·综述·

神经退行性疾病的小脑症状与影像学特征☆

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【摘要】小脑的病理、病理生理及神经影像改变可发生于阿尔茨海默病、帕金森病、肌萎缩侧索硬化症等神经退行性疾病中。小脑特定区域的神经元激活和神经变性，可能参与了神经退行性疾病中多种临床症状的发生和病理进程。本文综述了神经退行性疾病中小脑相关症状的临床评估方法和神经影像研究。研究结果提示小脑的结构和功能的异常与神经退行性疾病中运动、认知功能障碍和情绪异常等症状的发生相关；建立基于小脑的多维度、系统性临床和影像评估方法，将有助于加深小脑参与神经退行性疾病发病机制的理解，并为疾病的早期症状识别、鉴别诊断、治疗等精准化诊疗方案的制定提供新的方向。

【关键词】小脑 神经退行性疾病 帕金森病 阿尔茨海默病 神经影像 运动功能障碍 认知功能障碍 临床评估方法

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【Abstract】 Pathological, electrophysiological, and neuroimaging changes in the cerebellum can occur in neurodegenerative diseases such as Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis. The activation and neurodegeneration of neurons in specific cerebellar regions may contribute to the clinical symptoms and pathological processes of these neurodegenerative diseases. This article reviews the clinical assessment methods and neuroimaging studies related to cerebellar symptoms in neurodegenerative diseases. The findings suggest that structural and functional abnormalities of the cerebellum are associated with symptoms such as motor, cognitive, and emotional dysfunction in these diseases. Developing a multidimensional, systematic clinical and imaging evaluation approach centered on the cerebellum will help deepen our understanding of the cerebellum's role in the pathogenesis of neurodegenerative diseases. It will also provide new directions for the early identification of symptoms, differential diagnosis, and the formulation of precise treatment plans.

【Keywords】 Cerebellum Neurodegenerative diseases Parkinson disease Alzheimer disease Neuroimaging Motor dysfunction Cognitive impairment Clinical assessment methods

神经退行性疾病（neurodegenerative diseases）是一类以神经元进行性变性和死亡为特征的疾病，常见类型包括阿尔茨海默病（Alzheimer disease, AD）、帕金森病（Parkinson disease, PD）、肌萎缩侧索硬化症（amyotrophic lateral sclerosis, ALS）等，目前缺乏有效的治疗手段，严重影响患者的生活质量和生命健康[1]。

近年来，越来越多的病理学、病理生理学和临床影像学证据建立了小脑与神经退行性疾病之间的关联[2-3]。小脑通过与大脑不同区域之间的投射连接参与多种功能调节，其皮质可分为感觉运动区、关联/认知区和边缘区[4-5]。除了已经明确的小脑-基底节-丘脑-皮质环路[6-7]，最新的研究发现小脑与中脑黑质、海马等脑区之间也存在直接/间接投射回路[8]，提示小脑可能通过与关键脑区的环路连接参与到神经退行性疾病的病理进程中[9]。另外，最近的结构和功能影

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像研究显示小脑特定脑叶的萎缩或激活，与神经退行性疾病中多种临床症状，如运动障碍、痴呆等症状的发生和进展相关[8, 10]。这些证据提示了对小脑的功能和结构异常的临床及影像学评估，可能有助于神经退行性疾病的早期识别和进展预测。

目前已有神经退行性疾病与小脑之间联系的总结，然而随着相关研究的逐年增多，有必要对近来年的最新进展进行更新[5]。另外，本综述主要关注以PD、AD、ALS为主的神经退行性疾病中小脑相关症状评估方法和小脑影像学研究进展，进一步探讨了近年来神经影像学和电生理等研究的新进展。通过以上将有助于建立基于小脑的全面系统评估，为疾病的精准化诊疗方案提供新的参考[11-12]。

1 小脑症状临床评估

小脑功能障碍的症状与神经退行性疾病中的一系列症状存在重叠[8]，提示小脑可能参与了神经退行性疾病的发病和病程进展，以及小脑功能评估在神经退行性疾病诊疗中的重要性。对小脑症状的评估方法，目前主要包括神经系统体格检查、相关功能的量表评测，以及特殊小脑功能的仪器检测设备等。

1.1 运动协调功能 小脑在运动控制中起着至关重要的作用，小脑功能障碍可能导致共济失调、姿势平衡障碍、震颤和眼球运动异常等[6, 8]。尽管PD患者的静止性震颤与小脑病变所显示的意向性震颤有所不同，但在疾病中晚期，PD患者通常合并多种不同形式的震颤类型。

