论　著　　临床研究

2型糖尿病患者脑功能连接强度的改变及其神经病理机制

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[摘要]　**目的**　探讨2型糖尿病(T2DM)患者脑功能连接强度的改变及其神经病理机制。**方法**　选取2017年10月—2021年3月在甘肃省人民医院就诊的56例T2DM患者为T2DM组，另选择48例健康对照者为对照组，采用静息态脑功能连接强度(FCS)和基于种子点的功能连接(FC)分析方法对T2DM患者脑功能改变进行前瞻性研究。两组均进行脑部功能磁共振扫描、临床变量采集及神经心理学测试；计算FCS值，评估静息状态下两组脑功能的变化，以组间差异显著的脑区为种子点与全脑行功能连接分析，并提取差异脑区的FCS及FC值，与空腹血糖(FPG)、糖化血红蛋白(HbA_{1c})、促甲状腺激素(TSH)水平等临床变量以及简易精神状态检查量表(MMSE)、蒙特利尔认知评估量表(MoCA)、画钟测验(CDT)、汉密尔顿抑郁量表(HAMD-24)、汉密尔顿焦虑量表(HAMA)评分行相关性分析。**结果**　与对照组比较，T2DM组HAMD-24、HAMA评分明显升高($P<0.01$)，MoCA评分降低($P<0.05$)；T2DM组右侧颞中回FCS值升高(GRF矫正，体素水平$P<0.001$，集簇水平$P<0.05$)，且右侧颞中回-左侧前扣带皮质间FC值降低(GRF矫正，体素水平$P<0.001$，集簇水平$P<0.05$)。相关性分析显示，T2DM患者右侧颞中回-左侧前扣带皮质间FC值与HAMD-24评分($r=-0.395$，$P=0.003$)、HbA_{1c}水平($r=-0.303$，$P=0.023$)呈负相关，与TSH水平呈正相关($r=0.324$，$P=0.017$)。**结论**　T2DM患者右侧颞中回FCS值升高，右侧颞中回-左侧前扣带皮质间FC值降低，可能是T2DM患者脑功能损害的重要神经影像学特征。HbA_{1c}可能在T2DM患者脑损害过程中起重要作用。

[关键词]　糖尿病，2型；磁共振成像；功能连接强度；认知障碍；抑郁

Alteration of brain functional connectivity strength in patients with type 2 diabetes and its neuropathological mechanism

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[**Abstract**]　**Objective**　To explore the change of brain functional connectivity strength in patients with type 2 diabetes mellitus (T2DM) and its neuropathological mechanism. **Methods**　Fifty-six T2DM patients who visited Gansu Provincial Hospital from October 2017 to March 2021 were selected as T2DM group, and 48 healthy controls were selected as control group. A prospective study was conducted on the changes in brain function in T2DM patients by analysis of resting state functional connectivity strength (FCS) and functional connectivity (FC) based on seed points. Brain functional magnetic resonance imaging, clinical variable collection, and neuropsychological testing of patients in two groups were performed. We calculate the FCS value,

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evaluate the brain function changes of the two groups in the resting state, take the brain regions with significant differences between the groups as the seed points and perform functional connectivity analysis with the whole brain. Correlation analysis was conducted between the FCS, FC values of the different brain regions and clinical variables such as fasting blood glucose (FPG), glycosylated hemoglobin (HbA_{1c}), thyroid hormone (TSH) levels, as well as the scores of mini mental state examination (MMSE), Montreal cognitive assessment (MoCA), clock drawing test (CDT), Hamilton Depression Rating Scale (HAMD-24) and Hamilton Anxiety Scale (HAMA). **Results** Compared with control group, the HAMD-24 and HAMA scores in T2DM group significantly increased (P<0.01), while the MoCA scores decreased (P<0.05); In T2DM group, the FCS value of the right middle temporal gyrus increased (GRF correction, voxel level P<0.001, clustering level P<0.05), and the FC value of the right middle temporal gyrus-left anterior cingulate cortex decreased (GRF correction, voxel level P<0.001, clustering level P<0.05). Correlation analysis showed that the FC value of right middle temporal gyrus-left anterior cingulate cortex in T2DM patients was negatively correlated with HAMD-24 score (r=−0.395, P=0.003), HbA_{1c} level (r=−0.303, P=0.023), and positively correlated with TSH level (r=0.324, P=0.017). **Conclusions** The increase of FCS value in the right middle temporal gyrus and the decrease of FC value in the right middle temporal gyrus-left anterior cingulate cortex may be important neuroimaging features of brain function damage in T2DM patients. HbA_{1c} may play an important role in the process of brain damage in T2DM patients.

