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老年神经退行性疾病的精神影像学研究进展

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摘要 精神影像学是一门结合脑科学、医学影像学和神经精神病学的新兴交叉学科, 该学科旨在采用多种医学影像技术显示正常和异常精神状态以及神经心理行为特征, 从而用于指导神经精神疾病的临床诊断并辅助神经调控对疾病进行治疗. 精神影像学可用于神经精神疾病的早发现、诊断以及预警, 并结合神经调控技术进行脑功能康复. 精神影像学用不同脑成像手段探索脑结构和功能, 揭示神经精神疾病发生及发展不同层面神经生物学机制, 为各类神经精神疾病的康复提供理论依据, 并为神经精神疾病的临床诊疗提供客观的辅助评估技术. 本文首先简介了精神影像学的理论基础, 进而系统回顾目前老年神经退行性疾病(以帕金森、阿尔茨海默病为主)的精神影像学现状及最新研究进展, 最后对老年神经退行性疾病精神影像学研究的发展进行了展望.

关键词 精神影像学, 神经放射影像学, 神经影像, 磁共振成像, 帕金森病, 阿尔茨海默病

以阿尔茨海默病(Alzheimer's disease, AD)和帕金森病(Parkinson's disease, PD)为代表的老年神经退行性疾病, 是21世纪老龄化社会面临的最大健康危机之一. 目前, 我国AD患者已高达1000万, PD患者300万, 分别占全球AD患者的1/4和PD患者的1/3, 这类疾病的特点是患病率高、早诊率低、病情不可逆、疾病负担重, 给个人、家庭和社会带来极大负担. 因此, 临床干预关键在于早发现、早诊断, 目前疾病传统诊断模式以临床症状评估、量表测试及病理检查为主, 患者确诊时往往已进入中晚期, 错过最佳干预时期, 而临床上缺乏客观指标, 难以实现早筛. 现有的潜在生物标记物主要包括常规脑影像、脑脊液、血生化及基因测序检查等, 但患者接受程度有限、临床普及度低、诊断精度不足, 难以用于疾病早筛. 精神影像技术的出现, 实现了脑结构与功能的可视化和可量化, 为疾病早筛早诊带来契机. 本文拟对精神影像学的发展现状及常见老年神经退行性疾病的精神影像学研究进展进行阐述.

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1　精神影像学的发展现状

医学影像学是医学领域发展最快的学科之一，磁共振成像(magnetic resonance imaging, MRI)是该领域的代表性技术之一. 相对于其他脑成像技术, MRI具有无创、可重复检查、操作简单等优点，同时兼具较高的时间和空间分辨率并且能够提供脑结构、功能、代谢等多模态信息，已成为系统研究大脑结构与功能活动以及二者与行为关系的重要手段[1].

精神影像学(psychoradiology, 又称“精神放射影像学”)是一门新兴交叉学科，采用影像技术显示正常和异常精神状态以及神经心理行为特征，用于指导神经精神疾病的临床诊断并辅助神经调控治疗[2]. 精神影像学采用以MRI技术为主的成像手段探索脑结构和功能，揭示神经精神疾病发生及发展的神经生物学机制，为疾病的临床诊疗提供客观的辅助评估技术，是一个集医学、神经科学、认知科学、心理学、计算机科学、人工智能等多学科交叉的新型学科领域[3]. 并且，该学科已形成与神经放射影像学(neuroradiology)并列的临床亚专业方向，其主要目的是以影像学方法来客观、定量地分析人脑活动机制，在采用各种新兴的MRI技术探索脑疾病发病机制的同时，探索这些技术在临床转化中的应用价值，最终实现通过影像学为神经精神疾病的诊断、预后判断及疗效评估提供客观依据[4,5].

基于精神影像学理论，我国学者对部分脑疾病的结构与功能影像表征及其机制进行了深入研究[6,7], 构建了“结构-功能-行为”解析模式, 提出了“脑行为偶联”假说，建立了生物学亚型的分类新方法，实现了基于影像表征对神经精神疾病的个体化分类、疗效预测及靶点可视化. 由于老年神经退行性疾病早期症状的变异性及其与相似病种症状的重叠性，以及在某些情况下病因共存的可能性，目前临床上主要采用量表测评存在一定的主观性偏倚，往往只能用作筛查. 临床诊疗急需从传统人为主观判断向精准定量分析模式转化，这一工作的完成将对临床早期精准识别、动态疾病监测及疗效实时评价提供强大的基础. 精神影像学的出现为建立老年神经退行性疾病规范化影像评估及早期预警体系，推动疾病临床诊疗向精准定量分析的新型模式转化带来契机.

