# 经嗅觉系统预测和治疗神经精神性疾病的研究进展

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**摘要** 人类嗅觉系统能感知大量化学物质。嗅觉障碍是一种常见的神经系统症状, 且其患病率和严重性随年龄增长而显著增加。嗅觉系统由于缺乏血脑屏障, 易成为异种生物的侵袭入口, 但同样也是诊断和治疗应用的理想解剖学窗口。许多精神性疾病和神经退行性疾病的发病早期都能检测到嗅觉障碍, 嗅觉能力的减退可被认为是某些神经退行性疾病认知能力下降的前兆。嗅觉障碍的高患病率及评估的简便性和低成本使其在临床应用方面具有极大的前景。了解嗅觉障碍与神经精神性疾病之间的联系有助于早期诊断和预测疾病进展。该文就嗅觉系统的特点、嗅觉障碍与神经精神性疾病的发病联系及可能的治疗方法作一简要综述, 旨在为神经精神性疾病的早期诊断和治疗提供新的思路。

**关键词** 嗅觉障碍; 神经精神性疾病; 鼻内递送; 芳香疗法; 细胞移植

# Advances in the Prediction and Treatment of Neuropsychiatric Diseases via Olfactory System

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**Abstract** The human olfactory system can perceive a large number of chemical substances. Olfaction disorders are common neurological symptoms, and their prevalence and severity increase substantially with aging. Due to the lack of blood-brain barrier, the olfactory system is a susceptible portal for xenobiotics, nevertheless, it serves as an ideal anatomical window for diagnostic and therapeutic applications. Olfaction disorders are detected in the early onset of various psychiatric and neurodegenerative diseases. Hypofunction of the olfactory system is considered as a precursor to cognitive decline in certain neurodegenerative diseases. The high prevalence of olfaction disorders, along with the simplicity and low cost of assessment, endows it with great prospects in clinical applications. Thus, understanding the relationship between olfaction disorders and neuropsychiatric diseases can help formulate early diagnosis and predict clinical progression. This review provides a brief summary of the characteristics of the

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olfactory system, the relationship between olfaction disorders and neuropsychiatric diseases, as well as possible treatments, in order to provide new ideas for early diagnosis and treatment of neuropsychiatric diseases.

**Keywords** olfaction disorders; neuropsychiatric diseases; intranasal delivery; aromatherapy; cell transplantation

嗅觉是人类的一项重要感觉功能, 嗅觉系统由于缺乏血脑屏障, 易成为异种生物的侵袭入口。嗅觉障碍是一种以气味阈值增加、气味辨别和识别准确性降低为特征的疾病, 伴有中枢嗅觉系统的结构和功能改变。嗅觉障碍会削弱对危险气味的感知能力甚至对生命安全构成威胁。

研究表明, 嗅觉障碍可见于神经精神性疾病的发病早期, 如重度抑郁症(major depressive disorder, MDD)、精神分裂症(schizophrenia, SCZ)、阿尔茨海默病(Alzheimer's disease, AD)和帕金森病(Parkinson's disease, PD)等[1-2], 暗示嗅觉障碍在检测和预测此类疾病方面有重要作用。另外, 嗅觉系统独有的经嗅觉途径无创治疗方法可为临床治疗神经精神性疾病提供新的选择[3-4]; 嗅觉相关细胞移植的治疗方法可被应用于以PD为代表的神经退行性疾病[5-6]和以脊髓损伤(spinal cord injury, SCI)为代表的神经损伤性疾病[7]的治疗。本综述就嗅觉系统的特点、嗅觉障碍在神经精神性疾病的预测中的作用及可能的治疗方法进行重点阐述, 旨在为神经精神性疾病的早期诊断和治疗提供新的思路。

## 1 嗅觉系统简介

人类的嗅觉系统对外界挥发性化学物质高度灵敏, 正常的嗅觉系统可以感知成千上万种气味。嗅觉系统按外周到中枢的排列顺序可分为三部分: 嗅上皮(olfactory epithelium, OE)、嗅球(olfactory bulb, OB)和嗅皮层(olfactory cortex, OC)(图1)。

