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运动技能学习的小脑环路机制

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摘要: 小脑在调控平衡、协调和姿势等运动功能以及认知和情绪等非运动功能方面均发挥关键作用。小脑发育障碍和病理性环路出现在多种运动障碍疾病以及伴有运动技能学习障碍的神经发育性疾病中。本文综述了运动技能学习的定义、特征和可能涉及的脑区, 总结了参与调控运动技能学习的小脑环路特征, 以及小脑发育异常与运动技能学习障碍的关联性。

关键词: 小脑; 运动技能学习; 环路发育; 神经发育性疾病

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Cerebellar neural circuits for motor skill learning

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Abstract: The cerebellum plays a key regulatory role in motor functions such as coordination, balance and posture, as well as in non-motor functions such as cognition and emotion. Motor skill learning disabilities account for many psychiatric and neurodevelopmental disorders. In order to clarify the mechanism related to motor skill learning in cerebellum, we summarize the definition and characteristics of motor skills learning, and the possible brain regions, and then mainly discuss circuits involved in motor skill learning, and the association between cerebellar dysplasia and motor skill learning disabilities.

Key words: cerebellum; motor skill learning; circuit development; neurodevelopmental diseases

哺乳动物以及人类个体获得复杂的运动技能需要学习许多不同的运动成分, 其中两个基本要素是校准感觉运动和完成任务所需的动作序列。这两个基本要素可能依赖于不同的神经基质和生理机制, 如小脑和初级运动皮层 (primary motor cortex, M1)。然而, 人们对加工这些成分的特定神经生理过程仍然知之甚少。小脑是人脑中最重要的区域之一, 与大脑运动皮层保持着大量的神经连接, 其体积仅为大脑总体积的 10%, 却包含了脑部超过 50% 的神经元, 控制着运动协调、精细运动和运动学习等运动功能, 也调控认知和动机过程等非运动过程^[1-2]。自 20 世纪 70 年代起, 关于小脑在运动技能学习中的作用研究逐渐增加。关于小脑发育障碍与多种疾病包括共济失调、肌张力障碍、震颤、精神分裂症、阅读障碍、孤独症谱系障碍 (autistic spectrum disorder, ASD)、注意缺陷与多动障碍 (attention deficit and

hyperactivity disorder, ADHD) 和脆性 X 综合征 (fragile X syndrome, FXS) 的关联性也逐渐被深入认识^[1, 3]。本文综述了运动技能学习的定义和特征、可能涉及的脑区, 重点阐述了小脑的结构、环路发育以及小脑环路损伤相关的运动技能学习障碍和神经发育性疾病。

1 运动技能学习

运动技能是指动作的精确执行, 例如, 网球运动员选择在正确的时刻激活肌肉, 以最大的精确度完成所需动作, 又如骑自行车、拉小提琴、用鼠标指针精确地指到屏幕目标点等^[4]。与习惯不同, 运

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动技能习得的技能未必会被重复使用,但会涉及到习惯的许多特征,它们都是后天习得的,经过一定强度的训练后,变得自动、定型且巩固^[5]。运动技能通常需要经过多次训练慢慢学习,直到表现达到近乎渐近准确完美的水平。在不同的实验范式中,技能获得的发展最初相对较快,后来当多次训练以逐渐增加完美性时,发展较慢^[6]。复杂的运动技能通常由固定的动作序列组成^[7],目前许多关于运动技能的研究都集中在序列学习上,在这种学习中,动作的执行顺序比动作本身的执行质量更受关注^[8]。学习以适当的顺序选择所要执行的每个动作,并最终自动或常规的方式生成序列^[9],这对于许多运动技能来说至关重要。

运动技能学习是指通过练习来更快、更准确地执行任务的过程。当系统产生错误时,会接收到一个有方向性的误差信息,利用这一反馈,系统进行针对性改正,基于对感觉线索的反应以调整所执行的运动任务,指导动作缓慢变化,逐步调整到比基线更好的行为结果。运动技能学习完全依赖于程序性记忆系统^[10],而不是陈述性记忆系统。探索性的、替代性的行为是技能学习早期的痕迹,而一旦技能巩固,自动的刻板印象就会出现。

