DOI: 10.13376/j.cbls/2020017
文章编号：1004-0374(2020)02-0125-14

小脑参与神经退行性病变过程的研究进展

韩 曼#，薛宪鹏#，李金泉，曾 燕*
(武汉科技大学脑科学先进技术研究院，大数据科学与工程研究院，武汉 430070)

摘 要：小脑与大脑之间存在丰富的神经网络连接，除了精确调控运动以外，还参与调控学习记忆、情感等高级脑功能。小脑不同区域的功能障碍还与阿尔茨海默病、帕金森病、亨廷顿病、额颞叶痴呆和肌萎缩侧索硬化等神经退行性疾病特定临床症状发生之间相互关联。本文综述了小脑调控高级脑功能，以及小脑病变在几种神经退行性疾病的病理特征和临床症状发生方面的研究进展，以期为认识小脑神经退行性病变与高级脑功能受损之间的关系提供资料。

关键词：小脑；认知；情绪；神经退行性疾病
中图分类号：Q42；R742 **文献标志码：**A

The advanced progress in understanding the cognitive function of the cerebellum and the relationship between cerebellum and neurodegenerative disorders

HAN Man#, XUE Xian-Peng#, LI Jin-Quan, ZENG Yan*
(Brain Research and Advanced Technology Institute, Big Data Science and Engineering Research Institute, Wuhan University of Science and Technology, Wuhan 430070, China)

Abstract: The cerebellum has a well-established role in controlling motor functions such as coordination, balance, posture, and skilled learning. There is mounting evidence that it might also play a critical role in non-motor functions such as cognition and emotion. It is therefore not surprising that cerebellar deficits are associated with a wide array of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, frontotemporal dementia and amyotrophic lateral sclerosis. While cerebellar neurodegeneration commonly manifest with alterations to motor function, it is now well established that the cerebellum governs non-motor function through regulation of widespread cortical and subcortical brain regions. It is thus of great clinical significance to understand the higher functions of the cerebellum. This review discusses the advance in recognition of cerebellum's involvement in high-level cognitive/emotional functions, and characterizes cerebellar pathological changes accompanying neurodegenerative disorders.

Key words: cerebellum; cognition; emotion; neurodegenerative disorders

小脑的主要功能在很长一段时间里被认为是维持躯体平衡、协调运动以及调节肌张力。自 20 世纪 70 年代起，关于小脑在高级功能中的作用研究不断增加[1-4]。1998 年，麻省总医院神经病理学家 Schmahmann 等[5]发现小脑受损后，患者会出现诸如抽象推理能力损伤和情绪调节障碍等变化，进一步拓展了小脑的研究范围。现如今，越来越多的证据表明小脑不仅调控运动功能[6-7]，还参与调控学习记忆、情感等高级脑功能[8-9]，且小脑病变在阿尔茨海默病 (Alzheimer's disease, AD)、帕金森病 (Parkinson's disease, PD)、亨廷顿病 (Huntington's disease,

收稿日期：2019-05-28；修回日期：2019-11-14
基金项目：国家自然科学基金项目(81870901)；武汉科技大学大学生科技创新基金项目(17ZRB063)
*通信作者：E-mail: yanzeng11@foxmail.com
#共同第一作者

HD)、额颞叶痴呆 (frontotemporal dementia, FTD) 和肌萎缩侧索硬化 (amyotrophic lateral sclerosis, ALS) 等神经退行性疾病患者脑中被检出，与这类患者某些特征性临床症状有关 [10-11]。小脑的神经退行性病变和传入传出神经连接损伤通常首先外在表现为运动功能改变，但也表现为非运动功能改变。小脑体积虽然只占全脑的 10%，但其却具有超过全脑 50% 的神经元。这些证据均暗示小脑可能在机体非运动功能中充当着更为重要的角色。本文综述了小脑参与调控高级功能以及小脑神经退行性病理变化特征方面的研究进展，以期为临床工作者认识小脑神经退行性病变在高级脑功能受损过程中的作用提供资料。

1 小脑参与调控认知功能及情绪的研究进展

小脑 (cerebellum) 位于大脑后下方的颅后窝内，分为绒球小结叶和小脑体两大部分，小脑体又分为中间的蚓部和两侧膨大的小脑半球 (图 1)。小脑在感觉运动处理过程中发挥着举足轻重的作用 [12]，是脊椎动物中枢神经系统 (central nervous system, CNS) 最复杂的区域之一，包含成人脑组织中超过一半的成熟神经元 [13]。虽然传统的神经科学研究多集中解析小脑在维持平衡、调节姿势以及控制运动方面的功能 [14]，认为小脑对完成完整的运动功能至关重要 [15]，但是越来越多的证据表明小脑在认知和情感处理中也发挥着重要作用，这使得小脑在非运动功能中的作用正被逐渐重视 [16]。