除了神经科查体，还可以通过肌电图的惯性测量单元（inertial measurement unit, IMU）等客观地评估震颤的频率，从而对不同类型的震颤进行分析和鉴别[13]。另外，一些新型的可穿戴设备也将有助于PD患者震颤症状的长期实时监测，例如最近研发的可穿戴帕金森病定量评估设备，通过运动传感器并由算法实时分析患者的震颤和运动迟缓等症状。另外，基于智能手机系统的手腕佩戴设备也可用于长时间监测震颤情况[14]。

姿势不稳和步态困难（postural instability and gait difficulty, PIGD）是PD常见的运动障碍类型，而PD患者到了后期往往会出现更严重的步态冻结（freezing of gait, FOG）[8]。有研究显示AD患者也可能出现步态的异常[15]。步态分析则可以通过记录个体行走时的步态模式来评估大脑和小脑对步态控制的影响，在PIGD运动亚型诊断和治疗中广泛应用[16]。目前，研究步态障碍主要使用的工具包括一些评估量表，如Tinetti平衡与步态量表、起立行走计时测试（timed up and go, TUG）和简易体能测试量表等，具有高度的可靠性和敏感性，这些测试适用于评估神经退行性疾病的疾病过程以及康复锻炼效果[17]。

尽管目前还没有证据显示PD等神经退行性疾病患者存在明显共济失调的症状[18]，对小脑共济能力的检查可能有助于鉴别其他小脑障碍性疾病[19-22]。除了相应神经查体方法，如指鼻试验、指指试验、快速轮替运动、精细手指运动和过指试验等，其他量化共济功能的方法主要有国际合作共济失调评定量表（international cooperative ataxia rating scale, ICARS）、共济失调评定量表（scale for the assessment and rating of ataxia, SARA）[23-24]、弗里德赖希共济失调（Friedreich ataxia, FRDA）等[25]。其他工具如多发性硬化症功能综合评分（multiple sclerosis functional composite, MSFC）[26]、非共济失调体征量表（inventory of non-ataxia signs, INAS）、脊髓小脑共济失调功能指数（spinocerebellar ataxia functional index, SCAF1）[27]、改良费里德赖希共济失调评定量表（modified Friedreich ataxia rating scale, mFARS）[28-29] 可用于需要鉴别的疾病的共济功能评估。

小脑也参与眼球运动的调节，小脑功能障碍的患者可能出现眼球震颤，例如水平眼球震颤、垂直眼球震颤、旋转性眼球震颤等[30]。PD患者眼动功能异常包括眼球震颤、眼动缓慢、注视保持困难和追踪运动障碍。常用的分析方法包括平滑追踪眼动（mooth pursuit eye movement, SPEM）测试、快速眼动测试、眼动电图（electrooculography, EOG）等[31]。另外，也有研究显示小脑可能参与肌张力调节[6]，肌张力检测方法包括临床评估（通过被动活动患者肢体评估阻力）、评分系统[如统一帕金森病评分量表（unified Parkinson's disease rating scale, UPDRS）]和肌电图（记录肌肉电信号评估张力）等[32]。

1.2 认知和情感功能 近年来的研究表明，小脑不仅参与运动协调等功能，还与认知、情感、社会功能等高级功能相关[8, 33]。小脑认知情感综合征（cerebellar cognitive affective syndrome, CCAS）是一组以执行功能、语言处理、空间认知和情感调节缺陷为特征的综合征，是因连接前额叶、后顶叶、上颞叶和边缘结构（包括杏仁核、海马和透明隔）的神经回路中小脑部分的破坏所致，已有证据表明CCAS/Schmahmann量表可用于评估AD、PD等神经变性病患者的认知和情感功能[34-35]。正电子发射计算机体层扫描（positron emission computed tomography, PET）研究发现，小脑氟脱氧葡萄糖摄取与认知功能评估量表简易精神状态检查（mini-mental state examination, MMSE）评分和临床痴呆评定量表

高度相关[36]。小脑中的可溶性纤维低聚物浓度与MMSE评分呈负相关，与脑斑块和神经原纤维缠结呈正相关[33,37]。另外，神经退行性疾病相关情绪障碍的评估方法如汉密尔顿焦虑量表（Hamilton anxiety rating scale, HAMA）和汉密尔顿抑郁量表（Hamilton depression rating scale, HAMD）等，其评分结果也显示与小脑半球、蚓部等脑区激活相关[38]。社会认知评估包括面部情绪感知和识别失礼行为的能力测试，如眼神读心测验（reading the mind in the eyes test, RMET）和社交失态识别测试（faux pas recognition test, FPRT）[39]等评分也与小脑影像异常有关，提示了小脑对社交等高级功能的参与作用。