Dayan 和 Cohen^[11]认为,运动技能学习的相对持续时间与任务相关。例如,学习简单的四分量按键序列的快速阶段可能持续几分钟^[12],而学习演奏复杂乐曲的快速阶段可能持续数月。技能的改变可以在训练期间进行,也可以在训练结束后休息状态下线下加工。线下加工可以使得技能稳定和提高,属于运动记忆的巩固阶段^[13-14]。训练期间和训练结束后技能的增长可以随着时间的推移而保持,从而长期保留^[15]。

2 大脑在调控运动技能学习中的作用

在哺乳动物中,参与调控运动技能学习和执行的大脑环路包括眶额叶皮质 (orbitofrontal cortex, OFC)、前额叶皮质 (prefrontal cortex, PFC)、前扣带回皮质 (anterior cingulate cortex, ACC)、运动前皮质 (premotor cortex, PMC)、辅助运动区 (supplementary motor area, SMA) 和运动皮质 (motor cortex, MC)。它们按照分层方式组织, OFC 参与抽象概念的评估和操作^[16], PFC 和 ACC 参与商议过程, ACC 也可能有助于新的序列学习^[17], 运动区参与行为的表达^[18], 它是大脑和肌肉骨骼系统之间的连接纽带。SMA 在序列运动中起着重要作用^[19], 该区的许多神经元

在特定的序列转换时变得特别活跃,而对非特定的运动则无反应^[20]。前辅助运动区 (PreSMA) 是位于 SMA 前面的皮质区域, Nakamura 等^[21]发现, PreSMA 中的许多神经元在学习新序列的过程中被激活,但在学习序列的执行过程中不被激活。此外,对 PreSMA 的功能性阻断导致了学习新序列的选择性缺陷^[22]; 在这些结果的基础上, Tanji^[19]认为 SMA 和 PreSMA 一起工作,以正确地产生序列动作。

除了 PreSMA, M1 也与运动学习有关^[23]; 在简单的运动学习过程中, M1 的功能^[24]和结构^[25]都发生了变化。为了协调控制多个关节,需要肢体动力学来补偿关节间的相互作用力。在灵长类动物和人类中的研究表明, M1 具有这种能力^[26]。技能的提高伴随着 M1 的可塑性变化,如手指顺序运动的速度和准确性的提高与 M1 中 GABA 激活的增加相关^[12, 27], 而 M1 上重复的经颅磁刺激则抑制其速度和准确性^[28]。除此之外, Darling 等^[29]发现,手指灵巧性运动受损的持续时间也与 M1 病变体积相关。综上, SMA 和 M1 均是参与运动技能学习的重要脑区。

此外,精确定时的运动学习通过增强少突胶质细胞的再髓鞘化,促进脱髓鞘损伤恢复^[30]。少突胶质细胞及其祖细胞的抑制导致运动学习和远程恐惧记忆巩固的缺陷,提示胶质细胞功能与学习过程之间的因果关系^[31]。然而,由于技术原因,形成髓鞘的神经胶质细胞如何调节神经环路以及影响学习和行为的潜在机制尚不清楚,仍需借助新技术阐明这一机制。

3 小脑结构与内部环路在加工运动技能学习中的作用

除了以上提到的大脑结构之外, Baldassarre 等^[7]发现早期运动训练学习与小脑内的功能联系显著相关。小脑小叶 VI 和 VII 是小脑中最宽的区域,它们的外侧半球从蚓部延伸得最远,属于新小脑或者皮层小脑^[32-33], 新小脑与大脑顶叶和前额叶皮质存在纤维联系^[34], 与杏仁核、海马等边缘区域也有着丰富连接^[35], 表明新小脑与大脑认知和情绪、自主神经功能以及感觉运动控制有着重要联系^[32]。

小脑皮层包含兴奋性神经元和抑制性神经元。兴奋性神经元利用谷氨酸作为主要神经递质 (谷氨酸能神经元), 包括颗粒细胞 (granule cell, GC) 和单极刷状细胞 (unipolar brush cell, UbC)^[36]。抑制性神经元利用 γ -氨基丁酸 (GABA) 和 (或) 甘氨酸 (以

下简称 GABA 能神经元)为主要神经递质, 包括浦肯野细胞 (purkinje cell, PC) 和中间神经元, 如高尔基细胞 (Golgi cell, GoC) 和星状细胞 (stellate cell, SC)。篮状细胞 (basket cell, BC) 是一种 GABA 能中间神经元, 将轴突投射到 PC, 存在于哺乳动物的小脑中。小脑分子层中间神经元在调节小脑输出和运动学习方面起着重要作用, 它们通过 GABA 能化学突触和电突触相互连接^[37]。

