·综述·

中枢胆碱能系统参与帕金森病步态和平衡障碍的研究进展

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【摘要】 步态异常和平衡障碍是帕金森病的常见临床特征，目前越来越多的证据表明，中枢胆碱能神经元变性是导致帕金森病步态异常和平衡障碍的重要因素。文中就中枢胆碱能系统参与帕金森病步态和平衡障碍机制的相关研究进行综述，旨在为帕金森病步态异常和平衡障碍的治疗提供新方向和思路。

【关键词】 帕金森病；　步态异常；　平衡障碍；　胆碱能神经

Research progress on the role of central cholinergic system in gait deficits and balance disturbances in Parkinson's disease

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【Abstract】 Gait deficits and balance disturbances are prevalent clinical features in Parkinson's disease (PD). There is an increasing body of evidence pointing towards the degeneration of central cholinergic neurons as a crucial factor leading to these disturbances in PD. This paper presents a comprehensive review of the relevant research on the involvement of the central cholinergic system in the mechanisms underlying gait deficits and balance disturbance in PD. The aim is to provide new perspectives and insights for the treatment of gait deficits and balance disturbances in PD.

【Key words】 Parkinson disease;　Gait deficits;　Balance disturbances;　Cholinergic neurons

Conflicts of interest: None declared

步态异常和平衡障碍是帕金森病（Parkinson's disease）的常见临床特征，可具体表现为步速慢、步幅小、转身慢、步态冻结、姿势不稳和跌倒。步态障碍和跌倒是帕金森病患者生活质量下降的主要原因[1]，并且增加照料者负担[2]。左旋多巴和脑深部电刺激术对帕金森病患者步态异常和平衡障碍的治疗效果不佳[3]，提示非多巴胺能系统参与帕金森病的步态异常和平衡障碍。目前越来越多的证据表明，中枢胆碱能神经元变性是导致帕金森病步态异常和平衡障碍的重要因素[4-7]。我们以"Parkinson's disease/PD""gait""balance""fall""cholinergic"为英文关键词在 PubMed 数据库检索 2024 年 1 月前发表的相关文献。文中就中枢胆碱能系统参与帕金森病步态和平衡障碍机制的相关研究进行综述，旨在为帕金森病步态异常和平衡障碍的治疗提供新方向和思路。

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一、中枢胆碱能系统的神经解剖学特征及在帕金森病中的病理变化

中枢胆碱能系统参与调节人类多种行为功能，如奖赏、注意力、记忆、恐惧和应激反应、体温调节、食物摄入和睡眠[8]。中枢胆碱能神经元分为远端投射神经元和局部中间神经元两类。胆碱能中间神经元存在于纹状体、伏隔核和新皮质[8-10]。基底前脑和中脑脑桥被盖区的胆碱能神经元是大脑中大多数胆碱能投射的起源，与脑干、纹状体、丘脑、下丘脑和大脑皮质有着广泛的联系[11]。基底前脑包括四群胆碱能神经元（Ch1~Ch4）：内侧隔核（Ch1）和斜角带核垂直部（Ch2）发出投射纤维至海马；斜角带核水平部（Ch3）发出投射纤维至嗅球；Meynert 基底核（Ch4）发出投射纤维至大脑皮质和杏仁核[12-15]。Meynert 基底核是基底前脑重要的胆碱能投射纤维核心，又称无名质[16]。脚桥核位于中脑脑桥被盖区，主要发生投射纤维至丘脑，部分纤维投射到小脑、基底神经节、黑质致密部、脑干和脊髓等[17]。中枢胆碱能系统通过其广泛的轴突纤维投射释放乙酰胆碱调节许多生理功能：中脑边缘投射负责奖赏反应；前额叶皮质投射负责决策、计划；海马和杏仁核投射负责注意力、记忆、恐惧和应激反应；下丘脑投射负责体温调节、食物摄入和睡眠等稳态反应[8]。胆碱能系统还具有促进突触可塑性和神经元发育的作用[18]。