小脑参与调控脑认知功能的部分主要是新小脑。根据纤维联系，小脑可分为接受前庭器官输入的前庭小脑 (绒球小结叶)、接受脊髓输入的脊髓小脑 (蚓部和小脑半球内侧部)，以及接受大脑皮层输入的皮层小脑 (图 1)。皮层小脑为小脑半球的外侧部，在进化上出现最晚，也叫做新小脑 (neocerebellum)。与小脑的其他小叶相比，小叶 VI 和小叶 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 [11]，具有认知加工 [17]、功能执行 [18]，以及高阶思维过程调控等功能 [19]。如图 1 所示，新小脑与大脑皮质相关区域，特别是顶叶和前额叶皮质区域存在纤维联系 [20-21]。这些复杂的、完整的连接表明新小脑与大脑认知和智力神经回路以及情绪、自主神经功能和感觉运动控制有着重要联系 [22]。因此，小脑和大脑之间正确的相互作用对于认知功能来说是必要的 [5,23]。本文将从结构、环路及细胞分子水平阐述小脑的高阶功能。

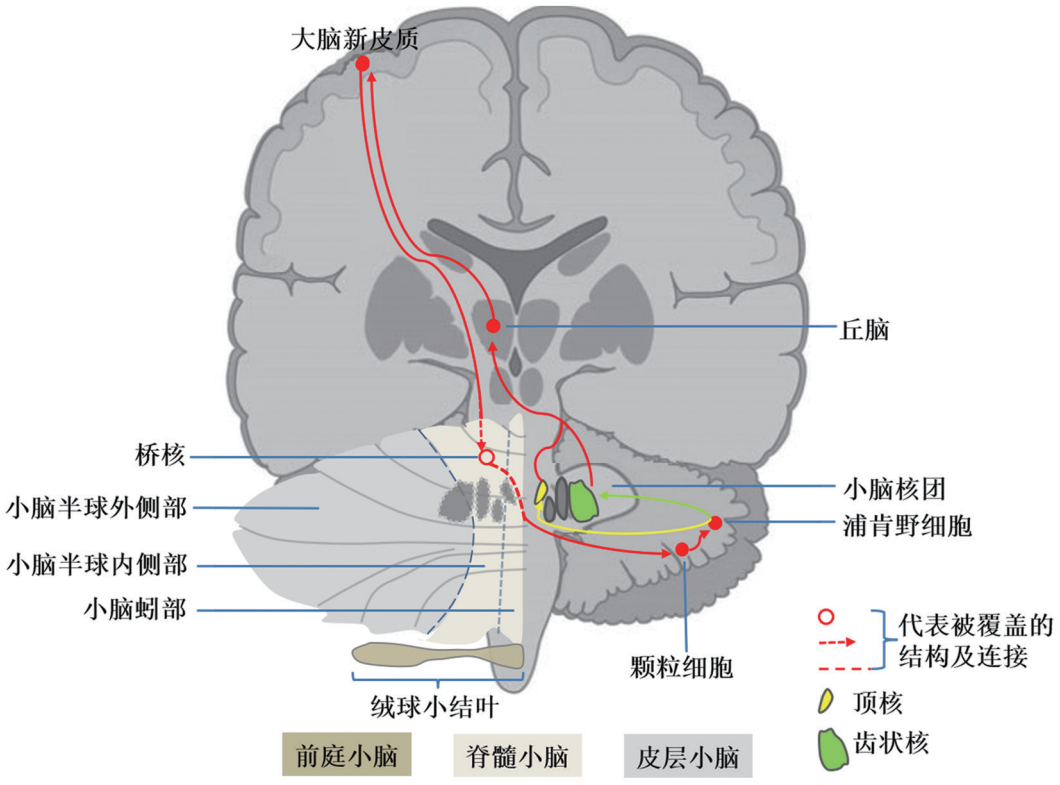

图1 小脑结构及大脑、小脑主要的输入和输出回路示意图

1.1　工作记忆

工作记忆是一种允许在认知任务中临时存储和处理信息的系统[24]，如推理、学习和语言理解[25]，工作记忆任务的成功完成需要对信息进行编码、存储和检索[26]。多项研究指出小脑调节言语工作记忆，小脑损伤患者会出现言语工作记忆障碍[27-29]。Küper等[30]对受试者进行n-back任务的功能性磁共振成像(functional magnetic resonance imaging, fMRI)，检测结果表明，在工作记忆任务中，小脑皮质的激活随着执行需求的增加而扩大，并且在工作记忆任务后的新皮质激活也会对更高的工作记忆负荷做出反应，就像小脑激活时的反应一样[31]。小脑激活增加可以映射到4个不同的区域：(1) 小叶VI和Crus I的边界区域；(2) 小脑外侧下部(小叶Crus II、VIIb、VIII、IX)；(3) 小脑旁蚓皮层的后部(小叶VI、Crus I、Crus II)；(4) 小脑下蚓部(小叶VI、VIIb、VIII、IX)，尤其是外下侧小脑在响应更高的执行需求时活性明显增强。此外，齿状核也被激活[30]。小叶VIIb和VIII也已被公认为工作记忆的参与者[32]，其具体功能与维持阶段的信息存储有关[33]。