2 神经退行性疾病小脑影像特征

PET、MRI和CT等影像学手段已经在神经退行性疾病的治疗过程中广泛应用。最近多项结构影像学证据已经发现PD和AD患者的小脑存在明显的萎缩，其中小脑皮质不同脑叶的萎缩可能与运动障碍或认知功能障碍进展有关。另外，随着功能性磁共振成像（functional magnetic resonance imaging, fMRI）的广泛应用，已有大量证据提示了小脑特定区域的激活与神经退行性疾病不同症状发生之间的联系。见表1。

2.1 运动障碍与小脑影像特征 结构MRI-VBM研究发现，与健康个体相比，PD患者小脑灰质内的萎缩程度更高[40]，并且小脑灰质体积的减少与运动迟缓相关[10]。相关研究还发现，震颤型PD（tremor-dominant PD, TD-PD）和非震颤型PD患者的小脑灰质减少模式不同[40]。TD-PD患者的小脑中脚和上脚存在白质异常，其小脑整体功能连接密度高于运动刚性型PD（Akinetic-Rigid PD）患者[41-43]。基于MRI的弥散张量成像（diffusion tensor imaging, DTI）研究发现，PD患者小脑-丘脑-大脑皮质环路的多个白质纤维束的平均扩散系数和轴向扩散系数增加，这表明PD患者小脑的白质纤维束存在改变，涉及小脑内和小脑-皮质的多个环路，其中小脑-丘脑-大脑皮质环路在PD震颤中发挥着重要作用。此外，不同运动亚型的PD患者具有不同的小脑功能连接模式。例如，TD-PD患者的小脑后叶低频振幅值（amplitude of low-frequency fluctuations, ALFF）较高，而姿势不稳定步态障碍型PD患者（postural instability and gait difficulty PD, PIGD-PD）的小脑后叶和双侧壳核的ALFF值较低。双侧小脑后叶的ALFF值与震颤评分呈正相关，而双侧壳核的ALFF值与PIGD评分呈负相关[40]。另一项回顾性静息态fMRI研究发现，在5年随访期内，FOG的PD患者与未发生FOG的患者相比，运动小脑与顶叶-枕叶-颞叶关联皮质之间的功能连通性显著增加[44-45]。

在ALS的影像学研究中，基于超高场fMRI的全脑分析发现，感觉运动皮质和双侧小脑Ⅵ脑叶之间的功能连接出现中断，提示小脑结构改变可能参与到ALS的病理过程和运动功能异常[46]。另外，VBM研究发现，ALS患者小脑灰质体积显著降低，ALS患者双侧小脑的灰质体积增加，小脑前叶的功能连接（functional connectivity, FC）减少[47]，meta分析显示小脑蚓部、左侧小脑Ⅵ、Crus Ⅰ、Crus Ⅱ脑叶灰质萎缩最明显[48]。DTI研究显示ALS患者锥体运动系统、额颞区、边缘系统和小脑的各向异性分数值（fractional anisotropy, FA）降低和扩散率升高，提示白质纤维束完整性的降低[49]。

2.2 认知、情感功能障碍与小脑影像特征 大部分神经退行性疾病中都可能存在不同程度的认知和情绪功能障碍。在AD研究中，VBM结果提示AD和轻度认知功能障碍（mild cognitive impairment, MCI）患者的小脑均发生明显萎缩[50-51]。与Lewy体痴呆（dementia with Lewy bodies, DLB）相比，AD患者小脑Ⅵ和Crus Ⅰ/Ⅱ脑叶萎缩更为显著[52-54]；小脑白质体积比灰质体积下降得更快[55]，并且与认知功能评分相关[56-57]。静息态fMRI数据显示MCI和AD患者皮质-小脑的功能连接在不同区域下均受到了显著破坏[58]。PET数据表明，AD小脑葡萄糖代谢显著降低[50]。在PD中，认知功能受损的PD患者在小脑蚓部与前额叶皮质和前额叶背外侧皮质之间的功能连接减弱，而双侧小脑小叶Ⅰ~Ⅵ与感觉运动皮质之间的FC增强[59-60]。PET检查显示PD患者的小脑蚓部和脑桥的葡萄糖代谢升高，而额叶和顶叶活动减少[61]。代谢增强的程度与认知功能障碍的严重程度正相关。任务态fMRI结果显示，轻度认知功能障碍的PD患者在提醒注意任务期间双侧小脑激活程度增高[8]。