嗅上皮是一种分层的神经上皮, 是感知气味的第一级结构, 位于鼻腔后部[8]。主要由三种细胞构成: 嗅觉感觉神经元(olfactory sensory neurons, OSNs)、支持细胞和基底细胞(包括水平基底细胞和球形基底细胞)。其中, OSNs是介于支持细胞间的双极神经元细胞, 主要起着受体、中继和传导的作用。当环境因素诱发细胞损伤和死亡时, OSNs能够通过基底干细胞和祖细胞群实现再生, 终生不断更新替换, 以维持正常的嗅觉功能。

嗅觉系统的神经冲动从嗅上皮传递到嗅球, 再传递至嗅皮层及其在大脑中的主要投射区域。嗅球是第一级中枢, 其向前连接嗅神经纤维, 向后伸出嗅束, 与脑区如大脑中皮质和皮质下区域相联系, 是嗅觉冲动传向中枢的中继站, 还可汇集嗅觉冲动, 调节嗅觉信息的传入。嗅皮层位于大脑皮质区, 包括嗅前核、嗅结节、梨状皮质、杏仁核和内嗅皮质, 接收来自嗅球神经元的信号输入。

## 2 嗅觉障碍与神经精神性疾病的预测

嗅觉系统和边缘大脑区域的神经解剖结构接近, 使得嗅觉系统与神经精神性疾病具有很高的相关性[2]。研究表明, 嗅觉障碍通常在神经精神性疾病, 如MDD、SCZ、AD、PD等发病早期出现, 并对疾病的发生发展起到重要的作用, 故嗅觉障碍检测可被应用于MDD、SCZ、AD、PD等神经精神性疾病的早期检测和进展预测(图2A)。