在小脑内部环路中, 小脑皮层接受两个主要的输入: 一个包括苔藓纤维 (mossy fiber, MF) 系统, 它将感觉信息从各种小脑前核传递到 GC 树突, GC 树突再通过平行纤维 (parallel fiber, PF) 传播这些信息 (图 1); 另一个源来自攀缘纤维 (climbing fiber, CF) 系统, CF 起源于下橄榄, 并“攀爬”到 PC 树突上。通过 CF 传递到 PC 的信息对于小脑的联想学习至关重要^[38]。MF-PF 系统和 CF 系统共同构成对 PC 的兴奋性输入。PC 接受局部 GABA 能分子层中间神经元的抑制性输入, 分子层中间神经元继而接收来自 PF 的突触输入。此外, GC 的兴奋性输入受到位于 GC 层的抑制性神经元 GoC 的调控, GoC 还接收来自 MF 的输入^[39]。PC 抑制其他邻近的 PC 和中间神经元^[40], 分子层中间神经元抑制其他分子层中间神经元的空间结构^[41-42], GoC 抑制其他 GoC^[43]。在某些区域, PC 的侧支与 GC 接触, 并在输入层形成额外的循环连接^[44]。

以往研究表明, 小脑是一台“有监督的运动学习”机器。小脑的“内部状态”不断地被 MF“命令”信号, 以及被来自外周感觉或运动反馈的 CF“错误”信号所改变。PF 和 PC 之间的突触可塑性 (主要是长时程抑制) 被认为是基于小脑的运动学习的一种机制^[45]。通过 MF 进入小脑的信号在颗粒层被处理并传输到 PC, 而侧支通路激活小脑深部核团 (deep cerebellar nucleus, DCN), PC 反过来抑制 DCN, 使

小脑皮层作为控制 DCN 的侧环运作。最近有研究表明, 小脑 IV/V 叶存在一条 GABA 能 PC 环路, 投射到顶核的 CaMKII α + 神经元, 调控感觉运动协调功能^[46]。Schonewill 等^[47] 和 Sugihara 等^[48] 也曾发现小脑半球外侧部 PC 靶向投射到齿状核和间位核的腹侧区域, 参与眼球运动的控制。现在已经知道, 学习是通过颗粒层、分子层和 DCN 中多个突触连接的可塑性来实现的, 这扩展了运动学习理论的最初概念。利用先进的生理记录和计算模型对小脑动力学进行研究, 为进一步认识小脑网络如何进行内部计算提供了新的线索^[49]。

4 小脑与外部连接环路在加工运动技能学习中的作用

小脑的输入信号有以下三种: (1) 通过脑桥核传递的大脑皮层信号; (2) 脑干核团 (包括丘核、前庭核、脑干网状结构核团和下橄榄核) 信号; (3) 经脊髓小脑背侧束和脊髓小脑腹侧束传递的脊髓信号。

小脑的输出信号仅通过小脑深部核团发出, 小脑深部核团自身投射到各种脑干核团 (主要是脑干网状结构核团、红核、前庭核、下橄榄核), 并通过丘脑发送到大脑皮层。小脑深部核团分为顶核、间位核和齿状核三个核团, 其中顶核投射到前庭核, 最终到达脊髓; 间位核与齿状核投射到丘脑的红核和腹外侧核, 最终到达运动皮层^[50]。前庭小脑部分直接投射到位于脑干的前庭神经核。

关于大脑-小脑环路的经典观点认为, 小脑与对侧大脑存在多突触环路相互连接。新皮质区域的信息, 包括额叶、顶叶、颞叶和枕叶的一部分^[51], 传入到达丘脑底核, 经由脑桥核传递, 然后交叉到小脑^[52]。传递到小脑的信息由小脑内部环路加工, 输出信号首先到达小脑深部核团, 然后投射到丘