研究报道帕金森病患者的 Meynert 基底核中存在胆碱能神经元丢失和路易小体形成[19-24]，Meynert 基底核胆碱能神经元丢失约 30%~70%[19-20, 25]。研究发现帕金森病基底前脑与黑质的病变同时发生，帕金森病患者基底前脑胆碱能神经元内 α-突触核蛋白的沉积与黑质内路易小体的形成和多巴胺能神经元的丢失病变程度一致[26]，提示胆碱能神经元变性可发生在帕金森病疾病的早期。帕金森病患者基底前脑胆碱能神经元变性导致皮质失胆碱能神经支配，脑干胆碱能神经元变性导致丘脑失胆碱能神经支配[4, 27-30]。与胆碱能神经功能障碍相关的体征和症状包括认知能力下降、步态异常、步态冻结和跌倒、快速眼球运动睡眠行为障碍、嗅觉障碍和神经精神症状[18]。注意力下降是中枢胆碱能神经功能障碍的重要特征之一[31]。文献报道帕金森病患者失胆碱能神经的速度和进展是多变的[29, 32]。基底前脑胆碱能系统退化在帕金森病早期出现，并随着痴呆的出现而恶化[33]。

二、中枢胆碱能系统的评估

评估中枢胆碱能系统功能的技术主要有 3 种：药理学、体内神经成像和神经电生理学技术。药理学技术是使用乙酰胆碱酯酶（acetylcholinesterase，AChE）抑制剂增加中枢乙酰胆碱的含量。AChE 抑制剂（多奈哌齐或卡巴拉汀）通过抑制 AChE 增加胆碱能突触内的乙酰胆碱浓度[34]。

体内神经成像（SPECT 和 PET）利用靶向胆碱能标志物示踪剂来评估胆碱能系统。胆碱能活性的标志物包括突触前[胆碱乙酰转移酶（choline acetyltransferase，ChAT）、囊泡乙酰胆碱转运体（vesicular acetylcholine transporter，VAChT）和 AChE]和突触后[$\alpha_4\beta_2$ 烟碱乙酰胆碱受体（nicotinic acetylcholine receptors，nAChRs）和毒蕈碱乙酰胆碱受体（muscarinic acetylcholine receptors，mAChRs）]标志物[4, 18]。ChAT 是催化乙酰胆碱合成的特异性酶，目前尚没有可用于 ChAT 体内成像的示踪剂。VAChT 定位于胆碱能神经元末端的突触囊泡膜上，其功能是将乙酰胆碱从细胞质转运到囊泡中。[^{18}F]FEOBV 是一种可与 VAChT 结合的 PET 成像示踪剂，用于体内胆碱能末端密度的测量。[^{123}I]IBVM 是一种靶向 VAChT 的 SPECT 成像示踪剂。AChE PET 成像可用于评估大脑中两个主要的胆碱能投射系统：皮质系统（起源于基底前脑）和皮质下系统（起源于脑干脚桥核和外背侧被盖核）。因此，皮质 AChE 活性反映基底前脑胆碱能神经元的完整性，丘脑 AChE 活性代表脚桥核胆碱能神经元的完整性[4]。[^{11}C]PMP 和[^{11}C]MP4A 是可与 AChE 结合的 PET 成像示踪剂，用于检测体内 AChE 的活性。[^{11}C]NMPB 是一种可与 mAChRs（M1 或 M2 亚型）结合的 PET 成像示踪剂，2-[^{18}F]FA-85380 是一种可与 $\alpha_4\beta_2$-nAChRs 结合的 PET 成像示踪剂[18]。

利用经颅磁刺激测量短潜伏期传入抑制（short latency afferent inhibition，SAI），是一种用于研究皮质胆碱能活动的电生理技术[35-36]。在给予皮质刺激之前约 20~25 ms，在腕部正中神经先给予一次电刺激，那么运动诱发电位的波幅一般就会被抑制，这种现象称为 SAI，该参数被认为是反映中枢胆碱能活动的指标[35]。胆碱能神经功能障碍导致 SAI 减少（记录的运动诱发电位波幅减少得更多）。在健康受试者中，静脉注射东莨菪碱（一种毒蕈碱受体拮抗剂）后发现 SAI 显著减少，证实了中枢胆碱能系统对 SAI 的贡献[35]。

三、中枢胆碱能系统参与帕金森病步态和平衡障碍的机制

（一）胆碱能系统和步态

步态是认知和运动等多功能和系统协同的生物学行为，正常步态的维持需要注意力和执行功能等多维认知领域参与[37]。与健康受试者相比，帕金森病患者的步态特征是步速减慢、步长缩短和步态变异性增加[38]。帕金森病患者在行走时注意力增加[39]。行走对帕金森病患者来说是一项具有挑战性的运动，特别是在同时执行运动或认知任务时[40-41]。与单任务条件相比，双任务条件下步态表现的下降被认为反映了步态控制的自动性受损和（或）使用认知过程（如注意力）来控制步态的需求增加[37]。目前认为帕金森病步态障碍可能主要是通过认知功能障碍介导的[42-44]。与皮质胆碱能神经功能障碍相关的额外的执行功能和注意力障碍会加剧步态问题[45]。