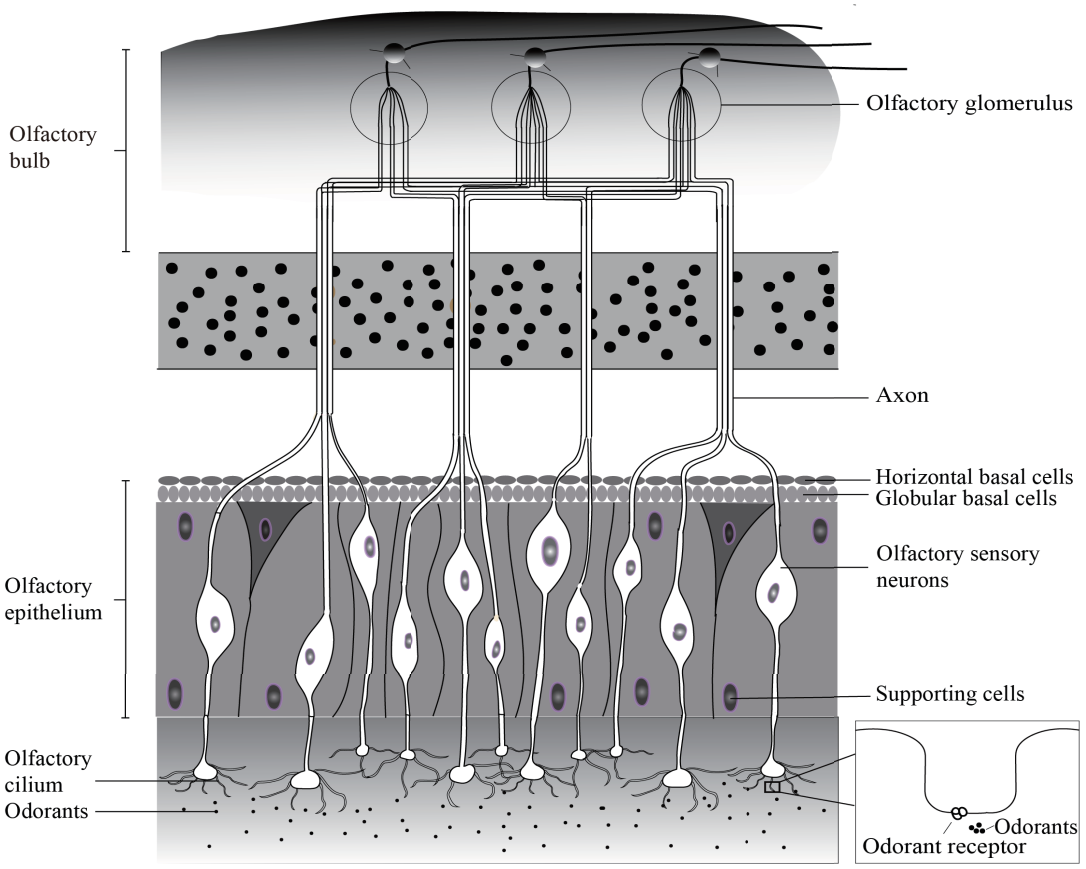
### 2.1 嗅觉障碍预测重度抑郁症的作用

MDD是一种以持续性情绪低落为主的严重精神障碍, 是抑郁症中最普遍、最严重的类型, 通常以心境低落、兴趣缺失、快感缺乏、内疚加深、记忆缺陷和痛苦的躯体症状等为特征[9]。目前, 大量研究表明, 抑郁和嗅觉障碍之间可能存在某种联系。

首先, 对抑郁大脑的检查发现, 边缘系统的结构发生了变化, 包括眶额皮质、前扣带皮质、后扣带皮质、岛叶、杏仁核、海马和丘脑等, 而这些区域也与嗅觉处理相关, 提示嗅觉处理和抑郁存在重叠脑区[10]。

其次, 在啮齿动物中, 双侧嗅球切除抑郁模型通过破坏双侧嗅球结构, 引起5-羟色胺和多巴胺浓度的改变, 导致抑郁症样的行为[11], 表明嗅觉系统的损伤可能是导致抑郁症的原因之一。在非双侧嗅球切除抑郁模型, 如慢性皮质酮给药抑郁模型[12]、慢性不可预测轻度应激抑郁模型[13]中也有嗅觉障碍的报道, 表明抑郁常常会伴随嗅觉障碍的出现。

嗅球切除后引起室管膜下区和海马成年神经发生的减少和破坏, 可能是造成抑郁的原因之一。室管膜下区(其新生神经元将迁移到嗅球)和海马终




气味分子穿经鼻腔时, 与嗅纤毛上的气味受体相结合产生电信号, 嗅纤毛为OSNs的树突, 在树突产生的电信号进一步整合, 经OSNs的轴突进一步传送, 随轴突终止于嗅球中离散的嗅小球, 进而被编码成不同的嗅觉信息, 并通过嗅束被传递到嗅皮层的不同区域。

When the odorant molecules pass through the nasal cavity, they bind to the odorant receptors on the olfactory cilia, which are the dendrites of OSNs. Electrical signals generated and integrated by the olfactory cilia are further transmitted by the axons of OSNs and terminated in the discrete olfactory glomerulus in the olfactory bulb. They are encoded into different olfactory information and transmitted to different regions of the olfactory cortex through the olfactory tracts.