2　PD精神影像学研究进展

PD是中枢神经系统常见的退行性疾病，好发于中老年，核心病理改变为路易体病理沉积持续损害大脑黑质神经元，破坏运动神经环路平衡，引起静止性震颤、运动迟缓、姿势平衡障碍、肌强直等运动症状. MRI成像可以多角度检测黑质及相关神经环路功能障碍.

He等人[8]的磁敏感加权成像(susceptibility weighted imaging, SWI)研究发现，与健康对照相比，PD患者双侧黑质及起病对侧红核磁化率值、起病对侧黑质横向弛豫速率(R2*)值明显升高, 且双侧黑质磁化率值与患者运动症状及病程呈正相关. 黑质及基底节核团铁沉积在PD疾病不同分期表现不同，比如，随着疾病进展，铁沉积脑区逐渐增加[9]，PD不同亚型的脑铁沉积模式不同[10]，而且铁沉积模式受发病年龄的影响，晚发型PD患者壳核铁含量更高[11]，此外黑质铁沉积还可引起脑功能网络拓扑结构重构，并受纹状体功能连接的影响[12]. 3D T1加权高分辨结构成像结合SWI, 通过对中脑及桥脑径线的人工测量为PD与进行性核上性麻痹及多系统萎缩的鉴别提供了不容忽视的帮助[13]. 这些研究表明，脑深部核团铁沉积是PD疾病进展重要的生物标记物，有助于疾病早期诊断. 神经黑色素敏感磁共振成像(neuromelanin-sensitive magnetic resonance imaging, NM-MRI)作为一种新型的影像检查技术，能检测到含神经黑色素神经元的丢失[14]. 神经黑色素主要分布在中脑黑质致密部，是多巴胺能神经元的产物. Li等人[15]发现，PD患者蓝斑的神经黑色素信号显著降低，与患者的执行功能显著相关; Martín-Bastida等人[16]发现，PD患者黑质的神经黑色素信号显著降低, 与黑质-纹状体系统的多巴胺转运体显著相关. NM-MRI能反映PD患者核心病理改变——蓝斑和黑质的退变，监测疾病进展，且震颤为主型PD与特发性震颤的黑质神经黑色素信号改变模式不同[17]，有助于疾病鉴别诊断.

采用人脑连接组学方法[18]，Suo等人[19]发现PD患者脑功能网络异常主要位于感觉运动网络和默认网络，脑功能连接强度随Hoehn-Yah分期加重而逐渐降低，揭示了不同疾病分期脑功能特征演变规律. 冻结步态是PD中晚期常见的症状，能增加患者跌倒的概率, 具有高致残性. Li等人[20]横断面研究发现, PD冻结

步态患者在感觉运动网络、额顶叶网络、视觉网络、皮层下网络的功能连接存在明显改变，这些网络连接异常影响大脑对步态的调控；随后纵向研究发现，脑功能网络拓扑结构的重构，尤其是额中回的损伤，与PD病人将来发生冻结步态显著相关[21]. 除运动症状外，PD临床表现还包括非运动症状，如认知损害、快动眼睡眠行为异常、抑郁、嗅觉减退/缺失、自主神经功能障碍等，可先于运动症状出现[22]. 轻度认知功能障碍(mild cognitive impairment, MCI)是PD痴呆发生的重要危险因素之一，约50%的患者确诊后10年内转化为痴呆. Suo等人[23]通过脑血流动力学研究发现，PD伴有MCI患者较认知功能正常PD患者和健康对照的脑血流动脉通过时间明显延长，在默认网络、额顶网络、视觉网络等多个网络功能连接明显改变[24~28]. 约50% PD常伴发抑郁, 会降低患者生活质量、加重功能残疾[29]. Luo等人[30]基于静息态功能MRI研究发现，PD合并抑郁患者脑功能的特征性改变，即眶额叶区域活动增加而前额叶-边缘网络的功能连接减低，基于表面的形态学分析发现前额叶皮层厚度降低[31]，从脑结构-功能偶联的层面阐明PD抑郁改变的神经功能基础.

随着人工智能分析方法的发展，基于影像数据对脑疾病患者进行个体化诊断、预测已成为研究热点，也为基于客观影像标记物建立辅助诊断方式提供了契机. Suo等人[32,33]运用支持向量机结合多模态MRI，不仅可以区分PD患者和正常人，还可用于PD不同亚型分类，如以震颤症状为主亚型*vs.*以运动迟缓和肌强直为主亚型、伴有MCI型*vs.*认知功能正常型. Guo等人[34]采用数据驱动算法，利用白质纤维和多种临床症状结合非监督学习，识别出PD抑郁为主的临床亚型，该亚型患者脑结构和功能网络拓扑结构存在显著改变. Langley等人[35]的NM-MRI研究发现，PD患者黑质致密部R2*值诊断性能优于黑质网状部R2*值，铁含量及神经黑色素定量分析结合燕尾征征象改变能显著提高早期PD疾病的诊断效能[36]. NM-MRI除了有助于更好地理解PD病理改变，在区分PD患者和正常人上也具有较高的灵敏度和特异度[37,38]，表明其在PD诊断中具有较高的潜在价值. 虽然这些结果暂时还不能应用于临床，但表明使用机器学习方法从个体水平研究PD诊断及亚型分类是值得探索的方向，是把现有研究结果推向临床应用的关键步骤.

