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脑类淋巴系统磁共振成像在帕金森病认知障碍中的最新研究进展

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摘　要

帕金森病(Parkinson’s disease, PD)是临床常见的神经退行性疾病，认知障碍是其高发且严重影响预后的非运动症状。脑类淋巴系统作为中枢神经系统代谢废物清除的重要通路，其功能异常与PD认知损害的发生发展密切相关。磁共振成像(magnetic resonance imaging, MRI)具有无创、可定量、可重复的优势，已成为活体评估类淋巴系统结构与功能的重要手段。本文围绕PD认知障碍的临床特点、脑类淋巴系统的结构功能及其主要影响因素、类淋巴系统损伤介导PD认知损害的病理机制进行阐述，重点综述对比增强MRI、沿血管周围间隙扩散张量成像分析(diffusion tensor image analysis along the perivascular space, DTI-ALPS)、脉络丛容积、血管周围间隙(perivascular space, PVS)、自由水成像以及全局血氧水平依赖性(global blood oxygen level dependent, gBOLD)信号与脑脊液(cerebrospinal fluid, CSF)耦合系数等影像学标志物在PD认知障碍中的最新研究进展，并对未来研究方向进行展望，旨在为PD认知障碍的早期识别、机制研究与临床评估提供神经影像学参考。

关键词

帕金森病，认知障碍，类淋巴系统，磁共振成像

Advances in Magnetic Resonance Imaging of the Glymphatic System in Parkinson’s Disease-Related Cognitive Impairment

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disorder in clinical practice. Cognitive impairment is a highly prevalent non-motor symptom that severely affects the prognosis of PD. As a critical pathway for metabolic waste clearance in the central nervous system, dysfunction of the brain glymphatic system is closely associated with the pathogenesis and progression of cognitive impairment in PD. Magnetic resonance imaging (MRI), with its advantages of being non-invasive, quantitative, and reproducible, has become an important tool for in vivo evaluation of the structure and function of the glymphatic system. This article reviews the clinical characteristics of cognitive impairment in PD, the structure and function of the brain glymphatic system and its major influencing factors, as well as the pathological mechanisms underlying glymphatic system dysfunction-mediated cognitive decline in PD. It focuses on the recent advances of multiple imaging biomarkers, including contrast-enhanced MRI, diffusion tensor image analysis along the perivascular space (DTI-ALPS), choroid plexus volume, perivascular space (PVS), free water imaging, and global blood oxygen level-dependent (gBOLD)-cerebrospinal fluid (CSF) coupling coefficient, in cognitive impairment in PD. Future research directions are also prospected. This review aims to provide neuroimaging references for the early identification, mechanistic investigation, and clinical evaluation of cognitive impairment in PD.

Keywords

Parkinson's Disease, Cognitive Impairment, Glymphatic System, Magnetic Resonance Imaging

1. 帕金森病认知障碍的简介

帕金森病以黑质多巴胺能神经元退行性丢失与 α-突触核蛋白(α-synuclein, α-Syn)异常聚集为核心病理改变，认知障碍是其最常见且致残性较强的非运动症状之一[1] [2]。根据认知损害程度，PD 认知障碍可分为帕金森病轻度认知障碍(PD-MCI)与帕金森病痴呆(PDD)，且随病程延长进展风险显著升高[3] [4]。PD 认知障碍主要累及执行功能、注意力、情景记忆及视空间能力，病理机制涉及异常蛋白沉积、神经环路退变、脑小血管病及神经炎症反应等[5] [6]。近年来，GS 清除功能障碍被认为是驱动 PD 认知损害的重要环节，MRI 为无创评价 GS 功能、揭示其与认知障碍关联提供了可行途径[7] [8]。