ALS患者主要涉及运动神经元的变性和死亡，认知和情感功能障碍研究较少，可能与小脑和大脑皮质之间的灰质体积、白质体积微观结构和FC有关[48,62-63]。

3 其他小脑功能评估方法

神经电生理技术在神经退行性疾病临床评估中同样存在重要作用。尽管小脑电极仅作为特殊电极，在脑电图检查中很少应用，但近期已有越来越多的研究在小脑区安置头皮电极或通过源定位，分析小脑的电生理改变。$APP^{swe}/PS1\Delta^{E9}$转基因AD小鼠研究结果显示，在AD疾病的早期阶段就已出现小脑脑电的变化[56]。有研究通过小脑脑电检测症状前AD的风险，发现小脑后外侧叶对AD相关的神经损

Tab.1　Imaging characteristics of the cerebellum in neurodegenerative diseases

表1　神经退行性疾病中小脑的影像学特征

疾病名称	影像学检查方法	分组	小脑影像特征	参考文献
PD	VBM	PD (*n*=31) *vs.* HC (*n*=12)	小脑灰质体积↓	[40]
		TD (*n*=14) *vs. non*-TD (*n*=10)	小脑Ⅵ脑叶灰质体积↓	[41]
	DTI	PD (*n*=60) *vs.* HC (*n*=26)	小脑-丘脑-大脑皮质环路白质纤维束的平均扩散系数↑，轴向扩散系数↑	[42-43]
	静息态-fMRI	TD (*n*=12) *vs.* PIGD (*n*=19)	TD小脑后叶ALFF↑，PIGD小脑后叶和双侧壳核ALFF↓	[40]
		伴FOG PD (*n*=26) *vs.* 不伴FOG PD (*n*=61)	小脑与顶叶-枕叶-颞叶关联皮质FC↑	[44-45]
		认知受损PD (*n*=43) *vs.* 非认知受损PD (*n*=38)	小脑蚓部、前额叶皮质、前额叶背外侧皮质FC	[59-60]
		认知受损PD (*n*=23) *vs.* HC (*n*=25)	双侧小脑Ⅰ-Ⅵ脑叶与感觉运动皮质FC↑	[59-60]
	任务态-fMRI	PD (*n*=41) *vs.* HC (*n*=22)	双侧小脑激活↑	[8]
	PET	PD (*n*=22) *vs.* HC (*n*=7)	小脑蚓部和脑桥代谢率↑，额叶和顶叶代谢率↓	[61]
AD	VBM	AD (*n*=48) *vs.* DLB (*n*=41)	小脑Ⅵ和Crus Ⅰ/Ⅱ脑体积↓	[52]
		AD (*n*=191) *vs.* MCI (*n*=398) *vs.* HC (*n*=229)	AD小脑体积↓，MCI小脑体积↓	[50-51]
		AD (*n*=20) *vs.* MCI (*n*=20)	小脑后叶体积↓	[50-51]
	静息态-fMRI	AD (*n*=28) *vs.* MCI (*n*=26)	皮质-小脑FC↓	[59-60]
	PET	AD (*n*=68) *vs.* HC (*n*=13)	小脑颞叶和顶叶代谢↓	[50]
ALS	超高场fMRI	ALS (*n*=12) *vs.* HC (*n*=9)	运动皮质和双侧小脑Ⅵ脑叶FC↓	[46]
	VBM	ALS (*n*=60) *vs.* HC (*n*=60)	双侧小脑的灰质体积增加，小脑前叶的FC↓	[47]
		ALS (*n*=3) *vs. non*-ALS (*n*=11)	小脑蚓部、左侧小脑Ⅵ、Crus Ⅰ、Crus Ⅱ脑叶灰质体积↓	[48]
	DTI	ALS (*n*=24) *vs.* HC (*n*=24)	锥体运动系统、额颞区、边缘系统和小脑的各向异性分数↓扩散率↑	[49]

注：VBM：基于体素的形态学分析；DTI：弥散张量成像；fMRI：功能性磁共振成像；PET：正电子发射计算机体层扫描；PD：帕金森病；TD：震颤型帕金森病；PIGD：姿势不稳定步态障碍型帕金森病；FOG：步态冻结；HC：健康对照组；AD：阿尔茨海默病；ALS：肌萎缩侧索硬化症；MCI：轻度认知障碍；ALFF：低频振幅；FC：功能连接性 FA：各向异性分数。