研究表明，小脑可能通过皮质-小脑环路调节基底神经节(basal ganglia, BG)的信息过滤过程[34-35]，参与工作记忆的执行控制，阻止无关信息进入工作记忆[36-37]。Luis等[38]通过对一组健康老年人工作记忆的研究发现，在需要更高执行需求的任务中，除了前额叶皮层、顶叶皮层和BG等可能处理加工工作记忆功能的区域活性增强以外，小脑也被明显激活，特别是小脑内部小叶VIIIA/Crus I与小叶VI之间的连接，以及前额叶区与小叶VIIIA/Crus I之间的皮质-小脑连接增强。此外，在静息状态功能连接性研究中也发现，小叶Crus I和VI与额叶和顶叶一起参与执行控制网络(executive control network, ECN)[39]。影像学研究表明，小脑损伤影响额叶皮质-小脑顶核环路网络的功能，从而导致加工工作记忆受损[40]。

Du等[41]使用小脑经颅磁刺激(transcranial magnetic stimulation, TMS)和同步脑电图(electroencephalography, EEG)检测刺激后受试者前额皮质区域的电活动，并使用磁共振波谱(magnetic resonance spectroscopy, MRS)检测前额皮质γ-氨基丁酸(γ-aminobutyric acid, GABA)和谷氨酸水平来确定它们是否与这些电活动相关。结果表明，小脑刺激引起的前额皮质电活动受到GABA调节，与工作记忆相关。对灵长类动物的追踪研究也提示小脑齿状核-前额皮质投射参与工作记忆[42]，如图1所示。也有研究表明，代谢型谷氨酸受体1/5 (metabotropic glutamate receptor 1/5, mGluR1/5)参与小脑中长时程增强(long-term potentiation, LTP)和长时程抑制(long-term depression, LTD)的形成，进而调控陈述性和程序性记忆的形成。而小脑浦肯野细胞(Purkinje cell, PC)中抑制或缺乏mGluR1/5信号转导会导致PC功能障碍，抑制平行纤维-LTD的产生[43]。Martin等[44]对PC缺失的小鼠进行延迟位置匹配任务的研究结果表明，小脑在空间工作记忆中起着次要或间接的作用。2019年，研究人员对小鼠小脑PC进行光遗传学刺激发现，小鼠通过降低在工作记忆中有效保留过去信息的能力从而减弱了决策能力，表明小脑可以影响工作记忆的准确维持[45]。2018年的动物研究还发现，小鼠依靠额叶皮质-小脑顶核环路来控制运动前的感觉分辨和下一步运动方向的计划，如果损毁小脑顶核则导致小鼠这一功能受损，但不影响小鼠对运动任务的执行[46]。

1.2　语言功能

小脑是神经科学研究过程中较晚被探索的结构，特别是如何参与调控语言功能则更少被关注。韦尼克早期关于失语症的著作中，也仅仅推测了小脑可能参与语言功能的调控[47]。大约25年前开始，随着语言功能研究领域的变革，人们对小脑参与控制语言功能的兴趣持续增加[48]。研究人员使用词语流畅性实验范式(如动词生成、言语流畅、口头工作记忆)发现，小脑的后外侧右半球(小叶VI、Crus I和II)与语音和语义处理有关[36,49-51]；使用动词和单词生成范式也会激活小叶VI、Crus I和VIIIA的右后侧区域[36]；此外，几项使用TMS或经颅直流电刺激(transcranial direct current stimulation, tDCS)的脑刺激研究也已经说明了小脑对语言功能的贡献[52-53]。这两种刺激方法都可以通过增强或破坏刺激部位的神经功能起作用，即当使用TMS时，发现小脑接受刺激(特别是右侧小脑半球)后，会损害音素流畅性和词汇决定准确性，同时也会增强词汇联想性[52,54]；当使用tDCS时，在右侧小脑上施加刺激有助于促进动词生成任务的表现[27,55]。D'mello等[56]使用tDCS和fMRI相结合的方法，发现语义预测任务中小脑右侧Crus I/II的激活增加，皮质-小脑连接也增强。

Argyropoulos等[57-60]开发的一项词汇决策任务表明小脑在语言预测中的作用。小脑患者可能出现前馈语言控制系统受损，对受干扰的听觉反馈的预

期反应减弱，这表明小脑对于保持准确的语言前馈控制至关重要，但相对不参与反馈控制[61-64]。在语言预测过程中，fMRI 显示右后外侧小脑 (推测为 CrusI/II) 的活动与即将到来的目标词的可预测性相关，小脑区域的活动也与实验结果中的预测误差有关[63-64]。Bonhage 等[65] 也使用 fMRI，发现单词和单词类别的预测在包括丘脑、海马以及小脑的网络中诱发活动。正确的预测不仅会引起右小脑 Crus I/II 活动的升高，还会加强右小脑 Crus I/II 与大脑阅读 / 语言网络之间的静息状态功能连接[56,66]。小脑蚓部 / 副蚓部受损的患者阅读错误数量增加，这可能是由于小脑到不同的大脑皮层和皮层下结构的连接系统改变所致[67]。Gizewski 等[68] 利用 fMRI 技术对盲人在阅读盲文时的小脑激活进行研究，发现所有阅读盲文的盲人都表现出右侧小叶 IV、V 和 VIIIA 的内侧激活以及双侧 Crus I 的强烈激活，以右侧更为明显。