一项有关帕金森病患者的步速与中枢胆碱能系统功能的研究，利用 AChE PET 影像学将帕金森病患者分为低胆碱能和正常胆碱能组，结果发现，皮质低胆碱能的帕金森病患者步速显著减慢[（0.97±0.22）m/s]，而皮质正常胆碱能的帕金森病患者步速[（1.12±0.20）m/s]与健康对照组的步速[（1.17±0.18）m/s]无显著差异，提示皮质失胆碱能神经支配

与步速减慢相关[46]。此研究还发现脚桥核-丘脑失胆碱能神经支配与步速无关。基底前脑胆碱能神经元在记忆、注意等高级认知功能中发挥重要作用，基底前脑胆碱能神经元退变导致皮质失胆碱能神经支配，使帕金森病患者的步态更慢、更谨慎。步速对认知功能障碍敏感，步速减慢预示老年人认知能力下降[47-48]。因此，步速减慢可能是帕金森病患者基底前脑胆碱能退变的早期标志，可对识别认知功能下降高风险的帕金森病患者提供信息[45, 49-50]。此外，认知功能也是帕金森病患者步速的重要预测因素[40]。步长和跨步时间变异性亦与中枢胆碱能神经元功能有关。步长被认为是高度依赖于认知功能的步态特征[51]。研究发现，步长缩短和步态变异性增加是预测帕金森病患者认知减退的敏感指标[52]，而且提高帕金森病患者的注意力后可使患者的步长增加[53]。3项针对AChE抑制剂的Ⅱ期临床试验研究结果显示，与对照组相比，在单任务和双任务条件下（同时完成认知或运动任务的步态评估），接受AChE抑制剂治疗的帕金森病患者步速显著提高，跨步时间变异性减少，跌倒次数减少[54-56]。两项有关帕金森病的MRI研究结果显示，Meynert基底核体积和灰质密度的减低与步态参数的典型变化（跨步时间变异性增加、摆动时间和步长缩短）和步速减慢有关[57-58]。

冻结步态的发生也与中枢胆碱能神经功能障碍有关[59]。一项采用[^{11}C]PMP和[^{11}C]PIB（β-淀粉样蛋白靶向PET显像剂）的多示踪PET成像研究结果表明，皮质失胆碱能神经支配与发生冻结步态的风险增加有关，特别是在伴有皮质淀粉样蛋白沉积的情况下，而脚桥核-丘脑失胆碱能神经支配对冻结步态没有影响[60]。最近的一项研究指出，与非冻结步态组相比，冻结步态组的纹状体、海马体和杏仁核的胆碱能末梢密度显著降低[61]。然而，其他研究发现冻结步态患者脚桥核的MRI异常，包括灰质萎缩和自由水池的信号增加[62-63]。有报道称，帕金森病伴冻结步态患者的弥散张量成像显示脚桥核与小脑、丘脑、额叶和前额叶皮质多个区域之间的结构连通性降低[64-65]。以上研究结果提示，冻结步态的发生与神经网络和神经递质异常有关，其中胆碱能系统功能障碍可能只是诸多复杂因素之一。

（二）胆碱能系统和平衡

皮质失胆碱能神经支配与认知障碍有关[31]，而脚桥核胆碱能神经元及其投射至丘脑的神经纤维退变与姿势控制障碍有关[29, 66]。研究结果显示，与没有平衡障碍的患者相比，帕金森病伴平衡障碍患者脚桥核中的胆碱能神经元更少[66]。对啮齿动物的研究结果表明，多巴胺能和胆碱能神经元双重损失导致跌倒显著增加[67]。与无跌倒的患者相比，帕金森病伴跌倒患者的丘脑胆碱能神经支配明显减少，但黑质纹状体失多巴胺能神经支配的程度没有差异[27]。丘脑AChE活性主要来源于脑干脚桥核神经元的末端，它在运动控制中起着关键作用[68]。因此，丘脑AChE活性下降可能反映脚桥核胆碱能神经元功能障碍或变性。对帕金森病患者给予多奈哌齐或卡巴拉汀治疗后跌倒率下降[69]。另有证据表明，可以直接靶向脚桥核来治疗平衡障碍，然而到目前为止，脚桥核脑深部电刺激治疗平衡障碍的效果好坏参半[70]。