[**Key words**] diabetes mellitus, type 2; magnetic resonance imaging; functional connectivity strength; cognition disorders; depression

2021年全球共有5.37亿糖尿病患者，预计在10年内将达到6亿[1]，其中2型糖尿病(type 2 diabetes mellitus，T2DM)为主要类型。长期慢性高血糖、血糖波动[1]或胰岛素抵抗会引起糖基化终产物积聚和炎性反应[2-3]，损害脑组织微结构的完整性，导致脑组织变性、脑萎缩[4]，可出现记忆下降、认知障碍，甚至发展为痴呆[5-6]。多项研究显示，糖尿病和抑郁之间存在双向联系[7-8]，其原因可能与下丘脑-垂体-肾上腺轴、免疫炎症系统及胰岛素抵抗相关[9]，且抑郁会对糖尿病患者生活质量和糖尿病结局产生不利影响[10]。然而，T2DM患者认知障碍及抑郁的机制仍不完全清楚。

静息态功能磁共振成像(resting-state functional magnetic resonance imaging，rs-fMRI)已被广泛应用于中枢神经系统的研究[11]。低频振幅、局部一致性可用于评估区域静息态脑活动[12-13]，但静息态功能连接(functional connectivity，FC)是一种假设驱动的基于种子点的方法，不能用于评估全脑的FC[14]。病理证据显示，糖尿病患者大脑中的神经退行性变呈弥漫性分布[15]，因此，基于体素的全脑FC分析可能对T2DM相关的功能改变提供更全面的信息。基于图论的全脑功能连接强度(functional connectivity strength，FCS)是一种数据驱动的方法，用于检测全脑之间的功能连接[16]，是分析体素水平脑功能连接的可靠测量指标[17-18]。已有研究显示，T2DM患者大脑多个区域FCS和密度发生改变[19-23]，但相关研究结果并不完全一致，这可能与患者并发症不同或样本量、性别构成存在差异有关。本研究拟通过比较T2DM患者和健康对照者FCS的差异，从全脑角度探索T2DM认知障碍及抑郁发生的潜在机制。

1 资料与方法

1.1 研究对象 选取2017年10月—2021年3月在甘肃省人民医院内分泌科就诊的56例T2DM患者为T2DM组，以年龄、性别、教育水平与之相匹配的48例健康对照者为对照组。所有T2DM患者均符合世界卫生组织T2DM的诊断标准(1999)，且未出现任何严重的并发症，如糖尿病肾病、糖尿病视网膜病变或周围神经病变等。上述并发症的诊断和分类标准均参照中国2019年版2型糖尿病医疗救治标准[24]。该前瞻性研究方案经甘肃省人民医院医学伦理委员会批准(2017-188)，并在研究前获得每位受试者的书面知情同意书。纳入标准：(1)年龄18~70岁，性别不限；(2)惯用右手；(3)受教育年限≥6年；(4)入组前2个月内未服用任何精神类药物；(5)健康对照者指尖随机血糖3.9~7.8 mmol/L。排除标准：(1)中枢神经系统器质性病变；(2)严重头部创伤史；(3)精神障碍或精神疾病史；(4)电休克治疗和磁刺激史；(5)有酒精依赖及毒物使用史；(6)患有重大躯体疾病(如癌症、严重心脏病、肝或肾功能受损)；(7)有严重视力或听力障碍；(8)有MRI禁忌证。

1.2 方法

1.2.1 临床变量采集 收集两组临床数据，包括性别、年龄、体重、T2DM病程等。T2DM患者在通宵禁食后于上午8:00采血检测空腹血糖(fasting plasma glucose，FPG)、糖化血红蛋白(glycated hemoglobin，HbA_{1c})、促甲状腺激素(thyroid-stimulating hormone，TSH)水平。健康对照组指尖采血进行随机血糖评估。

1.2.2 神经心理评估 对两组均进行一系列神经心理评估，包括简易精神状态检查量表(mini mental state exam，MMSE)、蒙特利尔认知评估量表(montreal cognitive assessment，MoCA)、画钟测验(clock drawing test，CDT)、汉密尔顿抑郁量表(hamilton depression rating scale-24 version，HAMD-24)、汉密尔顿焦虑量表(hamilton anxiety scale，HAMA)测评，评估每位受试者的神经心理状态。