害敏感[64]。基于小脑的脑电图也被用于评估PD患者小脑脑电振荡变化，PD患者在休息、运动和执行认知任务时小脑脑电振荡均异常[65]。小脑脑电振荡同样与PD患者姿势不稳和步态冻结密切相关[66-67]。肌电图结合脑磁图数据显示PD震颤相关的大脑网络内存在异常振荡活动，包括震颤手对侧的小脑-间脑-皮质环路和皮质运动和感觉区的异常[8]。

4 总结与展望

鉴于越来越多的病理和神经影像证据提示小脑可能参与神经退行性疾病的病理进展和发病机制中，随着神经科学研究技术的进步，多种基于小脑的评估方法可能有助于神经退行性疾病临床和机制研究的开展。这些研究可能提供了一个新的视角，特异性地评估小脑与神经退行性疾病不同症状之间的关系。然而，小脑究竟是如何参与到不同神经退行性疾病的发病机制和神经环路连接，还有待进一步研究来明确。

未来研究应重点关注多模态影像学研究、纵向队列研究、新技术应用和临床应用，以更好地理解小脑在这些疾病中的作用，并开发新的诊断和治疗方法。高灵敏度的可穿戴设备已被用于PD的早期诊断、运动监测、预后评估等，其使用不受时间或地点的限制。因此，这些设备可作为未来远程医疗的理想选择。靶向小脑的经颅直流刺激（transcranial direct current stimulation, tDCS）[68-70]和近红外脑功能成像（functional near-infrared spectroscopy, fNIRS）[71]等新兴神经调控技术显示出治疗潜力，但需进一步验证其疗效和机制。已有研究将fNIRS与经颅磁刺激（transcranial magnetic stimulation, TMS）、tDCS、神经反馈和脑机接口（brain-computer interface, BCI）等技术结合应用，这种整合有望优化刺激参数，推进个性化神经康复。这些创新方法为神经退行性疾病的治疗提供了新的非侵入性选择，未来研究和临床试验将有助于验证其安全性和有效性。随着技术的进步，临床评估方法将继续为小脑功能研究提供更多启示，并为相关疾病的诊断和治疗提供新思路。

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参考文献

[1] BOSCO F, RUGA S, CITRARO R, et al. The effects of *Andrographis paniculata* (Burm.F.) Wall. ex Nees and andrographolide on neuroinflammation in the treatment of neurodegenerative diseases[J]. Nutrients, 2023, 15(15): 3428.

[2] METOKI A, WANG Y, OLSON I R. The social cerebellum: A large-scale investigation of functional and structural specificity and connectivity[J]. Cereb Cortex, 2022, 32(5): 987-1003.

[3] BRISSENDEN J A, SOMERS D C. Cortico-cerebellar networks for visual attention and working memory[J]. Curr Opin Psychol, 2019, 29: 239-247.

[4] STOODLEY C J, SCHMAHMANN J D. Functional topography of the human cerebellum[J]. Handb Clin Neurol, 2018, 154: 59-70.

[5] SAMSON M, CLAASSEN D O. Neurodegeneration and the Cerebellum[J]. Neurodegener Dis, 2017, 17(4-5): 155-165.

[6] BOSTAN A C, STRICK P L. The basal ganglia and the cerebellum: Nodes in an integrated network[J]. Nat Rev Neurosci, 2018, 19(6): 338-350.

[7] MILARDI D, ARRIGO A, ANASTASI G, et al. Extensive direct subcortical cerebellum-basal ganglia connections in human brain as revealed by constrained spherical deconvolution tractography[J]. Front Neuroanat, 2016, 10: 29.

[8] LI T, LE W, JANKOVIC J. Linking the cerebellum to Parkinson disease: An update[J]. Nat Rev Neurol, 2023, 19(11): 645-654.

[9] STOODLEY C J. The cerebellum and cognition: Evidence from functional imaging studies[J]. Cerebellum, 2012, 11(2): 352-365.

[10] ROSANO C, BENNETT D A, NEWMAN A B, et al. Patterns of focal gray matter atrophy are associated with bradykinesia and gait disturbances in older adults[J]. J Gerontol A Biol Sci Med Sci, 2012, 67(9): 957-962.

[11] SCHMAHMANN J D, GUELL X, STOODLEY C J, et al. The theory and neuroscience of cerebellar cognition[J]. Annu Rev Neurosci, 2019, 42: 337-364.

[12] LIANG K J, CARLSON E S. Resistance, vulnerability and resilience: A review of the cognitive cerebellum in aging and neurodegenerative diseases[J]. Neurobiol Learn Mem, 2020, 170: 106981.

[13] PALMERINI L, MELLONE S, AVANZOLINI G, et al. Quantification of motor impairment in Parkinson's disease using an instrumented timed up and go test[J]. IEEE Trans Neural Syst Rehabil Eng, 2013, 21(4): 664-673.