目前，PD主要的治疗手段仍是药物治疗，然而在中晚期可产生药物诱发运动并发症. 神经调控技术, 如深部脑刺激(deep brain stimulation, DBS)可以改善与长期药物使用相关的运动障碍[39]. 然而DBS需要在麻醉的条件下植入电极，是一种侵入性治疗，同时也增加感染出血的风险. MRI技术可以用于脑刺激治疗术前定位引导，术后疗效评估. 磁共振引导下聚焦超声(MR guide focused ultrasound, MRgFUS)是一种较新的神经调控技术，是MRI技术与聚焦超声技术的结合，俗称“磁波刀”, 采用MRI进行靶点定位, 利用聚焦超声产生的热效应选择性使靶组织凝固性坏死，对病灶实施热消融, 达到治疗目的. 2014年, Magara等人[40]报道了以苍白球丘脑束为靶区的MRgFUS治疗, 9例慢性药物难治性PD患者治疗后震颤症状明显改善. 之后，以丘脑腹中间核为靶区的MRgFUS研究报道了7例难治性震颤为主型PD患者治疗后震颤症状也明显改善[41]. 2016年，MRgFUS正式被美国食品药品监督管理局批准用于治疗脑部疾病. 2018年，Martínez-Fernández等人[42]报道了经丘脑底核MRgFUS消融治疗，10例药物治疗效果不佳的PD患者运动症状在术后6个月较术前得到改善. 同年, Jung等人[43]发现经苍白球MRgFUS治疗，8例药物难治性PD患者运动症状在术后6和12个月均较术前有所改善. 2019年, Gallay等人[44]单中心研究发现，经MRgFUS消融苍白球丘脑束后，除震颤症状，其他运动症状，如僵直、运动迟缓、肌张力障碍等也明显改善. 2021年，Xiong等人[45]报道了我国MRgFUS治疗PD的临床研究，结果显示视觉区可能参与患者震颤控制，或许可用于预测经丘脑腹中间核MRgFUS消融术后震颤症状改善情况；术后随访一年发现，临床症状改善与神经重塑相关，脑灰质结构形态学的重塑伴随着脑血供重新分布且与多巴胺系统调控密切相关[46]. MRgFUS治疗PD可选择的靶区较多[47]，主要依赖于解剖标记间接定位, 未考虑个体差异, 近期研究表明纤维束追踪定位技术可提供直接定位的方法，优化MRgFUS治疗靶点定位[48]，为个体化精准治疗奠定基础.

^{18}F-氟代脱氧葡萄糖(^{18}F-Fluorodeoxyglucose, ^{18}F-FDG)正电子发射型计算机断层显像(positron emission tomography, PET)反映葡萄糖代谢模式，研究一致发现, 帕金森病相关模式(Parkinson’s disease-related pattern)，不仅有助于PD患者与健康对照的区分[49]，还有助于PD与多系统萎缩、进行性核上性麻痹等非典型

帕金森综合征的鉴别[50]、PD前驱期的识别及疗效评估[51], 如大脑后部顶枕叶的代谢减低可以区分PD痴呆与MCI, 并与患者的视空间、记忆及执行功能相关[52]. 多巴胺能PET显像直接显示多巴胺能神经元含量及活性, 分为突触前(多巴胺转运体显像和囊泡单胺转运体显像)和突触后(多巴胺受体显像)多巴胺能显像, 常用于PD早期诊断、亚临床期筛查、疾病进展监测及疗效预测等[53~56]. 然而这些研究多是从单一模式开展研究, PET-MRI作为一种新兴的成像技术, 弥补了PET在脑结构显示的局限性, 一次扫描同时获得大脑代谢、结构和功能信息, 能提高PD诊断准确性[57]. 近年来, Aβ-PET和Tau-PET成像也逐渐应用于PD认知障碍的研究[58,59], 虽然PD原发病理改变是α-突触核蛋白异常沉积, 但随着疾病进展, 患者合并认知障碍损伤, 也会出现tau蛋白异常沉积[60]. 由于PET检查费用昂贵、对仪器设备及操作者要求高, 同时又存在一定辐射性、缺乏标准化等局限, 目前仍未被作为常规检查手段广泛应用.