2. 脑类淋巴系统的简介及其影响因素

2.1. 脑类淋巴系统的结构与功能概述

GS 是中枢神经系统内负责液体交换与代谢废物清除的重要通路，主要由 PVS、星形胶质细胞终足、水通道蛋白 4 (AQP4)及脑膜淋巴管共同构成[9]。CSF 沿动脉周围间隙进入脑实质，在 AQP4 介导下与间质液(ISF)交换，携带代谢废物经静脉周围间隙及脑膜淋巴通路排出，实现毒性蛋白清除并维持脑内微环境稳定[10]。GS 正常运转依赖完整解剖结构与协调动力学驱动，任一环节异常均可导致清除效率下降。

2.2. AQP4 及星形胶质细胞对类淋巴系统的影响

AQP4 特异性表达于星形胶质细胞终足并呈血管周围极性分布，是驱动 CSF-ISF 跨膜交换的关键分

子[11]。星形胶质细胞终足完整及AQP4极性正常是GS发挥功能的重要前提，AQP4表达下降或极性丧失可直接导致液体转运与废物清除障碍[12]。PD脑内α-Syn异常聚集可损伤星形胶质细胞、破坏AQP4极性分布，削弱类淋巴清除能力，形成“蛋白沉积—清除障碍—进一步沉积”的恶性循环，加重认知损伤[13]。

2.3. 动脉血管搏动对类淋巴系统的影响

动脉搏动是推动CSF沿PVS流动的主要动力，搏动强度下降会直接降低GS循环效率[14]。脑小血管病、血管硬化及血流动力学异常可进一步削弱动力驱动，加剧GS功能损伤[15]。PD患者常伴随脑血管调节异常，认知相关脑区灌注下降及血管搏动减弱，不利于毒性蛋白清除，促进其蓄积并加速认知功能衰退[16]。

2.4. 睡眠对类淋巴系统的影响

睡眠是调控GS功能的重要生理因素，慢波睡眠阶段脑内代谢废物清除效率显著升高[17]。睡眠紊乱、片段化及快速眼动睡眠行为障碍(RBD)会持续抑制清除功能，促进蛋白沉积与神经炎症[18]。PD 患者睡眠障碍发生率高，睡眠异常与GS功能下降密切相关，还可进一步加重认知损害[19]。

3. 脑类淋巴系统在PD认知损害中的病理作用机制

GS功能障碍通过多条通路介导PD认知损害：废物清除受阻导致α-Syn、Aβ、磷酸化Tau等在认知关键脑区异常聚集，引发神经元损伤与突触功能障碍[20]；代谢废物蓄积激活小胶质细胞诱发神经炎症，炎症因子进一步破坏GS结构与功能[21]；GS障碍引发PVS扩张、白质微结构破坏及认知相关网络连接异常，从结构与网络层面促进认知下降[22]；血脑屏障通透性改变与血管周围水肿加重液体循环障碍，形成恶性循环，推动认知功能进行性下降[23]。

4. MRI评估脑类淋巴系统的主要影像学标志物及其在PD认知障碍中的研究进展

4.1. 对比增强MRI

动态对比增强MRI (DCE-MRI)可示踪对比剂在CSF及通路中的分布与清除，直观评估GS引流与清除功能[24]。鞘内给药可直接示踪类淋巴流动但侵入性较强，静脉给药更安全，可间接反映脑膜淋巴引流效率[25]。Ding等研究发现，PD认知障碍患者脑皮质动脉周围及基底节区可见异常强化，延迟期对比剂清除率降低，直接证实GS引流功能受损是PD认知损害的重要病理基础[26]；He等纵向研究证实，特发性PD患者脑膜淋巴引流速率下降，且降幅与MoCA评分呈正相关，提示GS清除效率下降程度可直接反映PD认知损害程度[27]。该技术目前多用于基础研究或无创标志物验证[28]。