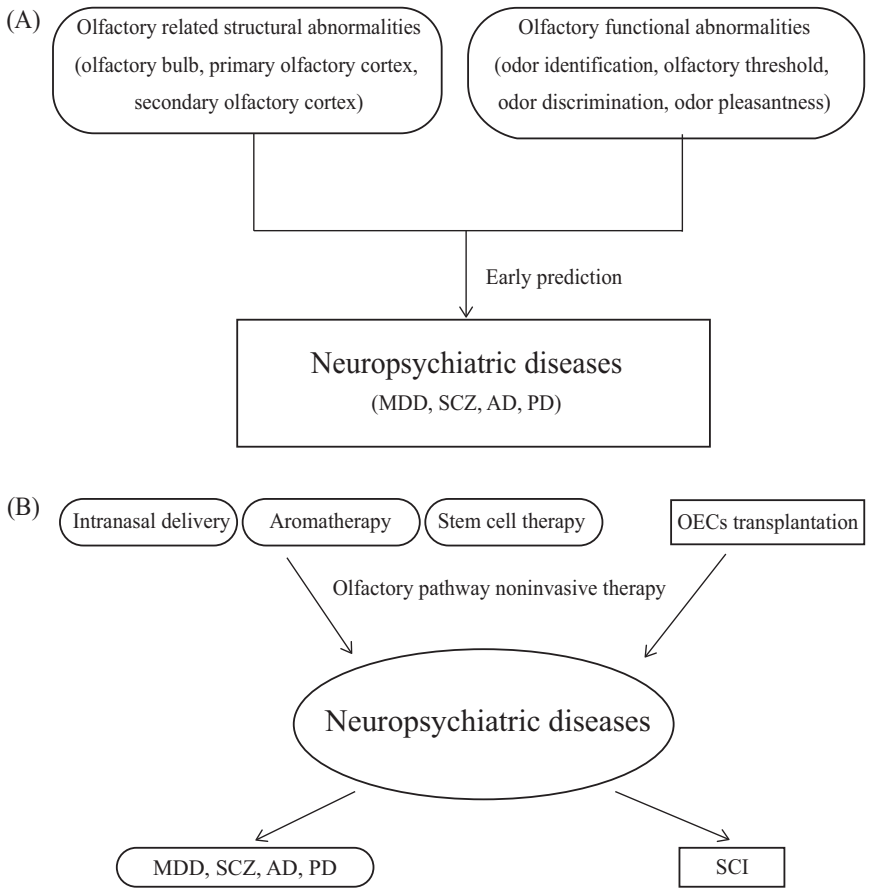
**图1 嗅觉系统的解剖结构**

**Fig.1 Anatomy of the olfactory system**

生都有持续存在的神经发生[9], 但在MDD患者中, 这些相关结构的神经发生减少, 而这些新生神经元不仅与嗅觉辨别和短期气味记忆密切相关, 还与情绪、学习记忆等相关[14]。另外, 行嗅球切除术的大鼠室管膜下区中细胞增殖显著减少[15], 提示嗅球结构破坏也可以阻碍室管膜下区的神经发生[13], 从而对抑郁的发生发展产生影响。海马的齿状回是啮齿动物、灵长类动物和人类的主要嗅觉信息接收区[16]。研究发现, 双侧嗅球切除模型会导致海马结构和功能出现异常: 海马体积减小[17](这与MDD患者的海马萎缩[18]一致); 齿状回中的细胞增殖抑制和成年神经发生破坏; 学习记忆功能下降, 神经元功能减退。药物治疗改善海马和室管膜下区的神经发生, 可以减轻嗅觉障碍, 缓解抑郁症状[19]。

此外, 伴随嗅觉损伤可出现类似于MDD的情绪、学习和记忆障碍等。32名出生即丧失嗅觉的患者中, 有29%的人介于轻微和严重抑郁之间[20]。嗅觉丧失的患者, 其海马对情感线索(如有情感暗示的图片)反应迟钝[21]; 内嗅皮质和嗅球的病变会导致空间工作记忆和逆向学习的缺陷[22]。临床观察和动物实验也指出, 嗅觉障碍可诱导抑郁的出现, 且抑郁症患者和健康对照组之间的嗅觉差异可在治疗后消失[11]。而MDD患者也存在嗅觉结构和功能的异常。MDD患者的嗅球体积减小, 嗅觉敏感性下降, 并且其抑郁评分与嗅球体积和嗅觉灵敏度呈负相关[23]。嗅球体积较小可能是抑郁症易感性的一个因素: 嗅觉输入减少可能会对情感处理产生影响, 从而使人们更易遭受抑郁症的困扰[24]。

综上, 解剖结构、动物模型和人体实验等方面的证据表明, MDD和嗅觉障碍之间可能存在一定的




A: 嗅觉障碍与神经精神性疾病紧密联系。嗅觉相关结构异常, 包括嗅球、初级嗅觉皮质和次级嗅觉皮质(重叠脑区)结构异常; 嗅觉功能异常, 包括气味识别、嗅觉阈值、气味辨别和气味愉悦性功能异常, 这两者可以作为神经精神性疾病(如MDD、SCZ、AD和PD等)的早期预测指标; B: 嗅觉途径无创疗法, 包括鼻内递送、芳香疗法和干细胞疗法, 可以为神经精神性疾病的治疗提供思路; OECs移植修复也能为神经性疾病如SCI提供有前景的治疗策略。MDD: 重度抑郁症; SCZ: 精神分裂症; AD: 阿尔茨海默病; PD: 帕金森病; SCI: 脊髓损伤; OECs: 嗅鞘细胞。