3　AD精神影像学研究进展

AD是一种起病隐匿、进行性发展的神经系统退行性疾病, 临床表现为渐进性记忆障碍、认知功能减退和多种精神行为异常, 是老年人最常见的痴呆类型[61]. AD核心病理学改变是脑内β-淀粉样蛋白(amyloid β-protein, Aβ)沉积形成的老年斑、过度磷酸化tau蛋白形成的神经元纤维缠结及神经元缺失/变性[62]. 然而, AD疾病周期漫长, 从临床前期到MCI, 最后到AD痴呆, 可跨度二十余年, 当患者出现显著症状、就诊时, 疾病往往已发展至中晚期, 错过了最佳的干预时期, 而且目前尚无有效治疗措施, 因此探寻可以早诊的影像学标记物尤为重要.

脑结构MRI是最早应用于AD脑形态学研究的影像技术, 通过基于体素的形态学分析显示脑结构改变, 其中脑灰质体积变化最早发生在内侧颞叶[63], 疾病进展逐渐累及到顶叶、额叶和枕叶皮层, 最后是扣带回皮质, 说明AD脑结构改变是进行性的, 并不是局限在某一脑区[64], Yang等人[65]的荟萃分析进一步验证该理论假设. 国际标准已经将MRI内侧颞叶萎缩列为AD诊断的支持证据[66]. 基于ADNI(Alzheimer's Disease Neuroimaging Initiative)数据库的研究报道了从遗忘型轻度认知障碍(amnestic mild cognitive impairment, aMCI)到AD的脑萎缩轨迹, 发现包括双侧海马、海马旁回、颞上回颞极、岛叶、梭状回和扣带回等在内的多个脑区在aMCI中随年龄增长的萎缩速度比认知正常的健康人更快, 表现为非线性萎缩加速, 载脂蛋白E(apolipoprotein E, APOE)多态性与年龄对aMCI向AD转化过程中的脑萎缩轨迹存在复杂的交互作用[67]. 遗传影像联合研究显示, 抑郁症风险通过影响胎儿期海马神经元发育和Aβ蛋白结合进而影响海马体积, 增加aMCI向AD转化风险[68]. 对于AD患者, *APOEε4*基因携带者灰质萎缩更明显[69,70], *APOEε4*基因是海马体积改变的独立危险因素[71], 不仅影响脑结构改变, 还能导致认知功能下降[72]. 基于7 T高场强MRI发现, AD及MCI患者在低场强MRI不易显示的海马亚区萎缩改变[73]. 由于内侧颞叶部位测量对检查技术要求高, 且受不同阅片者间的主观性影响, 因此, 要得到一个客观且准确的结果, 后续研究重点是如何利用精神影像技术来建立AD影像数据质控技术链、规范化影像评估体系. 四川大学华西医院放射科团队已有12年的神经精神影像质控经验, 已发表多项包括AD在内的脑疾病MRI技术规范和团体标准[74,75], 为建立疾病早诊早筛的影像学规范奠定基础.

AD病理改变不仅累及灰质, 还可以引起脑白质纤维结构受损[76], 主要包括胼胝体、穹窿、扣带束、勾状束、上纵束、额叶皮层下白质等[77~80], 并受发病年龄影响[81]. Tau病变从内侧颞叶的海马体通过海马扣带纤维束扩散到默认网络后内侧区域, 尤其是后扣带回; 在Aβ阳性个体及MCI和AD患者中, 内侧颞叶及默认网络脑区(楔前叶和后扣带回)的Tau沉积与连接纤维束微观结构呈负相关, 而在Aβ阴性无认知功能障碍个体中呈正相关, 说明Tau病理和白质微观结构的关系依赖于是否有Aβ沉积[82]. 脑类淋巴系统是目前公认的分布于全脑的物质递送系统, 是脑内代谢废物排出的重要途径, 在AD等病理情况下受损, 导致Aβ沉积[83], 脑类淋巴系统障碍是痴呆的共同通路[84]. 有研究基于血管周围空间扩散张量成像评估AD患者的类淋巴系统活动, 结果表明AD患者血管周围间隙低扩散率反映其淋巴系统损伤情况[85,86]. 脑白质结构异常基本反映了AD神经病理学传播过程, Li等人[87]的荟萃分析也支持该理论假设, 即从海马、内嗅皮层等颞叶中部结构到颞叶皮层, 再到后顶区和前额区.