4.2. DTI-ALPS技术

DTI-ALPS通过检测PVS方向水分子扩散率计算ALPS指数，指数越低提示类淋巴清除功能越差[29]。该技术无需对比剂、可重复性好，与DCE-MRI结果一致性高[30]。PD病理条件下，α-Syn异常沉积会损伤星形胶质细胞终足并破坏AQP4极性分布，进而改变PVS微观结构与液体动力学环境，限制水分子沿PVS的定向扩散，最终表现为ALPS指数降低，这一改变与认知环路损伤直接关联。Wood等随访研究发现，PD-MCI患者ALPS指数显著低于认知正常PD患者，证实低ALPS指数可独立预测PD认知衰退风险[31]；Mao等纵向研究证实，进展为认知损害的PD患者ALPS指数持续降低，且与白质纤维完整性下降相关，提示ALPS指数下降通过破坏白质结构介导PD认知损害[32]；Tian等研究发现，高BMI PD患

者 ALPS 指数更低，且与运动症状、认知损害呈负相关[33]；Bae 等研究证实，ALPS 指数与 MoCA、MMSE 评分呈正相关，可作为 PD 认知水平的稳定量化指标[34]。因此，DTI-ALPS 是目前 PD 认知障碍中最具推广潜力、可稳定量化 GS 功能并直接反映认知损害程度的核心无创影像学指标。

4.3. 脉络丛容积

脉络丛(CP)参与 CSF 生成与稳态调节，体积增大提示 CSF 循环紊乱与 GS 清除功能异常[35]。MRI 可半自动/自动分割测量 CP 容积，操作简便、重复性好[36]。PD 相关的慢性神经炎症与脑血管搏动减弱会刺激脉络丛代偿性增生肥大，导致 CSF 生成与引流失衡，进一步加剧类淋巴系统废物清除障碍，形成“脉络丛异常-CSF 动力学紊乱－认知损害”的递进通路。Wang 等研究发现，PD 认知障碍患者 CP 容积显著大于认知正常者，且与认知评分呈负相关，提示 CP 容积增大是 PD 认知损害的重要结构标志[37]；Li 等研究证实，CP 体积增大通过损害 GS 清除功能加剧白质高信号进展，加速 PD 认知衰退进程[38]；Tu 等研究发现，合并睡眠障碍的 PD 患者 CP 容积增大与 ALPS 指数降低并存，提示 CP 异常通过 GS 通路参与 PD 认知损害[39]。因此，脉络丛容积可作为反映 CSF 动力学异常与 GS 功能受损、间接评估 PD 认知损害进展的辅助结构性标志物。

4.4. 血管周围间隙

PVS 是 GS 核心解剖通道，其扩大(EPVS)是 GS 功能障碍的重要结构性影像标志[40]。基底节区 EPVS 与 PD 认知损害关系最为密切[41]。在 PD 病理进程中，α-Syn 异常聚集会诱发局部炎症反应并重构 PVS 周围细胞外基质，破坏 PVS 的正常通透性功能与解剖结构，导致其病理性扩张；扩张后的 PVS 进一步阻碍液体交换与废物清除，加重认知相关核团的蛋白蓄积与神经元损伤。Donahue 等研究发现，PD 患者基底节 EPVS 数量与认知评分呈负相关，证实 EPVS 负荷升高可预测 PD 认知衰退[42]；Park 等临床研究证实，基底节 EPVS 是 PD 认知功能下降的独立危险因素[43]；Foreman 等研究发现，基底节 PVS 负荷升高主要与 PD 注意力、执行功能损害相关，具有认知域特异性[44]；Chen 等研究证实，合并脑小血管病的 PD 患者 EPVS 扩张更显著，与白质损伤、认知损害协同加重[45]。因此，PVS 影像评估可直观反映 GS 结构异常，在解释 PD 认知损害的结构基础与认知表型关联方面具有较高价值。