[14] ROVINI E, MAREMMANI C, CAVALLO F. How wearable sensors can support Parkinson's disease diagnosis and treatment: A systematic review[J]. Front Neurosci, 2017, 11: 555.

[15] CAJIGAS I, MORRISON M A, SAN LUCIANO M, et al. Cerebellar deep brain stimulation in cerebral palsy: Promising early results and a look forward to a larger clinical trial[J]. World Neurosurg, 2023, 174: 223-224.

[16] SCHNIEPP R, MÖHWALD K, WUEHR M. Clinical and automated gait analysis in patients with vestibular, cerebellar, and functional gait disorders: perspectives and limitations[J]. J Neurol, 2019, 266(1): 118-122.

[17] MONTERO-ODASSO M, SARQUIS-ADAMSON Y, SONG H Y, et al. Polypharmacy, gait performance, and falls in community-dwelling older adults. Results from the gait and brain study[J]. J Am Geriatr Soc, 2019, 67(6): 1182-1188.

[18] HONDA T, MATSUMURA K, HASHIMOTO Y, et al. Temporal relationship between impairment of cerebellar motor learning and deterioration of ataxia in patients with cerebellar degeneration[J]. Cerebellum, 2024, 23(4): 1280-1292.

[19] MARTINEZ-MANZANERA O, LAWERMAN T F, BLOK H J, et al. Instrumented finger-to-nose test classification in children with ataxia or developmental coordination disorder and controls [J]. Clin Biomech (Bristol, Avon), 2018, 60: 51-59.

[20] GAGNON C, MATHIEU J, DESROSIERS J. Standardized finger-nose test validity for coordination assessment in an ataxic disorder[J]. Can J Neurol Sci, 2004, 31(4): 484-489.

[21] WRIGHT M, SKAGGS W, NIELSEN F A. The cerebellum[J]. Wiki Journal of Medicine, 2016, 3(1): 1-15.

[22] SPENCER R M, IVRY R B, ZELAZNIK H N. Role of the cerebellum in movements: Control of timing or movement transitions?[J]. Exp Brain Res, 2005, 161(3): 383-396.

[23] SCHMITZ-HÜBSCH T, DU MONTCEL S T, BALIKO L, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale[J]. Neurology, 2006, 66(11): 1717-1720.

[24] TROUILLAS P, TAKAYANAGI T, HALLETT M, et al. International cooperative ataxia rating scale for pharmacological assessment of the cerebellar syndrome. The ataxia neuropharmacology committee of the world federation of neurology[J]. J Neurol Sci, 1997, 145(2): 205-211.

[25] DU MONTCEL S T, CHARLES P, RIBAI P, et al. Composite cerebellar functional severity score: Validation of a quantitative score of cerebellar impairment[J]. Brain, 2008, 131(Pt 5): 1352-1361.

[26] TANGUY MELAC A, MARIOTTI C, FILIPOVIC PIERUCCI A, et al. Friedreich and dominant ataxias: Quantitative differences

in cerebellar dysfunction measurements[J]. J Neurol Neurosurg Psychiatry, 2018, 89(6): 559-565.

[27] SUBRAMONY S H, MAY W, LYNCH D, et al. Measuring Friedreich ataxia: Interrater reliability of a neurologic rating scale[J]. Neurology, 2005, 64(7): 1261-1262.

[28] SCHWABOVA J, MALY T, LACZO J, et al. Application of a scale for the assessment and rating of ataxia (SARA) in Friedreich's ataxia patients according to posturography is limited[J]. J Neurol Sci, 2014, 341(1-2): 64-67.

[29] LYNCH D R, FARMER J M, TSOU A Y, et al. Measuring Friedreich ataxia: Complementary features of examination and performance measures[J]. Neurology, 2006, 66(11): 1711-1716.

[30] GORGES M, PINKHARDT E H, KASSUBEK J. Alterations of eye movement control in neurodegenerative movement disorders [J]. J Ophthalmol, 2014, 2014: 658243.

[31] PINKHARDT E H, JÜRGENS R, BECKER W, et al. Differential diagnostic value of eye movement recording in Psp-Parkinsonism, Richardson's syndrome, and idiopathic Parkinson′s disease[J]. J Neurology, 2008, 255(12): 1916-1925.

[32] SKORVANEK M, MARTINEZ-MARTIN P, KOVACS N, et al. Differences in MDS-updrs scores based on Hoehn and Yahr stage and disease duration[J]. Mov Disord ClinPract, 2017, 4(4): 536-544.