A: olfaction disorders are closely related to neuropsychiatric diseases. The olfactory related structural abnormalities in olfactory bulb, primary olfactory cortex and secondary olfactory cortex (overlapping regions), and olfactory dysfunctions in odor identification, olfactory threshold, odor discrimination and odor pleasantness, are early clinical prediction factors of neuropsychiatric diseases (such as MDD, SCZ, AD and PD); B: noninvasive treatment of olfactory pathway, including intranasal delivery, aromatherapy and stem cell therapy, can provide new ideas for treatment of neuropsychiatric diseases. Besides, OECs transplantation also provides promising therapeutic strategies for neurological diseases like SCI. MDD: major depressive disorder; SCZ: schizophrenia; AD: Alzheimer's disease; PD: Parkinson's disease; SCI: spinal cord injury; OECs: olfactory ensheathing cells.

**图2 嗅觉障碍与神经精神性疾病的联系及其应用**

**Fig.2 The relationship between olfaction disorders and neuropsychiatric diseases and their applications**

联系, 嗅觉的损伤会导致情绪、学习和记忆障碍等, 嗅觉障碍可以作为MDD的预测指标。

### 2.2 嗅觉障碍预测精神分裂症的作用

SCZ是一种慢性精神性疾病, 以阳性症状(如妄想、幻觉和瓦解症状)、阴性症状(如情感迟钝、言语贫乏、快感缺乏、社交退缩和意志减退)和认知障碍为特征[25]。目前, 大量研究表明, SCZ与嗅觉障碍之间可能存在某种联系。

有研究发现, SCZ患者嗅球和海马的体积均减小[26-27], 嗅球突触功能降低[28], 嗅沟(嗅觉系统神经发育的指标)变浅[29], 嗅上皮鼻活检发现OSNs的发育失调[30]。与MDD相似, 嗅觉的神经回路也与SCZ的相关脑区相重叠, 包括眶额皮质、杏仁核、海马和海马旁回的亚区等[31], 这些结构是负责嗅觉和情感、社会信息处理加工的重叠区域[29], 其结构异常不仅与嗅觉障碍有关, 还与SCZ的阴性症状有关[32]; 在SCZ的临床高危受试者中也发现了嗅觉系统结构的异常, 包括鼻腔、嗅球、嗅沟及内侧颞叶的初级嗅觉皮质等[33], 提示嗅觉相关结构的变化与SCZ存在潜在联系。SCZ患者的嗅束和视觉皮质之间(嗅觉和视觉整合)、前梨状皮质和伏隔核之间(多模态感觉整合)以及后梨状皮质和额中回之间(嗅觉辨别力和识别能力)存在连通性破坏[34], 这可能也是导致SCZ患者嗅觉障碍和嗅觉整合中断的原因。

在嗅觉功能上, SCZ患者在气味识别、嗅觉阈值和气味辨别方面均表现出不同程度的障碍。如在气味识别方面, SCZ患者表现出气味识别受损, 并且其受损程度与发病持续时间有关[35]; 在嗅觉阈值方面, 首发SCZ患者的嗅觉阈值明显高于复发SCZ患者, 提示随着疾病的进展, SCZ患者嗅觉敏感性增加。这可能是由于复发SCZ患者嗅觉和情感重叠脑区的异常激活了外周嗅觉系统的代偿机制所致[36], 而首发SCZ患者嗅觉敏感性却不高, 可能是因为重叠脑区的损害程度还较轻, 尚未引起明显的代偿机制[37]; 在气味辨别方面, SCZ患者的气味辨别评分较差(预示认知障碍)[30], 这可能与嗅觉和认知的重叠脑区有关[37]。

临床上, 超过80%的SCZ患者患有嗅觉障碍, 嗅觉障碍可在SCZ早期被发现, 并在确诊后随时间推移而继续发展[28]。SCZ患者对愉悦气味的识别准确性较差[38], 发病前出现该现象暗示更大的转变风险[39]。而未受SCZ影响的一级亲属嗅球体积减小, 其中超过55%的一级亲属伴有轻度嗅觉障碍[40-41]。

