function, EF)损害^[8], 本文将就近年来

ADHD 儿童 EF 的性别差异及机制的相关研究进行综述。

1 执行功能概述

EF 是一种具有目的性、目标导向行为的高阶神经认知功能, 比如抑制行为和情绪、改变认知模式、制定计划等, 关于其具体组成部分尚未达成一致意见^[9-10], 核心成分包括抑制控制、工作记忆和认知灵活性, 推理、问题解决和计划等属于高阶执行功能^[11]。抑制控制是个体控制自身的注意力、行为、思想和/或情绪, 以克服强烈的内部倾向或外部诱惑, 转而做更合适或更需要事情的能力^[11]; 工作记

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忆是一种服务于当下任务的临时信息储存和处理系统;认知灵活性是个体在不同任务或目标之间进行转换的能力。根据是否具有动机和情感参与,EF 又可分为冷 EF(cold executive function, cEF)和热 EF(hot executive function, hEF),前者通常指在中性、抽象和非文本化的问题情境中发挥作用的认知技能,而后者通常涉及显著的动机和情绪调节^[12-13]。

目前用于评估 EF 的方法很多。Stroop 色词测验(Stroop Color and Word Test, SCWT)^[14]、停止-信号任务(Stop Signal Task, SST)^[15-16]、反应/不反应任务(Go/No-Go Task, GNG)任务^[17]可用于评估抑制控制;倒背数字任务(Backward-digit Recall Task)^[18-19]、N-back 任务^[20-21]可用于评估工作记忆;威斯康星卡片分类测验(Wisconsin Card Sorting Test, WCST)^[19]可用于评估认知灵活性。棉花糖实验及其变式、延迟折扣任务^[22]、爱荷华博弈任务(Iowa Gambling Task, IGT)^[23-24]、饥饿驴任务(Hungry Donkey Task, HDT)^[11, 24-25]可用于评估 hEF。

2 ADHD 儿童的执行功能缺陷

执行功能缺陷是 ADHD 的核心缺陷,工作记忆缺陷是执行功能缺陷的核心所在,从最初的冷执行功能受损,到冷、热执行功能均有损害,对 ADHD 儿童执行功能缺陷的研究和认识日益深入^[8]。已有大量研究证明 ADHD 儿童执行功能受损,比如:ADHD 儿童在 GNG、SST 表现更差,提示抑制控制能力受损^[26];在语言和视觉记忆任务中错误率更高^[26],提示工作记忆能力受损;在流畅性测验中表现更差^[27],提示认知灵活性受损;在 IGT 和 HGT 中的有利选择少于对照组^[24],提示 hEF 受损。

3 ADHD 儿童的性别差异

ADHD 儿童在诸多方面存在性别差异。世界范围内男女患病率之比从 2:1 至 10:1 不等^[3, 28]。发病率的性别差异可能与男女童的临床表现差异有关。ADHD 女童更多表现为注意缺陷症状,而男童则更多表现为多动症状;ADHD 女童常见共病语言障碍及智力障碍,而男童则以抽动障碍、孤独症谱系障碍(autism spectrum disorder, ASD)及运动协调障碍的共病更常见;ADHD 女童更多出现内化问题,比如焦虑症、情绪障碍等,而男童则更多出现外化问题,如破坏性和攻击性行为、对立违抗行为等^[28-31]。由于多动症状少见、更多出现内化问题导致父母及教师对 ADHD 女童的识别减少,就诊率降低,可能导致发病率的性别差异。

4 不同性别正常人群的脑差异

ADHD 儿童性别差异需考虑性别本身带来的脑结构和功能差异的影响,虽有文献结果不一致,但已有多项研究确认男女性的大脑结构和功能存在差异。基于健康人群的研究发现:1)女童的脑发育快于男童^[32],部分高级联想区域,如前额叶皮层,在女童中率先发育^[33-34];2)女性大脑默认模式网络(default mode networks, DMN)连接性高于男性,而 DMN 是一组分散的、相互关联的大脑区域,在专注于外部刺激时受抑制,与认知控制功能密切相关^[35-36];3)部分研究发现女性存在更强的网络内连接,而男性存在更强的网络间连接,但也有研究的发现与之相反,执行功能与网络间的连接程度密切相关(比如有时需要感觉运动系统和视觉系统的相互作用^[37-38]);4)男性在对情绪刺激做出反应时的杏仁核激活更强^[37, 39]。

5 ADHD 儿童 EF 的性别差异及脑机制

5.1 反应抑制的差异 Cole 等^[40]发现相较于对照组,ADHD 男童在细微体征的身体和神经检查(Physical and Neurological Assessment of Subtle Sign, PNASS)中表现出更多的运动节律异常(出现时机或节奏不当的运动)及溢出(伴随着自主运动的产生而出现的非自主运动),均与抑制控制有关,而在 ADHD 女童和对照组女童之间无此差异,且随年龄增长,ADHD 女童运动溢出明显减少,而 ADHD 男童并无;Crasta 等^[41]发现相较于对照组,ADHD 男童和女童的溢出运动并无显著差异,但呈现出一种男童溢出运动更多的趋势,随时间推移,ADHD 男童溢出运动较健康对照男童减少得更多,而 ADHD 及健康对照女童之间并无此差异。提示 ADHD 男童运动抑制明显受损,两者随时间改善的程度也存在差异,这或许可以解释为何 ADHD 男童会比女童表现出更多的冲动症状。在 GNG 任务中,ADHD 男童的反应速度及错误率高于对照组,而女童无此差异^[42],提示男童抑制控制受损更严重;ADHD 女童的反应准备时间(视觉引导的扫视时间)较男童更长^[43],提示女童或许有更多的认知加工过程,两者的认知加工模式不同,可能涉及工作记忆及认知灵活性;有学者更改了 GNG 任务中的认知需求变量,发现相较于对照组,ADHD 男童在简单和复杂(需要记住飞船数量,认知需求更高)的任务中均表现出更高的错误率及组内变异,而女童仅在复杂任务中有此表现^[26, 44],提示 ADHD 男童的