人脑是最复杂的网络系统，复杂网络的定量分析为探索AD大脑结构和功能连接模式提供了一个新的视角. He等人[88]基于皮层厚度构建了92名AD和97名健康被试组水平脑结构网络发现，与健康被试相比，AD患者脑灰质形态学网络的集群系数和特征路径长度显著升高, 小世界属性值降低, 表明患者脑灰质形态学网络拓扑结构受损. 然而, 由于多个被试只能构建一个组水平网络, 损失了个体化脑结构信息. 为解决该问题，Tijms等人[89,90]开发了一种新的个体化脑灰质网络构建方法发现, AD患者脑灰质形态学网络拓扑结构有向随机网络偏移的趋势, 且与患者认知功能相关. 需要注意的是，Tijms方法构建的每个被试脑灰质形态学网络大小(节点数目)不同，而网络的拓扑结构特征会受网络大小的影响[91]. 最近一项基于ADNI数据库的研究发现，使用Brainnetome图谱将整个大脑划分为246个脑区，提取每个脑区灰质结构的影像组学特征构建个体水平影像学特征相似性网络, 发现AD患者脑形态学连接显著受损，其中双侧海马相关的连接与认知功能存在显著相关. 同时采用数据驱动的聚类分析将MCI分为两种亚型(即A-CI和N-CI)，不同亚型之间认知损伤、基因表达及影像特征存在显著差异，A-CI亚型较N-CI亚型具有较高AD转化风险及较低生存率[92]. 结合NIA-AA(National Institute on Aging and Alzheimer's Association)研究框架, 灰质网络拓扑属性与主观认知下降或MCI患者的Aβ总体病理程度相关, 如Aβ阳性患者皮层厚度网络的全局效率、模块化低于Aβ阴性个体；随着病程进展，Aβ病理导致脑白质结构网络有向规则网络转变的趋势，并伴随结构连接的广泛减低；基于静息态功能MRI的脑功能网络显示Aβ主要集聚在默认网络、额顶网络、注意网络及额颞网络[93]. 结构和功能网络的联合分析显示, AD患者脑网络的特征路径长度增加、默认网络的功能连接强度减低，然而只有在脑功能网络中, 患者出现集群系数及"富人俱乐部"连接降低[94]. 研究表明，默认网络功能连接降低与Aβ的关联性，不仅出现在AD患者，也可以发生于AD前驱期[95]及临床前期[96]. 然而，常规脑功能网络分析忽略了人脑活动的时变特性，近年来动态脑功能网络研究为探索大脑活动的时变模式提供了新的方向. 最新研究发现，AD和aMCI患者楔前叶(默认网络的核心脑区)的动态功能网络连接强度减低, 且与患者的认知功能受损程度相关[97]. 然而，动态脑功能网络分析也面临结果是否稳定及可重复的问题. 总体来说，与健康老年人相比, AD患者脑网络表现为小世界属性丢失(网络拓扑结构倾向随机或规则网络)、模块结构紊乱、内侧颞叶和默认网络核心节点变化[93].

除了前述几种在AD研究中应用较为广泛的MRI手段, 还有其他影像技术从不同角度研究AD脑结构功能异常, 如: 动脉自旋标记成像利用磁性标记的动脉血作为内源性对比剂定量测量脑部微血管灌注. 研究发现, AD患者后扣带、楔前叶等脑区的血流量较健康对照减低, 内侧前额叶的血流量较MCI减低[98], 同时纵向研究发现后扣带和内侧前额叶基线时间的脑血流量可以预测MCI向AD转化[99]; 在亚型分析中, 非aMCI早发型AD患者较aMCI脑血流灌注减低程度更严重、范围更广泛[100], 而在AD临床前期脑血流量却是增加的, 这可能是一种功能性代偿，来抵抗早期神经功能损伤[101,102]. SWI可将质子之间产生的相位差量化，敏感检测脑内铁沉积. 研究发现，AD患者在海马、顶叶、尾状核、齿状核的铁沉积水平高于健康对照组，且与其认知功能损伤的严重程度相关[103]. 此外，纵向研究发现，AD和MCI转化为AD的患者比健康对照和MCI稳定患者更易出现新的脑微出血，偶发脑微出血可能与AD进展有关[104,105]. 磁共振波谱成像是利用化学位移方法来检测体内代谢物水平变化. 研究显示，AD和MCI患者N-乙酰天门冬氨酸(N-acetyl-aspartate, NAA)、肌酸(creatine, Cr)水平较健康对照下降[106~108], 且代谢物水平可在脑结构出现变化之前存在异常[109], 其中枕叶皮层NAA/Cr比值可以预测MCI向AD的转归[110]；谷氨酸及谷氨酰胺水平降低对AD早期临床诊断有一定价值[111], 该复合物水平在患者服用乙酰胆碱酶抑制剂后短暂升高，可能有助于监测治疗后功能恢复情况[108].