上述结果表明，脑干胆碱能系统与帕金森病跌倒的发生有关，但基底前脑皮质胆碱能神经支配相关的认知障碍可能进一步加剧帕金森病患者跌倒的发生。在帕金森病中，认知储备可以补偿步态和平衡缺陷，但当认知储备减少时，步态和动态平衡可能不再通过注意力控制来补偿，从而导致跌倒风险增加。研究发现，跌倒次数的增加与注意力控制的较差表现相关[67]。此外，与单独的跑步机训练相比，将认知挑战、虚拟现实范式与跑步机训练相结合的干预措施可以减少跌倒发生[71]。这表明注意力可以调节步态和平衡障碍对跌倒风险的影响。除了帕金森病本身的病理外，胆碱能神经元活性降低可能是使用抗胆碱能药物的结果。抗胆碱能药物通常用于帕金森病的运动症状和非运动症状的治疗。反过来，这类药物也增加了跌倒的风险，降低身体的机能[72]。

除多巴胺能系统和胆碱能系统参与帕金森病步态和平衡障碍外，有研究报道帕金森病患者脑内淀粉样变与姿势不稳和步态障碍存在关联[73]。在有痴呆风险的帕金森病患者中，大脑皮质β-淀粉样蛋白的沉积与姿势不稳/步态障碍的严重程度相关[73]。猜测皮质淀粉样变是姿势不稳/步态障碍和认知功能障碍的共同机制，这可能也解释了为什么姿势不稳/步态障碍亚型的帕金森病患者容易发生痴呆。

四、总结

综上所述，中枢胆碱能神经系统退变是导致帕金森病步态异常和平衡障碍的重要因素，增加中枢胆碱能神经功能对未来帕金森病的治疗有重要意义。运动干预可以增加乙酰胆碱的产生，提示运动是一种有效的非药物替代疗法[74-75]。而且，包括认知成分的运动干预已被证明对活动和跌倒有益[75]。其他提高胆碱能输出的技术，如Meynert基底核脑深部电刺激术[76-77]和无创迷走神经刺激[78]，目前尚处于研究阶段。

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参　考　文　献

[1] Muslimovic D, Post B, Speelman JD, et al. Determinants of disability and quality of life in mild to moderate Parkinson disease[J]. Neurology, 2008, 70(23): 2241-2247. DOI: 10.1212/01.wnl.0000313835.33830.80.

[2] Schrag A, Hovris A, Morley D, et al. Caregiver-burden in parkinson's disease is closely associated with psychiatric symptoms, falls, and disability[J]. Parkinsonism Relat Disord, 2006, 12(1): 35-41. DOI: 10.1016/j. parkreldis. 2005.06.011.

[3] Sethi K. Levodopa unresponsive symptoms in Parkinson disease[J]. Mov Disord, 2008, 23 Suppl 3: S521-S533. DOI:

10.1002/mds.22049.

[4] Bohnen NI, Albin RL. The cholinergic system and Parkinson disease[J]. Behav Brain Res, 2011, 221(2): 564-573. DOI: 10.1016/j.bbr.2009.12.048.

[5] Yarnall A, Rochester L, Burn DJ. The interplay of cholinergic function, attention, and falls in Parkinson's disease[J]. Mov Disord, 2011, 26(14): 2496-2503. DOI: 10.1002/mds.23932.

[6] Bohnen NI, Jahn K. Imaging: what can it tell us about parkinsonian gait? [J]. Mov Disord, 2013, 28(11): 1492-1500. DOI: 10.1002/mds.25534.

[7] Morris R, Martini DN, Madhyastha T, et al. Overview of the cholinergic contribution to gait, balance and falls in Parkinson's disease[J]. Parkinsonism Relat Disord, 2019, 63: 20-30. DOI: 10.1016/j.parkreldis.2019.02.017.

[8] Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior[J]. Neuron, 2012, 76(1): 116-129. DOI: 10.1016/j.neuron.2012.08.036.

[9] Benagiano V, Virgintino D, Flace P, et al. Choline acetyltransferase-containing neurons in the human parietal neocortex[J]. Eur J Histochem, 2003, 47(3): 253-256. DOI: 10.4081/835.

[10] von Engelhardt J, Eliava M, Meyer AH, et al. Functional characterization of intrinsic cholinergic interneurons in the cortex[J]. J Neurosci, 2007, 27(21): 5633-5642. DOI: 10.1523/JNEUROSCI.4647-06.2007.

[11] Mesulam MM, Mufson EJ, Wainer BH, et al. Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1-Ch6) [J]. Neuroscience, 1983, 10(4): 1185-1201. DOI: 10.1016/0306-4522(83)90108-2.