综上, 一系列嗅觉相关结构的变化和嗅觉测试的证据表明, SCZ与嗅觉障碍存在一定关联, 嗅觉障碍可能是SCZ早期诊断、监测进展和预测结果的潜在标志。

### 2.3 嗅觉障碍预测阿尔茨海默病的作用

AD是老年人中最常见的神经退行性疾病, 主要临床特征是进行性认知功能障碍和行为损害。神经退行性病变的病理学特征包括淀粉样蛋白(amyloid-β, Aβ)的积累、过度磷酸化的Tau蛋白神经原纤维缠结、神经元缺失和胶质细胞增生[42-43]。大量研究表明, 嗅觉障碍是AD早期的临床标志, 也是疾病进展和认知能力减退的标志。

研究发现, 受AD影响最早的区域之一是嗅觉系统, AD与嗅觉障碍在神经病理学上体现出一定的相关性。在AD患者的嗅觉系统中可发现与中枢神经系统相同的AD病理学特征, 如嗅上皮、嗅球、前嗅核及嗅觉相关皮质中出现Aβ沉积和神经原纤维缠结[44-45], 并且这些变化可早于AD临床症状出现[46]。Aβ首先在嗅上皮中沉积, 且嗅上皮的厚度与Aβ的沉积呈反比; 3~4个月后, Aβ向嗅球、前嗅核和梨状皮质扩散, 这可能与早期嗅觉障碍有关; 9~10个月时, 在中心区域出现Aβ高水平沉积, 随后老年性斑块沉积物也发展到内部皮质[47]。内嗅皮质和海马是嗅觉和认知系统的重叠皮质[48], 当海马和内嗅皮质中出现老年性斑块大量沉积时, 会影响学习和记忆能力, 进而导致认知障碍。

从嗅觉检测缺陷到发展为空间记忆水平下降的结果显示, 通过嗅觉途径沉积在认知相关皮质区域的Aβ数量与嗅觉障碍的程度呈正相关[47], 提示早期的嗅觉障碍可以预测AD。另外, 嗅觉障碍还可作为轻度认知障碍(mild cognitive impairment, MCI)转化为AD的预测指标, 嗅觉正常的MCI患者中有11%最终发展为AD, 而嗅觉受损的MCI患者中最终发展为AD的比例高达47%[49]。

综上, 嗅觉系统中出现AD典型病理学特征的证据表明, AD与嗅觉障碍之间存在极大的相关性, 嗅觉障碍有助于表征AD的前驱期并预测其发生进展。

### 2.4 嗅觉障碍预测帕金森病的作用

PD是第二常见的神经退行性疾病, 其典型症状为静止震颤、肌肉强直、运动迟缓和姿势步态障碍。特征性病理改变为以α-突触核蛋白(α-synuclein, α-syn)为主要成分的路易小体的形成和中脑黑质致密部多巴胺能神经元的丢失。大量的研究证明, PD和嗅觉障碍之间可能存在某种联系。

BRAAK等[50]研究发现, α-syn的沉积始于嗅球、前嗅核、舌咽神经和迷走神经的背侧运动核, 与嗅觉障碍的早期发作病理部位一致, 随后通过延髓脑干扩散到大脑皮质[51-52], 嗅球及下脑干被认为是异常α-syn的沉积位点[53]。PD早期的边缘白质、皮质脊髓、枕颞和额颞下通路被破坏, 这种与嗅觉障碍相同的通路紊乱, 暗示嗅觉障碍是PD前驱期的主要症状[54]。磁共振成像显示, 与健康对照组相比, PD患者的嗅球体积减小[55], 且其减少程度显著大于非典型帕金森综合征(如多系统萎缩、进行性核上性麻痹、皮质基底节变性等), 这表明检测嗅球体积不仅可以将PD患者与健康个体区分开, 还可以将PD与非典型帕金森综合征区分开[56]。早期PD患者的嗅束扩散率增加[57], 提示嗅束结构的完整性遭到破坏。所有这些研究表明, PD患者嗅觉中枢的整体结构异常。

此外有研究表明, PD患者中神经递质水平的改变可能与嗅觉障碍有关[58]。PD中有多种神经递质发生改变, 其中多巴胺、乙酰胆碱和5-羟色胺已被证明与嗅觉丧失有关[59]。PD患者嗅觉功能与黑质、纹状体和海马中的多巴胺转运蛋白活性之间存在相关性[60]。在包括PD、AD在内的神经退行性疾病中,