[33] JACOBS H I L, HOPKINS D A, MAYRHOFER H C, et al. The cerebellum in Alzheimer's disease: Evaluating its role in cognitive decline[J]. Brain, 2017, 141(1): 37-47.

[34] HOCHE F, GUELL X, VANGEL M G, et al. The cerebellar cognitive affective/Schmahmann syndrome scale[J]. Brain, 2018, 141 (1): 248-270.

[35] SILFVERSKIÖLD B P. A 3 C/SEC leg tremor in a "cerebellar" syndrome[J]. Acta Neurol Scand, 1977, 55(5): 385-393.

[36] MEZEI G, CHANG E T, MOWAT F S, et al. Comments on a recent case-control study of malignant mesothelioma of the pericardium and the tunica vaginalis testis[J]. Scand J Work Environ Health, 2021, 47(1): 85-86.

[37] RÜB U, STRATMANN K, HEINSEN H, et al. The brainstem tau cytoskeletal pathology of Alzheimer's disease: A brief historical overview and description of its anatomical distribution pattern, evolutional features, pathogenetic and clinical relevance[J]. Curr Alzheimer Res, 2016, 13(10): 1178-1197.

[38] MASTAMMANAVAR V S, KAMBLE N, YADAV R, et al. Non-motor symptoms in patients with autosomal dominant spinocerebellar ataxia[J]. Acta Neurol Scand, 2020, 142(4): 368-376.

[39] BARON-COHEN S, WHEELWRIGHT S, HILL J, et al. The "reading the mind in the eyes" test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism[J]. J Child Psychol Psychiatry, 2001, 42(2): 241-251.

[40] CHEN H M, WANG Z J, FANG J P, et al. Different patterns of spontaneous brain activity between tremor-dominant and postural instability/gait difficulty subtypes of Parkinson's disease: A resting-state fMRI study[J]. CNS Neurosci Ther, 2015, 21(10): 855-866.

[41] BENNINGER D H, THEES S, KOLLIAS S S, et al. Morphological differences in Parkinson's disease with and without rest tremor[J]. J Neurol, 2009, 256(2): 256-263.

[42] LUO C, SONG W, CHEN Q, et al. White matter microstructure damage in tremor-dominant Parkinson's disease patients[J]. Neuroradiology, 2017, 59(7): 691-698.

[43] BARBAGALLO G, CALIGIURI M E, ARABIA G, et al. Structural connectivity differences in motor network between tremor-dominant and nontremor Parkinson's disease[J]. Hum Brain Mapp, 2017, 38(9): 4716-4129.

[44] JUNG J H, KIM B H, CHUNG S J, et al. Motor cerebellar connectivity and future development of freezing of gait in *de novo* Parkinson's disease[J]. Mov Disord, 2020, 35(12): 2240-2249.

[45] HETT K, LYU I, TRUJILLO P, et al. Anatomical texture patterns identify cerebellar distinctions between essential tremor and Parkinson's disease[J]. Hum Brain Mapp, 2021, 42(8): 2322-2331.

[46] BARRY R L, BABU S, ANTERAPER S A, et al. Ultra-high field (7T) functional magnetic resonance imaging in amyotrophic lateral sclerosis: A pilot study[J]. Neuroimage Clin, 2021, 30: 102648.

[47] CHIPIKA R H, MULKERRIN G, PRADAT P F, et al. Cerebellar pathology in motor neuron disease: Neuroplasticity and neurodegeneration[J]. Neural Regen Res, 2022, 17(11): 2335-2341.

[48] GELLERSEN H M, GUO C C, O'CALLAGHAN C, et al. Cerebellar atrophy in neurodegeneration-a meta-analysis[J]. J Neurol Neurosurg Psychiatry, 2017, 88(9): 780-788.

[49] KEIL C, PRELL T, PESCHEL T, et al. Longitudinal diffusion tensor imaging in amyotrophic lateral sclerosis[J]. BMC Neurosci, 2012, 13: 141.

[50] THOMANN P A, SCHLÄFER C, SEIDL U, et al. The cerebellum in mild cognitive impairment and Alzheimer's disease - A structural MRI study[J]. J Psychiatr Res, 2008, 42(14): 1198-1202.

[51] TABATABAEI-JAFARI H, WALSH E, SHAW M E, et al. The cerebellum shrinks faster than normal ageing in Alzheimer's disease but not in mild cognitive impairment[J]. Hum Brain Mapp,

2017, 38(6): 3141-3150.

[52] COLLOBY S J, O'BRIEN J T, TAYLOR J P. Patterns of cerebellar volume loss in dementia with Lewy bodies and Alzheimer's disease: A VBM-dartel study[J]. Psychiatry Res, 2014, 223(3): 187-191.