[12] Selden NR, Gitelman DR, Salamon-Murayama N, et al. Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain[J]. Brain, 1998, 121 (Pt 12): 2249-2257. DOI: 10.1093/brain/121.12.2249.

[13] Mesulam MM, Mufson EJ, Levey AI, et al. Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey[J]. J Comp Neurol, 1983, 214(2): 170-197. DOI: 10.1002/cne.902140206.

[14] Johnston MV, McKinney M, Coyle JT. Evidence for a cholinergic projection to neocortex from neurons in basal forebrain[J]. Proc Natl Acad Sci U S A, 1979, 76(10): 5392-5396. DOI: 10.1073/pnas.76.10.5392.

[15] Divac I. Magnocellular nuclei of the basal forebrain project to neocortex, brain stem, and olfactory bulb. Review of some functional correlates[J]. Brain Res, 1975, 93(3): 385-398. DOI: 10.1016/0006-8993(75)90178-x.

[16] Mesulam MM, Geula C. Nucleus basalis (Ch4) and cortical cholinergic innervation in the human brain: observations based on the distribution of acetylcholinesterase and choline acetyltransferase[J]. J Comp Neurol, 1988, 275(2): 216-240. DOI: 10.1002/cne.902750205.

[17] Pahapill PA, Lozano AM. The pedunculopontine nucleus and Parkinson's disease[J]. Brain, 2000, 123 (Pt 9): 1767-1783. DOI: 10.1093/brain/123.9.1767.

[18] Pasquini J, Brooks DJ, Pavese N. The cholinergic brain in Parkinson's disease[J]. Mov Disord Clin Pract, 2021, 8(7): 1012-1026. DOI: 10.1002/mdc3.13319.

[19] Arendt T, Bigl V, Arendt A, et al. Loss of neurons in the nucleus basalis of Meynert in Alzheimer's disease, paralysis agitans and Korsakoff's disease[J]. Acta Neuropathol, 1983, 61(2): 101-108. DOI: 10.1007/BF00697388.

[20] Nakano I, Hirano A. Parkinson's disease: neuron loss in the nucleus basalis without concomitant Alzheimer's disease[J]. Ann Neurol, 1984, 15(5): 415-418. DOI: 10.1002/ana.410150503.

[21] Rogers JD, Brogan D, Mirra SS. The nucleus basalis of Meynert in neurological disease: a quantitative morphological study[J]. Ann Neurol, 1985, 17(2): 163-170. DOI: 10.1002/ana.410170210.

[22] Whitehouse PJ, Hedreen JC, White CL 3rd, et al. Basal forebrain neurons in the dementia of Parkinson disease[J]. Ann Neurol, 1983, 13(3): 243-248. DOI: 10.1002/ana.410130304.

[23] Candy JM, Perry RH, Perry EK, et al. Pathological changes in the nucleus of Meynert in Alzheimer's and Parkinson's diseases[J]. J Neurol Sci, 1983, 59(2): 277-289. DOI: 10.1016/0022-510x(83)90045-x.

[24] Ruberg M, Ploska A, Javoy-Agid F, et al. Muscarinic binding and choline acetyltransferase activity in Parkinsonian subjects with reference to dementia[J]. Brain Res, 1982, 232(1): 129-139. DOI: 10.1016/0006-8993(82)90615-1.

[25] Tagliavini F, Pilleri G, Bouras C, et al. The basal nucleus of Meynert in idiopathic Parkinson's disease[J]. Acta Neurol Scand, 1984, 70(1): 20-28. DOI: 10.1111/j.1600-0404.1984.tb00798.x.

[26] Braak H, Del Tredici K, Rüb U, et al. Staging of brain pathology related to sporadic Parkinson's disease[J]. Neurobiol Aging, 2003, 24(2): 197-211. DOI: 10.1016/s0197-4580(02)00065-9.

[27] Bohnen NI, Müller ML, Koeppe RA, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity[J]. Neurology, 2009, 73(20): 1670-1676. DOI: 10.1212/WNL.0b013e3181c1ded6.

[28] Müller ML, Albin RL, Kotagal V, et al. Thalamic cholinergic innervation and postural sensory integration function in Parkinson's disease[J]. Brain, 2013, 136(Pt 11): 3282-3289. DOI: 10.1093/brain/awt247.

[29] Bohnen NI, Albin RL. Cholinergic denervation occurs early in Parkinson disease[J]. Neurology, 2009, 73(4): 256-257. DOI: 10.1212/WNL.0b013e3181b0bd3d.