均能观察到梅纳特基底核中乙酰胆碱神经元的大量丢失, 暗示神经退行性疾病之间的嗅觉障碍可能存在一个共同的机制[58]。

嗅觉障碍是PD最早的非运动特征之一, 其出现至少早于经典运动症状5年[61], 且与PD发生风险之间存在关联[62], 伴有嗅觉障碍的PD患者在诊断后10年内其痴呆的风险会增加。研究发现, PD患者的无症状但表现出嗅觉减退的亲属有10%发展为临床PD; 另外, 12%的嗅觉减退亲属出现了黑质纹状体系统的亚临床变性, 提示在嗅觉减退前提下发生PD的风险可能高达22%[63]。另一项研究发现, 嗅觉障碍也与PD的严重程度、持续时间有关[60,64], 在PD患者表现出运动症状后, 嗅觉障碍并没有停止, 而是随着时间的推移继续发展, 这种嗅觉障碍与PD的运动和非运动特征均相关[65]。

综上, 嗅觉系统的病理学变化、功能结构改变以及神经递质水平变化的证据表明, PD的发病风险与嗅觉障碍存在一定关联, 嗅觉检查可能是一种有用的PD筛查、进展预测工具。

除以上提到的疾病外, 嗅觉障碍也被认为是双向情感障碍(bipolar disorder, BD)、焦虑症(anxiety disorders)、强迫症(obsessive-compulsive disorder, OCD)、MCI等疾病发生的相关因素[1-2,66]。因此, 嗅觉障碍与神经精神性疾病之间存在密切的关系。

## 3 嗅觉途径无创治疗和细胞移植应用

除了对神经精神性疾病的早期检测和进展预测以外, 嗅觉系统还以其独有的直接鼻脑通路、细胞的可移植性和分化潜能等特征被广泛应用, 如嗅觉途径无创治疗为神经精神性疾病的临床治疗提供了一种新思路; 嗅觉相关细胞移植的治疗方法可被应用于以PD为代表的神经退行性疾病和以SCI为代表的神经损伤性疾病的治疗等(图2B)。

### 3.1 鼻内递送

鼻内递送(intranasal delivery, IN delivery), 又被称为鼻脑直接递送(direct nose-to-brain delivery, N-to-B delivery)[3], 是一种新型无创药物传递技术: 蛋白质和肽类药物通过OSNs轴突和嗅鞘细胞(olfactory ensheathing cells, OECs)之间的细胞外通道进入脑脊液, 进而迅速分布于整个中枢神经系统, 从而实现药物从鼻到脑的直接分布[67-68]。为减少非局灶性递送, 目前鼻内递送联合纳米颗粒、细胞穿透肽等给药方式, 在MDD、SCZ、AD和PD中已有一定的尝试。

BROWN等[68]利用加压嗅觉递送装置, 将具有抗抑郁作用的D1-D2干扰肽进行鼻内递送, 使脑中脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)的表达增加, 实现了抗抑郁作用。实验还发现, 鼻内递送所需剂量仅为静脉注射的7%, 可减轻动物模型的缺血性脑损伤, 且仅需10~30min就可在嗅球和前脑区域中检测到药物。该疗法作为MDD的无创疗法, 为临床治疗的进一步开发奠定了基础。

SAMARIDOU等[3]设计了一种核–壳纳米颗粒, 将负载有强神经保护活性的miR-132的纳米复合物经鼻内递送后, 可增加海马中miR-132水平, 进而改善AD小鼠的Tau代谢和记忆功能[69-70], 证明该方法对治疗AD具有巨大的潜力。

此外, 鼻内递送联合纳米颗粒及聚焦超声等技术, 也在SCZ[71]及PD[72]等的治疗中具有良好的应用前景。

### 3.2 芳香疗法

芳香疗法是一种利用植物中天然提取的芳香精华, 使身心健康得到平衡、协调和促进的方法[73]。服用抗抑郁药物可能会对胎儿及母乳喂养婴儿产生影响, 而芳香疗法则不存在这种问题[4], 如应用香兰素的芳香疗法可提高脑组织中5-羟色胺和多巴胺的水平, 进而减轻抑郁症状[74]。所以, 在许多国家, 芳香疗法正逐渐成为产后抑郁治疗的辅助疗法。