大量的神经影像学和刺激研究均证明了小脑在语言功能中的作用，且这种功能联系得到结构和功能连接分析的支持。静息态功能磁共振成像 (resting-state functional magnetic resonance imaging, RS-fMRI) 研究证据表明，小叶 VI、Crus I、Crus II 和 VIIb 接受前额叶、后顶叶和颞上皮质的投射，而这些皮质与语言功能有关[36,69-71]，如图 1 所示。Guediche 等[72] 对参与者进行的单词识别任务和 fMRI 分析表明，小脑右侧 Crus I 参与了语言感知的适应性变化，且适应期间大脑皮层血流动力学反应同步变化的功能相关性分析显示，小脑与颞叶和顶叶的语言相关区域之间存在功能连接。Alvarez 等[73] 的研究还发现了小脑与背侧额顶叶通路连接的语音回路，以及小脑与腹侧额顶叶通路连接的语义回路。通过建立一种静息状态的功能成像新技术，McAvoy 等[74] 对受试者进行语义处理任务的检测，发现了映射到左侧额叶、颞叶皮质和右侧小脑的优先语义处理区域。2018 年，一项关于控制语言能力发展的基因的研究指出，叉头框 P2 (*Forkhead box p2*, *FOXP2*) 基因在皮质 - 小脑回路中表达，其突变会导致严重的言语和语言障碍，功能成像显示在语言任务期间受影响的 KE 家族 (寻找 *FOXP2* 的工作始于对此家族的研究) 成员的大脑皮层和小脑的活动都发生了改变[75]。

1.3 空间认知

小脑损伤患者具有典型的周围书写困难症状，证实小脑参与了空间认知[76-77]。小脑有丰富的视觉空间信息，包含多个视觉空间的视网膜拓扑结构，视网膜区域定位的视觉选择性在小脑蚓部动眼神经、VIIb 和 VIIIb 三个簇中均有发现[78]。fMRI 结果显示，人类小脑小叶 VIIb/VIIIa 编码视觉空间认知的不同方面，且空间编码和视觉工作记忆处理之间功能分离，空间编码涉及小叶 VIIb/VIIIa 的背内侧，而依赖负荷的视觉工作记忆处理涉及腹侧，与额顶叶皮质形成功能连接[79]，如图 1 所示。

Iglói 等[80] 对受试者进行 fMRI 和虚拟现实技术检测的研究结果表明，导航的感觉 - 运动需求诱导小脑和皮质区域的活动，这些区域与运动回路和前庭处理有关。相比之下，认知相关的导航主要诱发小脑小叶 Crus I 的活动，还确定了在导航的非运动方面，连接小脑 Crus I 与内侧顶叶、内侧前额叶和海马的特定功能回路。这些结果突出了人类小脑在导航运动和认知方面的作用，并详细说明了根据任务的要求而发挥作用的皮质 - 小脑回路。虽然小脑 - 海马的直接投射已提出多年[81]，但其研究重点倾向于在空间导航中起着至关重要作用的小脑与顶叶等皮质区的多突触通路。此外，平行纤维 -PC 产生的 LTD 也涉及小脑参与大脑导航区域拓扑图的形成[82]。

与此同时，实验动物研究也发现，小鼠和大鼠的小脑 PC 被破坏后，它们在 Morris 水迷宫任务中的获取和性能受损[83-84]。对大鼠的另一项研究提出橄榄 - 小脑的神经再生与空间学习相关[85]。有研究指出，小脑损伤的金鱼没有产生任何可观察到的运动缺陷，却表现出严重的空间认知障碍[86]。也有研究人员用“孔板”任务训练了假手术和小脑切除的金鱼，要求它们定位有饵的线，切除小脑的金鱼与假手术金鱼相比，在空间精度、错误数、刻板搜索模式等方面存在明显的差异，对任务的获取和执行也受到显著影响[87]。

1.4 社会认知

社会认知是在非语言或语言输入条件下，感知和解释包括自我在内的人的行为和心理状态的过程[88-89]。解释另一个人的思想也经常被称为心智化。社会认知的扭曲常被认为是导致社会和情感功能严重异常的潜在功能障碍。针对社会认知和小脑进行的荟萃分析研究发现，在镜像网络、心智化网络和抽象判断等社会认知过程中，小脑中存在大量活跃的集群[18]。Van Overwalle 等[90] 通过荟萃分析连接建模 (Meta-analytic connectivity modeling, MACM)，为参与心智化和镜像活动的小脑区域连接到相应的

大脑功能网络提供了有力的证据。因此，小脑活动在社会判断中反映了不同的镜像和心智功能，参与更抽象，更复杂的心智化过程[91]，在社会认知中发挥着至关重要的作用。小脑 TMS 技术研究表明，背内侧前额叶皮层和小脑在调节内隐社会态度方面发挥作用[92]。社会认知的功能连接分析表明，背内侧前额叶皮层和右侧颞顶联合区与右侧小脑后区存在显著的连接，右侧小脑后区与左侧颞顶联合区也存在连接[93]，如图 1 所示。小脑损伤的患者表现出社交技能缺陷[94]。Clausi 等[95] 对小脑病变患者进行的社会认知能力测试及 RS-fMRI 扫描结果表明，患者在低级的直接知觉过程和复杂的心智化概念水平中受损。此外，小脑 Crus I、Crus II、小叶 IX 和小叶 VIIIa 的灰质减少，这些区域与投射到社会认知相关的大脑区域的功能连接降低。Badura 等[96] 减弱小鼠小脑中间神经元的输出并进行认知任务测试，结果表明小脑 Crus I/II 的活动调节社会偏好，并利用顺行跨突触示踪剂发现小脑后叶与眶额叶和前扣带皮层等有很强的联系。