多模态MRI脑结构和功能特征结合机器学习方法可对AD进行预测与分类. 最新的一篇综述系统回顾了2009~2020年关于AD的人工智能研究，结果显示基于卷积神经网络的深度学习模型最优，诊断准确率可达89%，高于非卷积神经网络、随机森林、逻辑回归、支持向量机及其他模型的诊断准确率(76%~86%)[112]. 利用高斯回归模型实现基于脑功能连接特征预测AD患者脑龄[113]，输出大脑年龄差距反映大脑衰老进度, 结合被试淀粉样蛋白的信息能提高模型预测精度[114]. 2021年，Yang等人[115]采用生成对抗网络算法，基于脑

结构MRI将AD分为4种不同的生物学亚型，纵向随访发现不用亚型之间的疾病进展模式存在差异. 近期研究显示，结合多组学特征，有助于推动AD疾病临床诊疗向精准定量分析的新型模式转化[116]. 四川大学华西医院放射科在国际上率先开展神经精神影像门诊及认知障碍神经精神影像规范化检查，累计检查3000多例，并在湘雅二院等30多家医院推广使用，针对临床诊断为痴呆的患者，精神影像检查脑萎缩的检测率可达91.7%, 明显高于常规影像(58.3%), 同时能定量检测到特定脑区萎缩程度[117]. 因此，精神影像学不仅有助于痴呆的早期诊断，还能提供客观、定量的影像学指标，体现了精神影像学的临床转化应用价值.

Aβ-PET成像通过示踪剂与脑内Aβ蛋白结合，可视化和量化活体脑组织内淀粉样蛋白的沉积情况，研究显示AD患者大脑存在Aβ蛋白沉积[118]，且不同的Aβ沉积模式有助于AD与其他非AD源性痴呆的鉴别[119]. 此外, 有研究发现在AD痴呆前阶段, 已经存在β淀粉样蛋白沉积, 且沉积模式与AD相似[120]. 因此, Aβ-PET成像还可以用来预测痴呆前阶段患者进展为AD的可能性以及提高高危人群中MCI诊断的准确性[121]. Tau-PET成像是另一种异常蛋白病理显像，可以评估脑内Tau蛋白的沉积情况, 多数Tau-PET和Aβ-PET成像的应用目的相同，如AD病理改变检测[122]、疾病进展预测[123]、药物治疗研发的评估[124~126]等. 有研究显示, Tau-PET在AD痴呆鉴别、亚型分类及进展预测方面较Aβ-PET具有优势[127~130]，而在AD疾病早期发现/诊断方面较弱，可能是与Tau蛋白病理改变在AD进展过程中出现相对较晚有关[131]. FDG-PET成像可以显示AD早期神经元的代谢情况, 典型变化是颞顶区和后扣带的对称性代谢减低, 随后逐渐蔓延至皮层, 在疾病分期、鉴别诊断及临床转归预测中也发挥重要作用[132]. 虽然FDG-PET检测的葡萄糖低代谢诊断AD敏感性高达94%，但特异性仅73%[133]，而且无法提供低代谢背后的神经病理学信息[132]. 目前PET成像在AD的研究仍然存在亟待解决的问题，比如影像检查流程的优化、图像的质控标准、高灵敏度、高特异性及安全性的示踪剂研发应用等.

目前临床上尚缺乏治疗AD的有效方式. 近年来，非药物治疗，如经颅磁刺激(transcranial magnetic stimulation, TMS)备受关注[134]. TMS经头部线圈刺激脑组织，通过诱导与认知功能相关脑区神经元兴奋性改变，改善认知功能[135,136]. Motta等人[137]通过评估长时程增强样皮层可塑性及短传入抑制测量的胆碱能活性发现, rTMS可预测AD认知功能下降的进展. 与单纯认知训练、药物治疗方式相比，TMS联合认知训练改善患者认知功能更显著[138,139]，且改善效果可持续12周以上[138]. rTMS不仅可以治疗AD患者认知功能障碍，还有助于AD与路易体痴呆、额颞叶痴呆等其他神经退行性痴呆的鉴别[140]. 目前TMS治疗AD认知功能的频率、强度及刺激部位等尚无明确建议，未来需在神经导航的基础上寻找新的刺激靶点、更合适的线圈设计. 四川大学华西医院放射科磁共振研究中心在国家自然科学基金委重大仪器项目的资助下，致力于研发基于精神影像体系的MRI诊疗一体化设备. 该设备在高场MRI上集成神经调控技术，结合虚拟现实与实时功能MRI分析技术，将精神影像表征用来指导脑疾病诊断和脑靶点精准干预.