4.5. 自由水成像

自由水成像基于双张量 DTI 分离自由水与结合水信号，自由水分数升高提示 ISF 潴留，间接反映 GS 清除障碍[46]。该技术对白质微结构水肿高度敏感[47]。PD 认知损害发生时，GS 清除功能不足会导致间质液与毒性代谢产物在白质通路内滞留潴留，引发局部微水肿；这种微结构改变会改变水分子扩散特性，表现为自由水分数升高，进而破坏认知相关白质纤维环路的结构与功能连接。Liguori 等研究发现，PD 认知障碍患者白质自由水分数显著升高，且与 ALPS 指数、认知评分呈负相关，提示自由水分数可反映 PD 认知损害中 GS 功能与白质微结构双重异常[48]；Lin 等研究证实，合并睡眠呼吸暂停的 PD 患者自由水分数升高，干预后分数下降、ALPS 指数回升、认知改善，提示自由水指标可反映 PD 认知损害的可逆性成分[49]；Wang 等研究发现，基底节自由水含量升高可独立预测 PD 向 MCI 进展风险[50]。因此，自由水成像是早期监测 PD 白质微环境紊乱、GS 清除障碍及认知损害风险的敏感影像学手段。

4.6. gBOLD-CSF 耦合分析

gBOLD 信号与 CSF 流入的动态耦合程度反映神经活动－液体清除偶联状态，耦合强度下降提示 GS 调控功能受损[51]。PD 病程中，神经炎症、蓝斑去甲肾上腺素能神经元变性及脑血管反应性异常，会破坏“皮质神经活动驱动 CSF 循环流入”的生理偶联关系，导致脑代谢增强与废物清除不同步，使得 α-Syn

等毒性蛋白无法被及时清除，进而加剧认知相关脑区的功能损伤。Han 等研究发现，PD 合并认知障碍者 gBOLD-CSF 耦合系数显著降低，且与内嗅皮层萎缩、认知评分下降密切相关，提示耦合解耦是 PD 认知损害的重要功能机制；Zhang 等研究证实，新发 PD 患者耦合强度低于健康对照，且与睡眠障碍严重程度呈负相关，提示睡眠紊乱通过解耦机制加剧 PD 认知风险[52]；Zeng 等研究证实，该指标可用于 PD 早期认知风险分层[53]。因此，gBOLD-CSF 耦合系数可从神经–液体动力学耦合角度评估 GS 调控功能，是反映 PD 早期认知损害风险的新型功能标志物。

5. 总结与展望

5.1. 研究总结

GS 功能障碍是 PD 认知障碍发生发展的核心病理机制，MRI 多模态技术可从结构、功能及动力学层面无创评估 GS 异常。DTI-ALPS、gBOLD-CSF 耦合、PVS、自由水分数、脉络丛容积及对比增强成像等标志物，为 PD 认知障碍的早期识别、危险分层与机制研究提供了重要影像学支撑。当前研究仍存在样本量偏小、标志物标准不统一、纵向随访不足、干预研究缺乏等问题。

5.2. 未来方向与临床转化

未来需开展多中心、大样本、纵向研究，建立标准化 GS 影像学评估体系，发展 AI 辅助定量技术，提升指标可靠性与可推广性。临床转化层面，以 GS 为靶点的干预策略可为 PD 认知障碍提供全新防治方向：1) 生活方式干预，优化睡眠结构、规律有氧运动、控制代谢危险因素可改善血管搏动、恢复 AQP4 极性、减轻神经炎症，从而增强 GS 清除功能，延缓 PD 认知衰退[54]-[56]；2) 药物干预，靶向 AQP4 极性保护剂、功能增强剂、抗炎药物及褪黑素等可直接或间接修复 GS 功能，减少 α-Syn 等毒性蛋白蓄积[57]-[59]；3) 物理干预，如光生物调节、低强度聚焦超声可促进 CSF 循环与废物清除，改善 PD 认知相关脑区微环境[60] [61]。本文所述无创 MRI 标志物可作为临床试验替代终点：以 DTI-ALPS 指数、自由水分数为核心功能指标，以 PVS 评分、脉络丛容积为结构指标，以 gBOLD-CSF 耦合为调控指标，构建多模态影像学评价体系，可高效、客观量化干预后 GS 功能修复程度与认知保护效果，缩短试验周期、降低研发成本，为 PD 认知障碍的精准防治与临床试验设计提供标准化影像学支持[62]-[64]。

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