

磁共振成像

月刊
总第156期
2010年1月创刊

2025年第16卷第6期
2025年6月20日出版

刊名题写：时任第十一届全国人大常委会副委员长韩启德

主管单位 中华人民共和国国家卫生健康委员会

主办单位
中国医院协会
首都医科大学附属北京天坛医院

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学科编辑 李金泽 王浩入
出版单位 《磁共振成像》
杂志社有限公司

发行范围 公开
发行单位 本刊发行部

国内发行 中国邮政集团有限公司
北京市报刊发行局
邮发代号 2-855
国外总发行 中国国际图书贸易集团有限公司
国外发行代号 M 8958
印刷单位 北京科信印刷有限公司

电 话 010-67113815
E-mail editor@cjmri.cn
网 址 www.chinesemri.com
定 价 每册30元

国内统一连续出版物号
CN 11-5902/R

国际标准连续出版物号
ISSN 1674-8034

广告发布登记证号 京西市监广登字20170242号
本刊刊出的所有论文不代表本刊编委会的观点，除非特别声明

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2 型糖尿病 (type 2 diabetes mellitus, T2DM) 是一种全球高发的慢性代谢性疾病, 与认知功能减退密切相关, 显著增加痴呆风险。近年来, 部分降糖药物如胰高血糖素样肽-1 受体激动剂 (如利拉鲁肽)、钠-葡萄糖协同转运蛋白 2 抑制剂 (如达格列净) 在改善 T2DM 相关认知功能方面展现出潜在益处, 传统降糖药物如阿卡波糖也用于二甲双胍疗效不佳时的联合治疗。已有研究初步证实这些降糖药物对认知功能具有一定改善作用。

然而, 现有研究多聚焦于单一药物或动物模型, 缺乏多种药物在 T2DM 人群中对认知改善作用的直接对比, 且其作用机制尚不明确, 尤其对脑区功能连接 (functional connectivity, FC) 层面的影响仍有待深入探索。已有研究提示 T2DM 认知障碍可能与嗅觉神经环路异常相关, 而嗅觉功能障碍也可能是认知退行性疾病的早期表现。因此, 嗅觉相关脑区的 FC 研究或可为药物疗效评估及机制探讨提供新线索。

近年来, 功能磁共振成像 (functional magnetic resonance imaging, fMRI) 广泛应用于 T2DM 脑功能研究, FC 指标能反映大脑不同区域间的协同活动水平。与传统局部脑区激活分析相比, FC 更能揭示脑网络层面的整合性变化。本研究聚焦于嗅觉相关脑区, 通过静息态 fMRI 分析不同降糖药物对 T2DM 患者嗅觉神经环路 FC 的影响, 为认知减退机制提供影像学依据。

本研究结合横断面研究与前瞻性、随机、平行分配的开放标签临床试验设计, 比较利拉鲁肽、达格列净和阿卡波糖三种降糖药对 T2DM 患者认知功能及嗅觉相关脑区 FC 的影响, 并设置正常对照组作为参照。研究基于自动解剖图谱与 Brodmann 模板, 提取 22 个嗅觉相关脑区作为感兴趣区 (regions of interest, ROI), 进一步获取各 ROI 的灰质密度并计算其与全脑体素之间的 FC。统计分析方面, 定量资料采用独立样本 *t* 检验进行组间比较, 定性资料采用卡方检验; 药物治疗组组在第 16 周进行重复评估, 采用配对样本 *t* 检验分析干预前后变化, 三组之间则通过 ANOVA 分析比较差异。结果显示, 利拉鲁肽治疗能够显著恢复 T2DM 患者嗅觉易损脑区与全脑其他脑区间的 FC 代偿性增强, 提示其可能通过调节嗅觉神经环路发挥神经保护作用, 为进一步揭示降糖药物改善 T2DM 认知功能的影像学机制提供了关键线索。详见正文第 10 页。

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磁共振成像

办精品期刊 促学科发展 惠百姓健康

官方网站	在线投稿	知乎平台	官方微博	搜狐平台	网易平台	哔哩哔哩	企鹅号	微信平台

CHINESE JOURNAL OF MAGNETIC RESONANCE IMAGING

磁共振成像 杂志社
www.chinesemri.com

CHINESE JOURNAL OF MAGNETIC RESONANCE IMAGING

ISSN 1674-8034, CN 11-5902/R, CODEN CCIHBW, Established in 2010 Monthly Vol. 16, No. 6, Jun 20, 2025