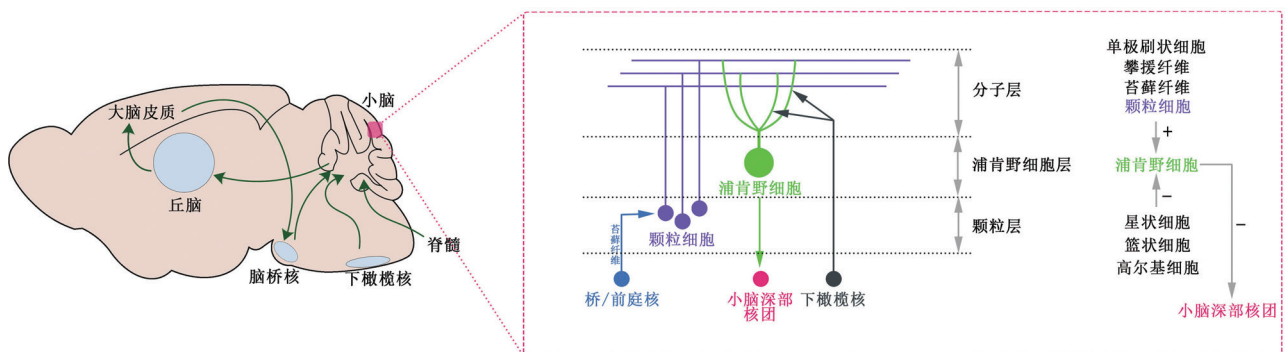


图1 大小脑主要的输入和输出环路示意图

脑的多个区域,在丘脑腹外侧核反馈回大脑的M1区^[53],进而投射到新皮质区域包括腹侧运动前区、背侧运动前皮层和辅助运动区、前额叶和后顶叶区域^[54-55]。与M1不同,Pre-SMA脑区虽然接受小脑的投射,但从整体看,Pre-SMA脑区以接收基底节的投射为主^[56]。因此,小脑与大脑皮层的联系被认为是一种从大脑皮层不同区域收集信息的手段^[57],以便在M1水平上影响运动的产生和控制。此外,小脑将感觉预测与实际感觉反馈进行比较^[58]。在存在错误或偏离预测的情况下,小脑会发出校正信号,这些信号可以通过脊髓直接影响运动或通过大脑皮层间接改变运动计划本身。另外,在持续偏离预测的情况下,小脑通过可塑性学习修改内部正向模型。Palesi等^[59-60]通过磁共振成像研究表明,几乎整个大脑皮层与小脑通过特定的双向通路进行交流。因此,小脑的输出完全在运动环路控制的范围内,这个环路中的异常活动将导致运动障碍。

5 小脑环路损伤相关的运动技能学习障碍与神经发育性疾病

小脑发育过程中产生的病理性环路缺陷与许多运动技能学习障碍有关,如小脑性共济失调(cerebellar ataxias, CA)和肌张力障碍,同时也与多种神经发育性疾病的行为障碍有关,如ASD、ADHD和FXS。

5.1 小脑性共济失调(CA)

CA是一组由遗传和后天原因引起的小脑及相关系统功能障碍引起的步态障碍。CA通常以缓慢进展的身体不协调为特征,可表现为典型的小脑运动缺陷,如步态共济失调、运动障碍、坐骨神经运动障碍、构音障碍和眼球震颤。其中,Friedreich共济失调症为隐性小脑性共济失调,由位于9号染色体长臂的FRDA基因缺陷所致。大多数患者初时表现为闭眼或在弱光环境下的步态障碍,随着病症发展,出现导致跌倒的步态不稳^[61]以及深腱反射的缺失,共济失调的小脑特征也逐渐明显。早期神经影像学研究显示小脑上脚和齿状核体积减少明显^[62],且与病程和严重程度有关^[63-64]。晚期脑白质受累,小脑灰质体积减少,其中I~VI小叶的体积减少最多^[64]。

5.2 肌张力障碍

肌张力障碍是一种以肌肉持续异常收缩为特征的神经系统疾病,经常导致异常的维持姿势。影像学研究揭示静息状态时肌张力障碍患者小脑新陈代

谢的变化,发现小脑与皮质感觉运动区之间的功能连接性降低^[65]。利用神经成像技术观察到原发性肌张力障碍患者的感觉运动区、运动前区和顶叶皮质、基底节、丘脑和小脑的灰质增加或减少和白质改变^[66]。有研究报道,在执行感觉运动任务时,眼睑痉挛^[67]和书写痉挛^[68]患者的小脑存在异常激活。尽管小脑环路异常可能导致肌张力障碍,但因果关系远未确立^[69],还需要进一步的研究。