1.5　学习

小脑参与多种认知学习过程。例如小脑后叶负责感知区域的学习[97]，还参与程序性学习、逆转学习、认知联想学习等[98-100]。Peterburs 等[101] 对受试者进行了基于 fMRI 的逆转学习任务测试，结果表明小脑会根据逆转学习过程中反应策略的变化进行不同的反馈处理，小脑后叶 (小叶 VI 和 VIIa/Crus I) 的激活增加。Lange 等[102] 通过激活似然估计 (activation likelihood estimation, ALE) 分析发现，小脑扁桃体、小叶 IV-VI 和山顶在恐惧条件刺激出现时激活，这些区域分别与恐惧获取、恐惧记忆的巩固和条件恐惧反应的形成有关。此外，还有研究发现，正常受试者的小脑经过 tDCS 后会影响序列学习[103]，并且 Nixon 和 Passingham[104] 对术后小脑损伤的猴子进行序列反应时间任务测试的结果也表明小脑参与序列学习。小脑损伤患者的认知联想学习功能受损[105-106]，并且 Chen 等[107] 对豚鼠的研究表明内侧前额叶皮层和小脑可能通过同步作用共同促进联想学习。Pidoux 等[108] 证明小脑为斑纹雀歌唱相关的 BG 提供了信息输入，小脑信号通过丘脑的双突触连接传递到 BG，然后传递到皮质和控制发声的运动前核，表明小脑和 BG 的皮层下环路参与声乐学习。Ito[109] 也强调了小脑 PC LTD 的研究与学习相结合的重要性，并指出 LTD 作为功能性抑制与突触和棘的结构变化有关。

1.6　情绪

神经影像学和临床资料表明小脑是加工情绪的关键区域[110]，不同的小脑区域选择性地参与不同的初级情绪[111]。Baumann 和 Mattingley[111] 发现小脑蚓部 (小叶 VI~IX) 的活动与几种主要情绪 (快乐、愤怒、厌恶、恐惧和悲伤) 相关。厌恶、悲伤和快乐与蚓部小叶 VIIIA 有关，而愤怒则涉及到小叶 IX 的激活。同样，荟萃分析也发现小脑蚓部的小叶 VI、Crus I、Crus II、VIII 和 IX 存在情绪相关活动[36,112]。对于情绪感知方面，有证据表明其由两个不同的神经系统支持：一个在有意识 (显式) 水平上工作，另一个在无意识 (隐式) 水平上工作[113]。积极情绪和消极情绪都被认为是通过小脑处理的[114]，也有人提出消极情绪处理占主导地位[115-116]。神经影像学研究表明，消极情绪与左侧小叶 VI、右侧小叶 IV/V、双侧 Crus I 的活动相关，而积极情绪与右侧小叶 VI 的活动相关[36,112]。采用经颅多普勒超声 (transcranial doppler, TCD) 记录情绪刺激时大脑中动脉的平均血流速度，再分析了小脑损伤患者的情绪感知发现，在健康受试者中，消极情绪刺激处理明显引起右侧大脑中动脉平均血流速度的升高，由于消极情绪刺激时这种升高在小脑病变患者中没有，因此小脑损伤导致在消极情绪刺激时激活大脑右半球的能力选择性受损，这一发现表明小脑在消极情绪刺激处理中起着重要作用[117]。通过 tDCS 也可以了解到小脑在情绪调节中的功能作用，受试者小脑接受刺激后显著增强对消极面部表情的反应，而积极和中性面部表情的反应不变[115]。当小脑损伤患者被要求通过情感评分量表来评估他们的情感状态时 (情感反应的效价和强度)，他们也无法明确地表达自己的负面情绪[118]，这一结果与 Scheuerecker 等[119] 的功能神经成像数据一致，显示了小脑处理情绪感知的隐式 / 显式差异，即小脑特定地参与显式自我监控[118]。对于情绪识别方面，有研究发现小脑卒中患者无论受到何种刺激 (视觉或听觉)，都表现出情绪识别能力受损，尤其是负面情绪[120]。此外，在某些情况下，情感症状有时是小脑病变患者的主诉。Annoni 等[121] 对一名左小脑卒中患者进行研究发现，该患者对生活情境的自我评价以情感淡漠为特征，他没有感受自己的情绪，也不关心别人的情绪状态。小脑顶核是一个经典的整合运动功能的皮下结构，结构上既是脊髓小脑束的终点，也与非运动系统广泛联系，包括脑干中介导内脏功能的核团、下丘脑和边缘系统。功能上除