[53] GUO C C, TAN R, HODGES J R, et al. Network-selective vulnerability of the human cerebellum to Alzheimer's disease and frontotemporal dementia[J]. Brain, 2016, 139(Pt 5): 1527-1538.

[54] REIMAN E M, QUIROZ Y T, FLEISHER A S, et al. Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: A case-control study[J]. Lancet Neurol, 2012, 11(12): 1048-1056.

[55] JERNIGAN T L, ARCHIBALD S L, FENNEMA-NOTESTINE C, et al. Effects of age on tissues and regions of the cerebrum and cerebellum[J]. Neurobiol Aging, 2001, 22(4): 581-594.

[56] YU H, WANG M, YANG Q, et al. The electrophysiological and neuropathological profiles of cerebellum in APP(SWE)/PS1 (ΔE9) mice: A hypothesis on the role of cerebellum in Alzheimer's disease[J]. Alzheimers Dement, 2023, 19(6): 2365-2375.

[57] MASCALCHI M, GINESTRONI A, TOSCHI N, et al. The burden of microstructural damage modulates cortical activation in elderly subjects with MCI and Leuko-Araiosis. A DTI and fMRI study[J]. Hum Brain Mapp, 2014, 35(3): 819-830.

[58] TANG F, ZHU D, MA W, et al. Differences changes in cerebellar functional connectivity between mild cognitive impairment and Alzheimer's disease: A seed-based approach[J]. Front Neurol, 2021, 12: 645171.

[59] MAITI B, KOLLER J M, SNYDER A Z, et al. Cognitive correlates of cerebellar resting-state functional connectivity in Parkinson disease[J]. Neurology, 2020, 94(4): E384-E396.

[60] FESTINI S B, BERNARD J A, KWAK Y, et al. Altered cerebellar connectivity in Parkinson's patients on and off L-dopa medication[J]. Front Hum Neurosci, 2015, 9: 214.

[61] BLUM D, LA FOUGÈRE C, PILOTTO A, et al. Hypermetabolism in the cerebellum and brainstem and cortical hypometabolism are independently associated with cognitive impairment in Parkinson's disease[J]. Eur J Nucl Med Mol Imaging, 2018, 45 (13): 2387-2395.

[62] ZHOU F, GONG H, LI F, et al. Altered motor network functional connectivity in amyotrophic lateral sclerosis: A resting-state functional magnetic resonance imaging study[J]. Neuroreport, 2013, 24(12): 657-662.

[63] QIU T, ZHANG Y, TANG X, et al. Precentral degeneration and cerebellar compensation in amyotrophic lateral sclerosis: A multimodal MRI analysis[J]. Hum Brain Mapp, 2019, 40(12): 3464-3474.

[64] PAITEL E R, NIELSON K A. Cerebellar EEG source localization reveals age-related compensatory activity moderated by genetic risk for Alzheimer's disease[J]. Psychophysiology, 2023, 60 (12): E14395.

[65] BOSCH T J, GROTH C, ELDRIDGE T A, et al. Altered cerebellar oscillations in Parkinson's disease patients during cognitive and motor tasks[J]. Neuroscience, 2021, 475: 185-196.

[66] BOSCH T J, KAMMERMEIER S, GROTH C, et al. Cortical and cerebellar oscillatory responses to postural instability in Parkinson's disease[J]. Front Neurol, 2021, 12: 752271.

[67] BOSCH T J, ESPINOZA A I, SINGH A. Cerebellar oscillatory dysfunction during lower-limb movement in Parkinson's disease with freezing of gait[J]. Brain Res, 2023, 1808: 148334.

[68] FERRUCCI R, BOCCI T, CORTESE F, et al. Cerebellar transcranial direct current stimulation in neurological disease[J]. Cerebellum Ataxias, 2016, 3(1): 16.

[69] FERRUCCI R, PRIORI A. Transcranial cerebellar direct current stimulation (TCDCS): Motor control, cognition, learning and emotions[J]. Neuroimage, 2014, 85(Pt 3): 918-923.

[70] FERRUCCI R, CORTESE F, BIANCHI M, et al. Cerebellar and motor cortical transcranial stimulation decrease levodopa-induced dyskinesias in Parkinson's disease[J]. Cerebellum, 2016, 15(1): 43-47.

[71] HUO C, XU G, XIE H, et al. Functional near-infrared spectroscopy in non-invasive neuromodulation[J]. Neural Regen Res, 2024, 19(7): 1517-1522.

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