5.3 孤独症谱系障碍(ASD)

高达80%的ASD儿童表现出运动协调缺陷,如缺乏协调性、姿势稳定性差,这些缺陷与自闭症严重程度和智商高度相关^[70]。运动障碍是ASD最早可识别的临床异常之一,被广泛研究^[71-72]。

ASD患者局部结构和运动功能异常,可以通过大脑-小脑环路与运动的关联性解释。有研究发现,小脑小叶IV、V和VIII的灰质减少与重复和刻板印象行为的严重程度相关^[73]。相较于同龄正常人,ASD患者的小脑在运动任务中激活减少,从而导致失误次数增加和反应时间较慢^[74]。Skefos等^[75]用系统抽样法检查ASD患者中PC密度的区域变化,发现PC密度在小脑crus I和crus II中受到最大影响,而仅在男性患者的小脑小叶X中降低,这个区域与前庭调节、注视协调以及患者使用社交眼神接触有关。

5.4 注意缺陷与多动障碍(ADHD)

30%~50%的ADHD儿童会出现运动问题,表现出较差的运动控制能力^[76],并且导致严重后果^[77]。研究报告发现,ADHD儿童的姿势摆动不良,这种姿势缺陷在闭眼时更加明显^[78-79]。ADHD儿童的平衡控制功能受到损害,可能是因为它需要整合来自各种感觉系统(即躯体感觉、视觉、前庭)的输入,以维持身体平衡。

与ASD一样,小脑结构异常是ADHD中最一致的发现之一^[80]。小脑的体积减少持续发生在ADHD患者的整个发育过程^[81],ADHD症状的严重程度随着小脑体积减少的程度而增加^[81-83],强调了小脑在ADHD临床诊断中的重要作用。此外,静息状态fMRI研究显示ADHD患者的大脑-小脑连接异常^[84],ADHD儿童的顶上皮质和小脑表现出比发育中儿童更低的功能连接密度,这与注意力不集中和冲动、多动等症显著相关。因此,越来越多的证据强调了小脑在ADHD的病理生理中起主要作用^[85]。此外,Hove等^[86]发现,大幅度摆动与后运动区较大的小脑区域体积有关,这为小脑参

与 ADHD 的病理生理提供了额外支持。

5.5 脆性X综合征(FXS)

运动技能学习障碍是 FXS 和 ASD 的共同特征^[87]。近年来的 FXS 发病机制研究多集中在大脑, 不过学界已经认识到 FXS 患者小脑发育异常与临床症状之间的关系可能被忽视^[88-89]。神经影像学证据表明 FXS 患者新小脑外侧部和蚓部结构异常^[88-89], 尸体解剖观察发现 FXS 病亡者小脑小叶 VI-VII 选择性发育异常、灰质变薄、体积减少, 白质也发育异常^[90]。这些小脑外侧区域结构异常与 FXS 患者中观察到的许多行为和认知异常一致, 可能是 FXS 患者运动技能学习障碍的原因。Koekkoek 等^[91]发现在作为 FXS 模型的 *Fmr1* KO 小鼠中, PC 上的树突棘拉长, 但树突棘总数没有受到影响。在行为上, 这些小鼠表现出经典延迟眨眼条件反射的缺陷, 这是一种依赖小脑的联想学习形式, 类似于 FXS 和 ASD 患者^[91-92], 并显示出显著的口腔运动缺陷, 这可能与 FXS 患者的发音缺陷有关^[93]。

6 总结

本文阐明了运动技能学习和运动技能学习障碍的小脑环路机制。小脑作为运动学习的主要脑区, 浦肯野细胞同时接受来自平行纤维和攀缘纤维的谷氨酸能神经投射, 与小脑内部颗粒层、分子层和小脑深部核团之间形成多突触可塑性, 大脑和小脑不断地得到信息反馈, 使动作更加完美, 且更适应于当时的环境条件和需要, 完成整个运动学习过程。小脑发育障碍和小脑病理性环路导致运动技能学习障碍, 可能是 ASD、ADHD 和 FXS 等神经发育性疾病的共同病理基础, 但是神经发育性疾病患者的小脑发育异常与运动技能学习障碍之间的关系研究还比较局限。因此, 未来探索 FXS 等神经发育性疾病患者运动技能学习障碍的小脑环路机制, 具有重要的科学意义。

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