了参与调节摄食、心血管和呼吸功能、排便、免疫也参与情感活动[122-123]。

小脑与包括杏仁核、海马等在内的边缘区域有着丰富连接[111]。Heath[1]在恒河猴脑的深部和皮层植入电极进行刺激并记录，结果表明小脑顶状核不仅和后腹外侧丘脑直接相连，而且与情绪相关的杏仁核和海马区有联系。Reiman等[124]研究发现，电影产生的情绪与枕颞顶叶皮层、小脑外侧、下丘脑以及包括前颞叶皮层、杏仁核和海马形成的区域的双侧活动显著增加有关，表明这些区域参与了对某些外部感觉刺激的情绪反应。Habel等[125]对受试者进行标准化的悲伤和快乐情绪诱导以及认知控制任务的fMRI检测，发现快乐在背外侧前额叶皮层、扣带回、颞下回和小脑产生更强的激活。Zinchenko等[126]采用定量功能磁共振荟萃分析发现，参与者动态面部表情相关的脑区涉及左侧杏仁核、左侧小脑等。

2017年的动物研究表明，小脑颗粒细胞编码对奖赏的期望。Wagner等[127]对行为小鼠使用双光子钙成像，结果显示颗粒细胞传递关于奖励期望的信息。一些颗粒细胞对奖励或奖励缺失有优先反应，而另一些则选择性地编码奖励预期。奖励信号遍布多个小脑小叶。在几天的学习中跟踪相同的颗粒细胞，发现具有奖励预期反应的细胞出现在那些在学习开始时就对给予奖励有反应的细胞中，而奖励缺失反应随着学习的进展而增强。在颗粒细胞中发现具有预测性的、非感觉运动的编码，显著丰富了突触后PC的传入信息，对小脑的认知加工具有重要意义。

总之，最近的证据表明，躯体感觉区域仅占小脑的相对较小部分，几乎一半的小脑参与认知控制和默认模式网络(default-mode network, DMN)[70]，环路研究证明小脑Crus I和Crus II是与DMN相连的主要小脑区域[71]。来自于人类的临床和神经影像学研究提供了令人信服的证据，证明小脑广泛地涉及认知、语言和情感功能[128-129]，功能成像研究强调了小脑Crus I在工作记忆中的作用。因此，小脑病变可能不只会导致运动症状，还会影响认知和情感功能。

2 小脑与神经退行性疾病相关研究进展

有人提出，小脑通过形成支持行为协调和技能学习的内部模型来促进认知和运动功能[10]。实际上，小脑具有多个相互作用的解剖回路模块，包括运动和感觉皮层，以及负责高级认知功能的区域，如前额叶皮层和顶叶皮层[70-71,130]研究表明，小脑 - 皮质连接异常在神经退行性疾病中出现[131-132]，通常与运动和认知障碍，甚至神经精神症状发生有关。在AD、ALS、FTD和PD患者的脑组织病检中，可以鉴定到具有不同小脑区域灰质萎缩模式的特异性神经变性。此外，在神经退行性改变过程中，这些被累及的小脑灰质萎缩模式与多种认知和情感领域的功能障碍有关[131-133]。其次，小脑病变也逐渐被确定为HD发病过程中的一个重要参与者[134-136]。

2.1 小脑与AD

AD是老年期痴呆的主要原因，影响超过40%的85岁以上的老人[137]，认知功能障碍往往是此类痴呆中最早出现的症状。目前的主流观点认为，脑组织中逐渐积累的病理蛋白沉积(包括老年斑中的Aβ肽和神经原纤维缠结中的tau蛋白)是AD发病的核心机制[138-140]。AD领域的大多数研究都集中在Aβ对内侧颞叶结构，特别是海马的毒性，因为它们的功能障碍被认为是AD中记忆丧失的主要原因[141-144]。然而，对家族性(FAD)和散发性AD患者的研究表明，小脑亦是AD发病过程中的易感区域[145-146]。

多个研究小组在AD患者的小脑皮层中发现了Aβ寡聚体水平升高和高水平过度磷酸化的tau蛋白，以及PC缺失[147-149]。小脑萎缩也是AD病理改变的另一个特征，小脑涉及到的萎缩区域有右侧小叶Crus I、Crus II和小叶VI[10]。小脑萎缩最初影响DMN中与小脑连接的部分，这是一组功能高度相关，且积极相互作用的脑区(包括角回、颞中回和前额叶皮层)，它们共同参与认知功能，并可能发生广泛的神经变性改变[150-151]，如图1所示。更重要的是，小脑相关区域已经在认知和情感功能中得到证实。具体来说，小脑Crus I、Crus II和小叶VI参与ECN、DMN和显著网络(salience network, SN)[39]，与海马和前额叶区域之间有连接[152]，这种萎缩模式与AD的主要认知障碍特征相吻合，包括阵发性和工作性记忆衰退[153]。

AD进程中小脑灰质萎缩模式的分析显示，小脑灰质体积(gray matter volume, GMV)的变化贯穿于AD的早期到晚期临床阶段，特别是小叶I~V和小叶VI的蚓部和副蚓部自早期起就开始受累，后期主要累及小叶VI和Crus I[154]。但也有研究提出，小脑萎缩导致AD的临床症状恶化主要发生在疾病晚期。然而，即使在晚期，小脑萎缩率也低于大脑