Responsible Institution

National Health Commission of the
People's Republic of China

Sponsor

Chinese Hospital Association
Beijing Tiantan Hospital of Capital
Medical University

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Magnetic Resonance Imaging

Publishing

Publishing House of Chinese Journal
of Magnetic Resonance Imaging

General Distributor

Domestic: Beijing Newspaper and
Periodical Distribution Bureau of China
Post Group Co., Ltd.
Postal Code: 2-855
Overseas: China International Book
Trade Group Co., Ltd., P.O. Box 399,
Beijing, China
Code No.: M 8958

Mail Order

Third Floor, Building 4, No. 358,
Yudaihe East Street, Tongzhou District,
Beijing 101100, China

Tel & Fax 8610-67113815

E-mail editor@cjmri.cn

Website www.chinesemri.com

Price: USD 30.00

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About the cover

Type 2 diabetes mellitus (T2DM) is a globally prevalent chronic metabolic disease that is closely associated with cognitive decline and significantly increases the risk of dementia. Anti-diabetic drugs such as glucagon-like peptide-1 receptor agonists (e. g., liraglutide) and sodium-glucose cotransporter 2 inhibitors (e. g., dapagliflozin) have shown potential benefits in improving cognitive function related to T2DM, while traditional antidiabetic drugs such as acarbose are also used in combination therapy when metformin is ineffective. Preliminary studies have demonstrated that these antidiabetic agents may exert certain improvements in cognitive function.

However, existing studies mostly focus on single agents or animal models, and lack direct comparisons of the cognitive effects of multiple drugs in T2DM patients. Moreover, the underlying mechanisms remain unclear, particularly regarding their impact on brain functional connectivity (FC), which warrants further investigation. Previous evidence suggests that cognitive impairment in T2DM may be associated with abnormalities in the olfactory neural circuitry, and olfactory dysfunction may serve as an early manifestation of neurodegenerative cognitive disorders. Therefore, exploring FC in olfactory-related brain regions may offer new insights for evaluating therapeutic efficacy and uncovering underlying mechanisms.

In recent years, functional magnetic resonance imaging (fMRI) has been widely used in brain function research in T2DM, with FC indices reflecting the degree of coordination between different brain regions. Compared with traditional analyses of localized brain activation, FC provides a better depiction of integrative changes at the network level of the brain. This study focuses on olfactory-related brain regions and utilizes resting-state fMRI to examine the effects of different anti-diabetic drugs on FC within the olfactory neural circuitry in T2DM patients, aiming to provide imaging-based evidence for mechanisms of cognitive decline.

This study combines a cross-sectional design with a prospective, randomized, parallel-group, open-label clinical trial to compare the effects of three anti-diabetic drugs- liraglutide, dapagliflozin, and acarbose- on cognitive function and FC of olfactory-related brain regions in T2DM patients, with a normal control group as reference. Using the Automated Anatomical Labeling atlas and Brodmann templates, 22 olfactory-related brain regions were identified as regions of interest (ROIs), from which gray matter density was extracted and FC between each ROI and whole-brain voxels was calculated. For statistical analysis, quantitative variables were compared between groups using independent sample *t*-tests, and categorical variables were analyzed using chi-square tests. Treatment groups were reassessed at week 16, with paired sample *t*-tests applied to evaluate changes before and after intervention, while intergroup differences were compared using ANOVA analysis. The results showed that liraglutide treatment significantly restored the compensatory enhancement of FC between olfactory-vulnerable brain regions and other areas of the brain in T2DM patients. This suggests that liraglutide may exert neuroprotective effects by modulating the olfactory neural circuitry, offering key imaging evidence for understanding how anti-diabetic drugs may improve cognitive function in T2DM. Please see text page 10.

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CORRECTION STATEMENT

- 131 Correction to: Predictive value of ADCmean combined with PSAD in clinically significant prostate cancer with PI-RADS score ≥ 3

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