4　其他常见老年神经退行性疾病精神影像学研究进展

除AD和PD外，老年神经退行性疾病还包括路易体痴呆、额颞叶痴呆、肌萎缩侧索硬化症等. 路易体痴呆(dementia with Lewy body, DLB)是发病率仅次于AD的老年性痴呆(≥65岁)类型，核心病理改变为细胞内路易体沉积，临床特点为波动性认知障碍、视幻觉、帕金森综合征[141]. 由于DLB病理改变、临床表现与AD和PD痴呆有重叠, 临床上区分比较困难. 精神影像学在探索神经机制、鉴别诊断、病情评估中提供了重要手段. 基于体素的形态学分析发现，DLB患者存在广泛的脑灰质体积减小[142]，而内侧颞叶较少受累，其中岛叶尤其是前岛叶的萎缩有助于DLB与其他类型痴呆的鉴别[143]，然而其临床应用价值还有待进一步验证[144]. DLB患者还可以出现广泛的脑白质结构完整性受损，如胼胝体、辐射冠、上纵束等[142]，且与AD患者的白质纤维受损模式不同[145]. 脑网络分析解释了DLB患者视幻觉、认知损害的神经功能基础, 涉及视觉网络、默认网络等连接异常[146,147]. 脑内Aβ-PET显像研究提示，与健康对照相比，DLB患者flortaucipir标准化摄取值每年升高，主要累及枕叶、颞顶叶皮层，且与这些皮层年萎缩率、认知测评下降有关[148]. 同时DLB患者表现为全脑匹兹堡化合物

(Pittsburgh compound B, PiB)摄取率减低, 该特征区分DLB与AD的准确率可达93%[149]. 多模态MRI联合多巴胺转运体显像(^{123}I-FP-CIT SPECT)、标记淀粉样蛋白沉积的PiB-PET及脑代谢的^{18}F-FDG分子影像能进一步提高DLB与AD的鉴别诊断性能[150]. 此外, Aβ PET结合^{123}I-FP-CIT SPECT研究发现, 具有DLB核心临床特征的MCI患者表现为低Aβ沉积伴多巴胺能活性降低, 高Aβ沉积的患者亚群APOEε4携带率更高, 认知评分更低, 而多巴胺能活性降低的患者亚群更可能出现快动眼睡眠行为障碍[151].

额颞叶痴呆(frontotemporal dementia, FTD)是以进行性执行功能损害、行为异常、语言障碍为主要表现的神经退行性疾病, 是晚发型痴呆(≥65岁)的第3大病因[152]. FTD临床表现复杂多样, 目前量表测评、脑脊液、血浆等诊断手段缺少特异性, MRI可显示大脑结构特征性萎缩改变, 然而出现脑萎缩时往往已处于疾病晚期, 从FTD确诊到死亡平均3~4年, 因此寻找高特异度的生物学标记物用于疾病早期诊断尤为重要[153,154]. 目前已知的生物学标记包括灰质萎缩、白质变性、脑代谢改变、脑脊液淀粉样β1-42、磷酸化tau及总tau水平[153]. 其他如脑白质高信号等脑小血管病征象与FTD的灰质萎缩相关, 可引起更严重的认知损害[155,156]. 脑灰质形态学特征可以用于FTD与AD、健康被试的鉴别[157], 结合神经心理学测评能提高模型准确性[158]. 针对FTD主要致病基因突变的研究发现, 不同基因突变亚型之间的临床表型及灰质萎缩模式存在差异[159]. MAPT突变携带者无症状期开始出现颞叶皮层萎缩加速, 进展成为症状期后患者皮层萎缩加速的范围扩展至顶叶和额叶皮层[160], 而GRN携带者无症状期皮层萎缩始于顶叶皮层, 继之额叶皮层, 而在进入症状期后才出现颞叶皮层萎缩加速[161]. 此外, 磁共振波谱成像研究显示, MAPT突变携带者在尚无临床表现时就已出现内侧额叶脑代谢指标变化, 且与症状的发生年龄相关[162]. PET可提供分子层面的代谢变化, 有助于FTD疾病评估、亚型鉴别、进展检测等[163], 然而目前尚缺乏高灵敏度、特异性的分子显像剂.