的平均萎缩率。这表明小脑受累是继发于大脑受累的，可能是由于网络连接异常的扩散，而与主要病理无关[155]。2019年，一项对AD患者死后新小脑的免疫组化检测发现，新小脑内小胶质细胞和神经血管系统发生改变，虽然这些变化没有导致AD中明显的神经病理学方面的缺陷，但可作为AD的驱动因子[156]。

2.2　小脑与PD

PD是最常见的进行性神经退行性疾病之一，其神经病理学标志是黑质和其他脑结构中的进行性多巴胺神经元丢失[157]。自从20世纪60年代发现纹状体中多巴胺浓度显著降低以来，BG就是PD的主要临床和研究靶点[158]。但越来越多的解剖学、病理生理学和临床证据表明，小脑病变可能对PD的临床症状有实质性的贡献。高达60%的PD患者存在非运动症状[159]，包括感觉、自主神经、认知和行为问题，与PD中的运动症状共存[160]，并且可能是某些PD患者的主要临床症状[161]。认知障碍在PD患者中很常见[162]，并涉及小脑多方面的缺陷，包括代谢障碍、组织萎缩及神经连接障碍等。

Huang等[163]确定了与认知表现相关的模式，特别是涉及PD患者的执行功能，这种PD相关的认知模式损伤特征是额叶和顶叶关联区域的代谢减少，以及小脑蚓部和齿状核的代谢增加。PD相关的认知模式损伤随着认知障碍的恶化而增加[164]，但与纹状体多巴胺能功能的下降无直接相关[165]，因此，小脑中的代谢亢进也可能是维持PD患者认知功能的补偿性作用。

除了代谢增加，小脑萎缩似乎也在PD的认知功能障碍中发挥了重要作用[133]，小脑GMV改变是PD患者的常见症状[166-168]。当研究PD患者的资料时，发现尤其是那些具有认知障碍的PD患者(如具有PD-轻度认知障碍的患者)表现出小脑萎缩，可以推测，PD患者的小脑变化与认知功能障碍的关系大于小脑变化与运动症状的关系[10]。2017年，一项研究发现，小脑Crus I区域的GMV差异涉及认知而非运动功能改变，这种差异可以将PD患者组与对照组分开，准确率达到95%[169]。另一项研究进一步支持了小脑Crus I对PD相关变化的重要性，显示了在静息状态下小脑右侧Crus I和丘脑底核之间的负功能耦合减少[170]。

由于小脑连接的异常变化似乎是某些PD的一个明确特征，因此在PD患者人群中已经检测到大脑-小脑和小脑-小脑连接的变化，大多数异常连接定位于小脑的DMN[171]。所以，BG和小脑的缺陷并不相互排斥，并且最近的研究表明，BG和小脑实际上是紧密相连的，并通过下丘脑核团相互投射[172]。DMN与认知过程高度相关，有研究提出认知未受损的早期PD患者DMN的功能连接减少，尤其是DMN后部，而DMN前部的功能连接增加。左侧内侧前额叶(前、腹侧、背侧)与小脑的功能连接明显增加(图1)，且前、腹侧功能连接增加与认知得分相关。DMN后部的功能连接明显下降，前部的功能连接代偿性增强，提示在出现认知障碍的临床证据之前患者DMN的早期功能紊乱，推测DMN连接功能障碍可能与PD认知功能下降有关[173]。

2.3　小脑与FTD和ALS

在家族性与散发性FTD和ALS中的最常见的基因缺陷是GGGGCC (G4C2)重复序列扩增[174-175]，它们是临床上两种不同的神经退行性疾病，但在遗传和病理方面有重叠且相互关联[176-178]。15%的FTD患者会发生ALS，而30%的ALS患者也会发生FTD[179]，意味着这两种神经退行性疾病共享临床谱的一部分，因此FTD和ALS被放在一起联合讨论。在ALS和FTD患者中，小脑的退行性病变普遍存在，这一点首先在*C9ORF72*突变携带者中发现[180]，后来又在散发性疾病患者中被鉴定出[132]。重要的是，全小脑萎缩与FTD和ALS患者的认知、运动和神经精神症状出现相关。ALS、行为变异型FTD (bvFTD)和ALS-bvFTD患者的基于体素的形态测定法(Voxel-based morphometry, VBM)的结构成像分析显示：(1) ALS-bvFTD患者的小脑整体灰质显著萎缩；(2) bvFTD患者的小脑前叶和Crus萎缩，ALS患者的小脑后叶和蚓部萎缩，因果协方差分析显示认知和神经精神症状与Crus的萎缩显著相关[132]。

在ALS患者中，小脑的Crus I和Crus II常常被累及，并且该萎缩簇位于蚓部而不是小脑半球；此外，ALS患者脑中的萎缩簇也在小脑下叶中发现，涉及到小脑半球的小叶V、VI和VIII，这表明了ALS患者中小脑出现的损伤比大脑更大[10]。小脑灰质变化与FTD亚型认知缺陷关系的研究指出，bvFTD萎缩程度最大，位于双侧Crus、左侧小叶VI、右侧小叶VIIb和VIIIb，语义性痴呆中的小脑改变位于左侧Crus I和小叶VI。无论FTD表型如何，双侧Crus I、Crus II和小叶VI萎缩与认知缺陷相关[181-182]。如小脑Crus I和小叶VI与bvFTD患者的记忆、语言、执行、情感和视觉空间领域的缺陷