[30] Kotagal V, Müller ML, Kaufer DI, et al. Thalamic cholinergic innervation is spared in Alzheimer disease compared to parkinsonian disorders[J]. Neurosci Lett, 2012, 514(2): 169-172. DOI: 10.1016/j.neulet.2012.02.083.

[31] Bohnen NI, Kaufer DI, Hendrickson R, et al. Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia[J]. J Neurol, 2006, 253(2): 242-247. DOI: 10.1007/s00415-005-0971-0.

[32] Shimada H, Hirano S, Shinotoh H, et al. Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET[J]. Neurology, 2009, 73(4): 273-278. DOI: 10.1212/WNL.0b013e3181ab2b58.

[33] Ruberg M, Rieger F, Villageois A, et al. Acetylcholinesterase and butyrylcholinesterase in frontal cortex and cerebrospinal fluid of demented and non-demented patients with Parkinson's disease[J]. Brain Res, 1986,

362(1): 83-91. DOI: 10.1016/0006-8993(86)91401-0.
[34] Colović MB, Krstić DZ, Lazarević-Pašti TD, et al. Acetylcholinesterase inhibitors: pharmacology and toxicology[J]. Curr Neuropharmacol, 2013, 11(3): 315-335. DOI: 10.2174/1570159X11311030006.
[35] Di Lazzaro V, Oliviero A, Profice P, et al. Muscarinic receptor blockade has differential effects on the excitability of intracortical circuits in the human motor cortex[J]. Exp Brain Res, 2000, 135(4): 455-461. DOI: 10.1007/s002210000543.
[36] Di Lazzaro V, Oliviero A, Tonali PA, et al. Noninvasive in vivo assessment of cholinergic cortical circuits in AD using transcranial magnetic stimulation[J]. Neurology, 2002, 59(3): 392-397. DOI: 10.1212/wnl.59.3.392.
[37] Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait[J]. Mov Disord, 2008, 23(3): 329-342; quiz 472. DOI: 10.1002/mds.21720.
[38] Hausdorff JM, Cudkowicz ME, Firtion R, et al. Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease[J]. Mov Disord, 1998, 13(3): 428-437. DOI: 10.1002/mds.870130310.
[39] Rochester L, Hetherington V, Jones D, et al. Attending to the task: interference effects of functional tasks on walking in Parkinson's disease and the roles of cognition, depression, fatigue, and balance[J]. Arch Phys Med Rehabil, 2004, 85(10): 1578-1585. DOI: 10.1016/j.apmr.2004.01.025.
[40] Lord S, Rochester L, Hetherington V, et al. Executive dysfunction and attention contribute to gait interference in 'off' state Parkinson's disease[J]. Gait Posture, 2010, 31(2): 169-174. DOI: 10.1016/j.gaitpost.2009.09.019.
[41] Bond JM, Morris M. Goal-directed secondary motor tasks: their effects on gait in subjects with Parkinson disease[J]. Arch Phys Med Rehabil, 2000, 81(1): 110-116. DOI: 10.1016/s0003-9993(00)90230-2.
[42] Rochester L, Nieuwboer A, Baker K, et al. Walking speed during single and dual tasks in Parkinson's disease: which characteristics are important? [J]. Mov Disord, 2008, 23(16): 2312-2318. DOI: 10.1002/mds.22219.
[43] Lord S, Baker K, Nieuwboer A, et al. Gait variability in Parkinson's disease: an indicator of non-dopaminergic contributors to gait dysfunction? [J]. J Neurol, 2011, 258(4): 566-572. DOI: 10.1007/s00415-010-5789-8.
[44] Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research[J]. Gait Posture, 2002, 16(1): 1-14. DOI: 10.1016/s0966-6362(01)00156-4.
[45] Rochester L, Yarnall AJ, Baker MR, et al. Cholinergic dysfunction contributes to gait disturbance in early Parkinson's disease[J]. Brain, 2012, 135(Pt 9): 2779-2788. DOI: 10.1093/brain/aws207.