### 3.3 嗅觉系统干细胞应用于帕金森病治疗

神经干细胞和间充质干细胞可在体外产生多巴胺能神经元[75-76]。嗅觉系统中的嗅球神经干细胞(olfactory bulb neural stem cells, OB-NSCs)能终生分化为神经元和神经胶质细胞, 以替代受损或丢失的细胞, 维持大脑的正常功能[77]。MAREI等[6]通过基因工程使OB-NSCs表达人类神经生长因子(human nerve growth factor, hNGF), 并将这种OB-NSCs移植到PD小鼠的纹状体后, 能够有效保护纹状体神经元, 减少退行性病变的发生, 恢复纹状体的正常组织结构, 并改善运动功能。MURRELL等[78]发现, 移植来源于健康人和PD患者的OB-NSCs都能改善运动功能, 且不会引起肿瘤生长, 提示PD患者自体移植OB-NSCs是一种可行的方法。因此, OB-NSCs对PD的治疗具有较大的应用前景。

嗅觉系统中另一种干细胞是位于嗅觉粘膜的嗅

外胚间充质干细胞(olfactory ectomesenchymal stem cells, OE-MSCs)。ALIZADEH等[5]发现, 生长因子可诱导OE-MSCs分化出多巴胺能神经元样细胞, 且与脐带间充质干细胞相比, OE-MSCs具有更高的多巴胺能神经元样标志物表达[79], 表明OE-MSCs具有更高的分化为多巴胺能神经元的潜力, 并可能应用于PD治疗。

由于胚胎干细胞和诱导多能干细胞在被用于移植时存在细胞来源伦理问题、细胞获取的难操作性、免疫原性问题和肿瘤形成风险等, 在治疗PD时, OB-NSCs、OE-MSCs更适合作为移植材料[5,80-81]。

综上, 基于OB-NSCs、OE-MSCs的PD干细胞疗法, 嗅觉系统干细胞将在未来PD的自体移植治疗中发挥重要作用。

### 3.4 嗅鞘细胞应用于脊髓损伤移植

SCI伴随原发性损伤而来的是炎症、自由基产生和兴奋性毒性损伤的继发性级联反应, 导致神经元、轴突和髓鞘的丧失, 进而引发永久性瘫痪[82], 但目前针对SCI的临床相关治疗策略疗效差且副作用大。

OECs源自于嗅觉系统, 兼具外周施旺细胞和中枢星形胶质细胞的特点[7], 同时存在于外周和中枢神经系统中, 且能够终身不断更新、再生。动物研究表明, OECs可介导SCI大鼠断离轴突的再生和重新连接, 且移植后发现大鼠神经元细胞的存活显著增加, 在损伤部位产生了功能正常的轴突[83-84]。Basso Beattie Bresnahan运动量表和其他几种测试都证明, 移植后大鼠的感觉、运动反射和功能明显恢复[84]。但是由于人体OECs取材困难、数量少, 单纯使用OECs进行SCI治疗仍存在局限性, 故建立快速且可再现的OECs扩增过程对于通过OECs移植治疗神经元损伤至关重要, 我们的前期研究表明, 鞘氨醇-1-磷酸可以通过S1PR1(sphingosine-1-phosphate receptor 1)/RhoA(ras homolog family member A)/YAP(Yes-associated protein)途径促进OECs的增殖[85], 进一步证明了OECs移植在SCI治疗中的潜力。综上, OECs移植是一种具有良好应用前景的治疗SCI有效策略。

## 4 总结

目前, 虽然暂不清楚嗅觉障碍与神经精神性疾病的具体机制和因果关系, 但比较明确的是, 嗅觉障碍与神经精神性疾病的发生发展关系密切, 嗅觉障碍检测在神经精神性疾病的临床应用价值较大, 前景广阔。鉴于嗅觉障碍与神经精神性疾病的潜在关联, 可将其作为早期诊断和进展预测的指标。另外, 嗅觉系统独有的嗅觉途径为神经精神性疾病如MDD、SCZ、AD和PD的治疗提供了新的思路; OB-NSCs、OE-MSCs和OECs等特殊细胞可被应用于神经退行性疾病、SCI的移植治疗等, 是极有前景的治疗方法。目前, 嗅觉障碍的治疗和如何通过治疗嗅觉障碍以达到预防或延缓相关疾病的发生还需要进一步的研究, 相关方面技术的突破可能为患者带来新的福音。

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