表现相关[183]，小叶 Crus I、Crus II、VIIIb 与社会认知缺陷相关[184]。2019 年的一项研究将 bvFTD 的临床现象学扩展到认知和行为之外，提出 bvFTD 患者存在身体成分和脂肪沉积的变化。这些变化不仅与饮食行为异常和行为改变相关，还与小脑等脑区的灰质萎缩有关[185]。小脑 Crus I 和 Crus II 区域与前额叶和顶叶区域有重要联系 (图 1)，产生执行功能、记忆和情绪处理过程中的共激活[186]，这可能解释了 FTD 中小脑萎缩与特定皮质变化之间的关系[131]。

2.4 小脑与HD

HD 是一种常染色体显性遗传疾病，其主要发病机制是进行性多谷氨酰胺或 CAG 重复[187-189]，有三个典型临床特征：运动、认知和神经精神病。HD 患者的显著临床变化也表现为心理运动和执行功能、记忆、情绪处理和社会认知领域损伤[190]。虽然认知和神经精神损伤特征不太明显，但对这些损伤的认识至关重要，因为这些损伤可能导致 HD 患者丧失独立生活能力，对患者本人和家庭产生巨大影响[191-193]。

研究发现，HD 患者的情绪识别和工作记忆缺陷与小脑萎缩有关[194-195]。这些情绪功能障碍是患者遭遇的一个非常痛苦的部分，患者对面部表情的识别发生改变，特别是不能很好地识别负面情绪 (如恐惧、愤怒、厌恶和悲伤)，其中愤怒识别的损伤尤为明显[196]，愤怒识别缺陷 (强度和准确性) 与小脑双侧 GMV 减少相关，甚至小脑 GMV 也可能影响了疾病持续时间和疾病严重程度[194]。情绪控制障碍在 HD 中很常见，HD 患者对情感刺激的反应更强烈，诱发的焦虑情绪与前额叶、顶叶、丘脑和小脑的活动普遍减少有关[197]。HD 患者最严重的神经病理学改变集中在 BG 区域[198]，这一区域有助于识别人类的愤怒和厌恶信号[199-200]。已知在 BG 和小脑之间存在直接的解剖学连接，即脑区之间的异常活动可能会通过神经网络传播，从而带来负面影响[201]。因此，涉及情感处理的广泛神经网络在 HD 患者中被严重累及。除了情绪障碍，在中等和高水平的工作记忆负荷下，HD 患者的前额叶、顶叶区域和右侧小脑的活性降低，处于低活化状态[195]，因此，小脑被认为介导了 HD 患者的认知功能障碍。

早期对非人灵长类动物的顺行及逆行追踪研究已经很好地记录了前额叶皮质到小脑的投射以及小脑齿状核通过丘脑到前额叶和顶叶皮质的投射，支持小脑在更高的认知和情感过程中发挥重要作用[202-205]，如图 1 所示。总之，小脑通过多突触纤维与大脑皮层的不同区域相连，连通性网络结构在大脑皮层和小脑之间广泛延伸[129]，形成大脑 - 小脑回路[206-207]。功能性神经影像学研究进一步将大脑皮层中的功能连接网络映射到不同的小脑区域[39,70]。因此，理解大脑 - 小脑的结构和功能连接对于理解神经退行性疾病的临床病理学相关性至关重要。神经退行性病变中小脑的改变可以为预测疾病进展和网络功能障碍提供重要的诊断和病理学见解。

3 总结与展望

本文归纳了小脑参与调节认知、情绪等高级脑功能方面的研究进展，并强调小脑不同区域的功能障碍与各种神经退行性疾病特定临床症状之间的关联。大量临床和实验动物研究均表明，小脑的认知功能集中于进化上出现最晚的新小脑区以及齿状核和顶核，尤其是小叶 VI 和 Crus I、Crus II，在工作记忆、语言、学习、空间和社会认知以及情绪处理等高阶功能中发挥重要作用。平行纤维 -PC 产生的 LTD 不仅在运动协调中起着重要的作用，还介导工作记忆、学习、空间导航等认知功能。PC 是从小脑皮质发出的唯一能够传出冲动的神经元，通过颗粒细胞 -PC- 小脑核团投射的小脑内连接组成完整的额顶颞叶皮层 - 新小脑闭合环路，参与 ECN、DMN 等认知功能相关网络。

虽然在诊断和治疗许多神经退行性疾病时，已经考虑到小脑病变，但是，到目前为止，针对神经退行性疾病的研究重点还只集中在大脑皮层，而忽略了小脑的相关作用。大量的临床研究似乎倾向于表明神经退行性疾病中的小脑病变是继发于大脑病变，小脑可能作为驱动因子促进神经退行性疾病相关症状的发生和发展，也可能是在大脑异常时发挥补偿性作用。因此，充分揭示神经退行性疾病中小脑区域的结构和功能缺陷，跟踪年龄依赖的小脑病理学改变，更准确地描述小脑退化水平和神经退行性疾病进展之间的联系，必将为神经退行性疾病的早期诊断和治疗提供新的思路。

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