[46] Bohnen NI, Frey KA, Studenski S, et al. Gait speed in Parkinson disease correlates with cholinergic degeneration[J]. Neurology, 2013, 81(18): 1611-1616. DOI: 10.1212/WNL.0b013e3182a9f558.
[47] Verghese J, Wang C, Lipton RB, et al. Quantitative gait dysfunction and risk of cognitive decline and dementia[J]. J Neurol Neurosurg Psychiatry, 2007, 78(9): 929-935. DOI: 10.1136/jnnp.2006.106914.
[48] Mielke MM, Roberts RO, Savica R, et al. Assessing the temporal relationship between cognition and gait: slow gait predicts cognitive decline in the Mayo Clinic Study of Aging[J]. J Gerontol A Biol Sci Med Sci, 2013, 68(8): 929-937. DOI: 10.1093/gerona/gls256.
[49] Alves G, Larsen JP, Emre M, et al. Changes in motor subtype and risk for incident dementia in Parkinson's disease[J]. Mov Disord, 2006, 21(8): 1123-1130. DOI: 10.1002/mds.20897.
[50] Taylor JP, Rowan EN, Lett D, et al. Poor attentional function predicts cognitive decline in patients with non-demented Parkinson's disease independent of motor phenotype[J]. J Neurol Neurosurg Psychiatry, 2008, 79(12): 1318-1323. DOI: 10.1136/jnnp.2008.147629.
[51] Morris R, Lord S, Bunce J, et al. Gait and cognition: mapping the global and discrete relationships in ageing and neurodegenerative disease[J]. Neurosci Biobehav Rev, 2016, 64: 326-345. DOI: 10.1016/j.neubiorev.2016.02.012.
[52] Morris R, Lord S, Lawson RA, et al. Gait rather than cognition predicts decline in specific cognitive domains in early Parkinson's disease[J]. J Gerontol A Biol Sci Med Sci, 2017, 72(12): 1656-1662. DOI: 10.1093/gerona/glx071.
[53] Baker K, Rochester L, Nieuwboer A. The immediate effect of attentional, auditory, and a combined cue strategy on gait during single and dual tasks in Parkinson's disease[J]. Arch Phys Med Rehabil, 2007, 88(12): 1593-1600. DOI: 10.1016/j.apmr.2007.07.026.
[54] Henderson EJ, Lord SR, Brodie MA, et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial[J]. Lancet Neurol, 2016, 15(3): 249-258. DOI: 10.1016/S1474-4422(15)00389-0.
[55] Chung KA, Lobb BM, Nutt JG, et al. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease[J]. Neurology, 2010, 75(14): 1263-1269. DOI: 10.1212/WNL.0b013e3181f6128c.
[56] Li Z, Yu Z, Zhang J, et al. Impact of rivastigmine on cognitive dysfunction and falling in Parkinson's disease patients[J]. Eur Neurol, 2015, 74(1-2): 86-91. DOI: 10.1159/000438824.
[57] Wilson J, Yarnall AJ, Craig CE, et al. Cholinergic basal forebrain volumes predict gait decline in Parkinson's disease[J]. Mov Disord, 2021, 36(3): 611-621. DOI: 10.1002/mds.28453.
[58] Dalrymple WA, Huss DS, Blair J, et al. Cholinergic nucleus 4 atrophy and gait impairment in Parkinson's disease[J]. J Neurol, 2021, 268(1): 95-101. DOI: 10.1007/s00415-020-10111-2.
[59] Snijders AH, Takakusaki K, Debu B, et al. Physiology of freezing of gait[J]. Ann Neurol, 2016, 80(5): 644-659. DOI: 10.1002/ana.24778.
[60] Bohnen NI, Frey KA, Studenski S, et al. Extra-nigral pathological conditions are common in Parkinson's disease with freezing of gait: an *in vivo* positron emission tomography study[J]. Mov Disord, 2014, 29(9): 1118-1124. DOI: 10.1002/mds.25929.
[61] Bohnen NI, Kanel P, Zhou Z, et al. Cholinergic system changes of falls and freezing of gait in Parkinson's disease [J]. Ann Neurol, 2019, 85(4): 538-549. DOI: 10.1002/ana.25430.
[62] Planetta PJ, Ofori E, Pasternak O, et al. Free-water imaging in Parkinson's disease and atypical parkinsonism[J]. Brain, 2016, 139(Pt 2): 495-508. DOI: 10.1093/brain/awv361.