肌萎缩侧索硬化(amyotrophic lateral sclerosis, ALS)是一种病因复杂、病程进展迅速且尚无有效治疗方式的严重致死性运动神经元病[164]. 精神影像学研究为ALS的早诊、进展检测及预后评估提供了客观定量的生物学依据. 基于表面的形态学分析发现, 运动脑区的皮层厚度比症状体征更敏感, 不仅可以区分ALS患者和健康对照, 还可以在出现明显临床表现之前监测到上运动神经元变性[165]. 脑灰质形态学研究在疾病严重程度分级、鉴别诊断中发挥作用, 如不同临床分期的散发性ALS患者海马亚区、下丘脑亚区萎缩表现不同且随着分期加重萎缩亚区增多[166,167], 内侧额叶-尾状核环路灰质萎缩模式可以区分ALS与FTD[168]. 脑白质形态学、微观结构的荟萃分析及脑白质结构网络研究均表明, ALS是一个多系统的神经退行性疾病, 不局限于运动区、皮质脊髓束, 还涉及运动外区域[169~171], 同时脑白质结构网络连接可以预测病情进展速度[171]. 在静息态功能MRI分析中, ALS患者可出现感觉运动网络功能连接减少或增加两种不同的表现, 这种差异与患者处于不同疾病阶段有关[172]. 而磁共振波谱成像分析较一致地发现ALS患者初级运动皮层的NAA值下降, 且与疾病进展及患者认知、行为障碍相关[173]. 这些精神影像学的发现促进了精神影像学特征作为ALS临床实践应用的潜在生物标志物.

5 总结与展望

老年神经退行性疾病目前诊断主要依靠临床症状学, 然而仅依据行为学量表不能满足疾病早期诊断, 以多模态MRI为主的精神影像学技术能够在活体无创评价大脑结构、功能以及代谢等信息. 目前国内外对老年神经退行性疾病的研究已逐步深入, 涉及的精神影像学改变包括脑灰白质形态学、脑代谢、不同大脑区域之间的连接、脑网络拓扑结构特征及铁沉积等, 为疾病的早期诊断、亚型鉴别、进展评估提供重要信息. 然而现有精神影像学研究所获取的数据多源自疾病临床阶段, 从正常老化到疾病转变过程的详细研究不足. 因此, 基于社区人群, 通过前瞻性的纵向随访, 探究老化的自然演变规律, 识别老年退行性疾病发生标记物和疾病早期转化的风险因素, 进而量化老年退行性疾病早期发生发展风险, 是该领域未来的研究重点. 尽管目前国内外已开展了队列研究, 如阿尔茨海默病神经影像学计划ADNI、中国认知下降纵向研究队列(Sino Longitudinal Study on Cognitive Decline, SILCODE)、北京老年脑健康促进队列(Beijing Aging Brain Rejuvenation Initiative, BABRI)等, 但不同队列

的数据采集流程、处理标准不同，致使不同研究间的数据资源难以相互流通及充分利用，故建立统一的数据采集及质量控制标准，规范化数据传递流程尤为重要.

另外，机器学习技术虽然已经在老年退行性疾病中展开了鉴别诊断、亚型分类、进展预测等方面的探索，但实际临床诊疗往往面对更复杂的情况、存在诸多挑战. 随着人工智能的快速发展、标准化多组学数据库的构建及多中心数据共享模式的形成[174,175]，使得研究更为复杂的临床实践、获得可解释性更强、泛化性能更好的模型成为可能. 与此同时, 针对现有药物治疗疗效有限的患者，MRI引导的神经调控技术成为治疗新方向，而靶点目前主要根据医师临床经验和患者个人情况而定，是否存在最佳靶点尚未可知，需要大样本、多中心、长期随访进一步验证. 最后，目前很难通过单一的生物学标记物实现老年神经退行性疾病的诊断，随着多模态MRI、神经电生理、基因组学和蛋白质组学等技术的融合应用[176]，如何根据大脑结构功能变化结合生物标记物、遗传信息等多组学特征，实现临床前病变/疾病前驱期的识别，并对风险人群制定个性化健康管理，最终实现老年退行性疾病早期预警将成为今后研究的重点方向.

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Research progress of psychoradiology in geriatric neurodegenerative diseases

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Psychoradiology is an emerging interdisciplinary field that uses various radiological imaging technologies to analyze normal and abnormal psychiatric conditions, neurophysiology, and mental health to guide the clinical diagnosis of neuropsychiatric disorders and assist in neuromodulation therapies. Psychoradiology can be employed for the early detection, diagnosis, and prevention of neuropsychiatric disorders and combined with neuromodulation techniques for brain function rehabilitation. Psychoradiology explores the brain anatomy and function using diverse radiological technologies to uncover neurobiological mechanisms underlying the occurrence and development of psychiatric illness, which provides a theoretical basis for the rehabilitation of neuropsychiatric disorders and objective auxiliary evaluation techniques for clinical diagnosis and treatment. This paper first introduces the theory of psychoradiology and then systematically reviews the current development and latest research progress on geriatric neurodegenerative diseases, mainly including Parkinson's disease and Alzheimer's disease, in psychoradiology, and finally proposes our prospects for the development of psychoradiology research on geriatric neurodegenerative diseases.

psychoradiology, neuroradiology, neuroimaging, MRI, Parkinson's disease, Alzheimer's disease

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