执行功能更容易受认知负荷的影响。也有荟萃分析表明,ADHD 男童在抑制控制及认知灵活性受损较女童更为严重,且抑制控制差异只表现在运动抑制方面^[4]。

抑制控制的性别差异可能与 ADHD 男童和女童脑皮层表面积和体积减少模式不同有关。男童中与基本运动反应控制相关的皮层,特别是初级运动皮层(primary motor cortex, M1),表现出表面积的减少,这可能与其抑制控制受损更严重有关;而女童则是与动机和情绪调节相关的前额叶皮层,特别是内侧眶额皮层(orbitofrontal cortex, OFC),表现出减少^[33,42,45-46],这可能与其 hEF 受损更严重有关。Mahone 等^[43]发现 ADHD 男童基底节体积较对照组减小、形态也有差异,且 ADHD 男童基底神经节受压变形区域位于运动前、动眼神经和认知(前额叶)控制回路内^[47];Tang 等^[48]发现 ADHD 男童的苍白球、壳核和丘脑、尾状核体积减小、形态异常,但女童中无上述发现^[48-50]。

5.2 工作记忆的差异 虽有文献结果不一致,但有部分研究发现 ADHD 儿童存在工作记忆的性别差异^[4,26,51]。有研究发现 ADHD 儿童的工作记忆缺陷涉及海马和额叶回路的结构和功能异常,这些区域的活性受糖皮质激素分泌的调节,而头发皮质醇浓度仅在 ADHD 男童中表现出与工作记忆缺陷症状呈负相关,因此下丘脑-垂体-肾上腺轴的性别差异或许与 ADHD 儿童 EF 工作记忆的性别差异有关^[52-53]。

5.3 认知灵活性的差异 ADHD 女童在复杂图形测验(评估 EF 的多个领域,包括计划、反应抑制、注意和组织能力)中表现差于男童^[46]。相较于对照组,ADHD 女童在 Delis-Kaplan EF 系统评估(D-KEFS)所有 EF 成分均有损害,包括基本和高级技能,而 ADHD 男童仅在更基本的功能(反应抑制)和工作记忆方面受损^[51]。提示女童在认知灵活性和高阶执行功能上受损更严重。

有研究发现,在工作记忆及转换任务中,相较于对照组,ADHD 男童表现为双侧额叶(包括运动前皮层和辅助运动区)、双侧顶叶皮层、左侧顶下小叶和右侧顶上小叶的低激活,右侧杏仁核和左侧颞上回的高激活,运动前皮层和辅助运动区参与运动序列和计划、工作记忆和视觉空间注意,右侧顶上小叶的下游部分与抑制、工作记忆和注意力过程有关;而 ADHD 女童则表现为基底节和小脑的低激活,其中,额-小脑回路与转换能力密切相关^[54-55]。以上发现或许可以解释女童为何在认知灵活性和高阶执行

功能上受损更为严重。

5.4 动机相关的执行功能差异 在 HDT 中,ADHD 男童表现优于女童,女童随时间的恶化更为明显^[24]。在延迟折扣任务中,ADHD 男童比女童更倾向于选择较大的延迟奖励^[56]。在 GNG 任务中加入动机因素(金钱收益或损失的反馈)后,相较于对照组,ADHD 男童在标准(无动机因素)任务中表现出更高的组内变异、在动机化任务中表现出更低的组内变异,而女童仅在动机化任务中组内变异高于对照组^[57],提示 ADHD 女童的执行功能更容易受动机的影响。

有研究发现,在延迟折扣任务中,ADHD 儿童纹状体区域的正功能连接更强,杏仁核区域的负功能连接更弱,对女童表现的影响更大;此外,ADHD 女童背侧前额叶的功能连接表现出额外异常,包括更强的前扣带回正功能连接和背外侧前额叶负功能连接^[56]。前额叶与联想功能有关。上述发现或许可以解释为何女童在 hEF 上受损更为严重,可能与女童会表现出更多的内化问题有关。

6 展 望

EF 缺陷是 ADHD 发病的重要一环,对 ADHD 儿童的 EF 研究已成为一大热点。大部分研究在男童中展开,仍需更多研究将女童纳入实验,在发病率、临床表现、诊断标准、预后、产生机制等多个领域展开广泛研究,从而制定个性化的评估及治疗方法,提高 ADHD 儿童的诊断率并改善其预后。大脑成像技术的飞速发展(例如,扩散张量成像和脑磁图)使人们在认知任务中能更准确、直接地观察到各脑区之间的功能和解剖关系,是机制研究的一大助力。目前的研究大部分借助脑成像技术、围绕神经解剖差异展开,少有分子生物学层面的研究,但神经解剖的差异源于性染色体差异,与男女发育过程中的激素及神经递质调节密不可分,有待进一步研究。此外,也需考虑男女的脑发育轨迹差异,不仅需要横断面研究,也需要前瞻性研究。

综上,ADHD 儿童 EF 存在显著的性别差异,主要体现在抑制控制、认知灵活性、hEF 上,但各研究结果不尽相同。对 EF 差异的机制研究并不多,大部分局限于脑功能区,少有分子生物学层面的研究。EF 缺陷是 ADHD 的核心缺陷,全面深入了解这些差异并探究其机制,有助于进一步了解 ADHD 的发病过程,促进其防治。

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