[63] Snijders AH, Leunissen I, Bakker M, et al. Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait[J]. Brain, 2011, 134(Pt 1): 59-72. DOI: 10.1093/brain/awq324.
[64] Schweder PM, Hansen PC, Green AL, et al. Connectivity of the pedunculopontine nucleus in parkinsonian freezing of gait[J]. Neuroreport, 2010, 21(14): 914-916. DOI: 10.1097/WNR.0b013e32833ce5f1.
[65] Fling BW, Cohen RG, Mancini M, et al. Asymmetric pedunculopontine network connectivity in parkinsonian patients with freezing of gait[J]. Brain, 2013, 136(Pt 8): 2405-2418. DOI: 10.1093/brain/awt172.
[66] Karachi C, Grabli D, Bernard FA, et al. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease[J]. J Clin Invest, 2010, 120(8): 2745-2754. DOI: 10.1172/JCI42642.
[67] Kucinski A, Paolone G, Bradshaw M, et al. Modeling fall propensity in Parkinson's disease: deficits in the attentional control of complex movements in rats with cortical-cholinergic and striatal-dopaminergic deafferentation[J]. J Neurosci, 2013, 33(42): 16522-16539. DOI: 10.1523/JNEUROSCI.2545-13.2013.
[68] Lee MS, Rinne JO, Marsden CD. The pedunculopontine nucleus: its role in the genesis of movement disorders[J]. Yonsei Med J, 2000, 41(2): 167-184. DOI: 10.3349/ymj.2000.41.2.167.
[69] Hunter H, Rochester L, Morris R, et al. Longitudinal falls data in Parkinson's disease: feasibility of fall diaries and effect of attrition[J]. Disabil Rehabil, 2018, 40(19): 2236-2241. DOI: 10.1080/09638288.2017.1329357.
[70] Wang JW, Zhang YQ, Zhang XH, et al. Deep brain stimulation of pedunculopontine nucleus for postural instability and gait disorder after Parkinson disease: a meta-analysis of individual patient data[J]. World Neurosurg, 2017, 102: 72-78. DOI: 10.1016/j.wneu.2017.02.110.
[71] Mirelman A, Rochester L, Maidan I, et al. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial[J]. Lancet, 2016, 388(10050): 1170-1182. DOI: 10.1016/S0140-6736(16)31325-3.
[72] Aizenberg D, Sigler M, Weizman A, et al. Anticholinergic burden and the risk of falls among elderly psychiatric inpatients: a 4-year case-control study[J]. Int Psychogeriatr, 2002, 14(3): 307-310. DOI: 10.1017/s1041610202008505.
[73] Müller ML, Frey KA, Petrou M, et al. β-Amyloid and postural instability and gait difficulty in Parkinson's disease at risk for dementia[J]. Mov Disord, 2013, 28(3): 296-301. DOI: 10.1002/mds.25213.
[74] Fordyce DE, Farrar RP. Enhancement of spatial learning in F344 rats by physical activity and related learning-associated alterations in hippocampal and cortical cholinergic functioning[J]. Behav Brain Res, 1991, 46(2): 123-133. DOI: 10.1016/s0166-4328(05)80105-6.
[75] Brown BM, Peiffer JJ, Martins RN. Multiple effects of physical activity on molecular and cognitive signs of brain aging: can exercise slow neurodegeneration and delay Alzheimer's disease?[J]. Mol Psychiatry, 2013, 18(8): 864-874. DOI: 10.1038/mp.2012.162.
[76] Barnikol TT, Pawelczyk NB, Barnikol UB, et al. Changes in apraxia after deep brain stimulation of the nucleus basalis Meynert in a patient with Parkinson dementia syndrome[J]. Mov Disord, 2010, 25(10): 1519-1520. DOI: 10.1002/mds.23141.
[77] Gratwicke J, Zrinzo L, Kahan J, et al. Bilateral deep brain stimulation of the nucleus basalis of meynert for Parkinson disease dementia: a randomized clinical trial[J]. JAMA Neurol, 2018, 75(2): 169-178. DOI: 10.1001/jamaneurol.2017.3762.
[78] Engineer ND, Møller AR, Kilgard MP. Directing neural plasticity to understand and treat tinnitus[J]. Hear Res, 2013, 295: 58-66. DOI: 10.1016/j.heares.2012.10.001.

·启事·

本刊关于论文发表后撤稿的规定

一、撤稿的目的

纠正论文中的谬误。

二、撤稿的原因

(1)已经证实论文存在较严重的不可信、学术不端(包括捏造数据和篡改数据)或者非主观的错误,以至于该论文所报道的发现和结果不可信。(2)论文存在剽窃问题。(3)论文所报道的研究违反医学伦理规范。(4)重复发表。(5)在稿件发表流程中存在严重缺陷。(6)其他。

三、撤稿的流程

在保证撤稿声明内容完整、清晰的基础上,编辑部将和所有作者就撤稿声明的内容达成一致,以保证各方的利益。但在无法就撤稿声明的内容与作者达成一致时,如已有充足证据表明必须撤稿,编辑部将尽快刊出撤稿声明。

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