1.2.3 MRI数据采集 MRI图像使用甘肃省人民医院放射科3.0T (MAGNETOM Skyra，德国西门子医疗)磁共振32通道头线圈采集。rs-fMRI通过回波平面成像(EPI)序列采集，参数如下：重复时间2000 ms，回波时间30 ms，层厚3.5 mm，层间距0.7 mm，翻转角90°，矩阵64×64，视野224 mm×224 mm；扫描后，每位受试者获得420个时间点[25]。此外，使用T_1加权MP-RAGE序列采集高分辨率3D结构图像：重复时间2530 ms，回波时间2.35ms，层厚1.33 mm，层间距0.66 mm，翻转角7°，矩阵256×256，视野256 mm×256 mm。受试者清醒平卧，固定头部，闭眼且尽量不做专注思维活动。

1.2.4 rs-fMRI图像预处理 采用基于Matlab的SPM8和DPABI_V4.2软件对rs-fMRI图像数据进行预处理。(1)剔除每位受试者的前10个时间点，剩余图像用于数据分析。(2)时间层校正、头动校正(剔除头动平动>2.0 mm，或转动>2.0°的受试者数据)。(3)空间标准化(重采样为3 mm×3 mm×3 mm)。(4)空间平滑(平滑核半高全宽为4 mm)。(5)去线性漂移和回归去除协变量(头动、脑脊液、脑白质和全脑均值信号)。(6)低频滤波(0.01~0.10 Hz)。

1.2.5 全脑FC分析 首先，计算所有体素对之间时间序列的Pearson相关性以构建每一位受试者的全脑功能连接矩阵；其次，为了增强数据分布的正态性，对相关值r值进行Fisher r-to-z变换转化成z值；最后，对于每一个体素，通过计算该体素与全脑其他灰质体素的连接权重总和得到FCS值。设相关性阈值(r)=0.25，以消除由于噪声影响而产生的弱相关[26]。

1.2.6 基于种子点的FC分析 选取FCS差异显著脑区的峰值MNI坐标为中心，设半径为6 mm的球形种子点为感兴趣区，与全脑各体素间进行FC分析。计算种子点的时间序列与全脑各体素时间序列之间的Pearson相关系数r。为提高数据的正态性，通过Fisher's r-to-z变换得到z功能连接图，再进一步统计比较。

1.3 统计学处理 采用SPSS 18.0软件进行统计分析。符合正态分布的计量资料采用双样本t检验，不符合者采用曼-惠特尼U检验；两组性别比较采用χ^2检验。将性别、年龄、受教育程度及头动参数作为协变量，采用基于Matlab的DPARSF软件统计模块中的双样本t检验比较FCS值及基于种子点的FC的组间差异，经GRF多重比较校正，以体素水平P<0.001，集簇水平P<0.05为差异有统计学意义。提取组间差异显著脑区的FCS及FC值分别与临床变量、认知心理量表评分进行Pearson或Spearman相关性分析。P<0.05为差异有统计学意义。

2 结　　果

2.1 两组人口学数据比较 与对照组比较，T2DM组HAMD-24、HAMA评分较高(P<0.01)，而MoCA和CDT评分较低(P<0.05，表1)。

表1 两组人口学数据比较

Tab.1 Comparison of demographic data between the two groups

指标	T2DM组(n=56)	对照组(n=48)	χ^2/t	P
男/女(例)	44/12	32/16	1.862	0.172
年龄(岁, $\bar{x}\pm s$)	55.6±8.0	53.3±3.4	1.928	0.058
受教育年限(年, $\bar{x}\pm s$)	13.00±3.27	12.73±3.39	0.413	0.681
BMI(kg/m^2, $\bar{x}\pm s$)	23.96±2.67	23.83±2.98	0.231	0.818
MMSE评分(分, $\bar{x}\pm s$)	27.66±1.80	28.31±2.25	−1.489	0.140
MoCA评分(分, $\bar{x}\pm s$)	24.29±3.91	27.28±1.49	−5.126	<0.001
CDT评分(分, $\bar{x}\pm s$)	2.30±0.69	2.66±0.65	−2.360	0.019
HAMD-24评分(分, $\bar{x}\pm s$)	9.75±7.22	3.59±3.43	5.404	<0.001
HAMA评分(分, $\bar{x}\pm s$)	6.32±4.74	2.69±2.01	4.898	<0.001
病程(年, $\bar{x}\pm s$)	9.36±6.02	NA	–	–
FPG(mmol/L, $\bar{x}\pm s$)	9.56±3.53	NA	–	–
RPG(mmol/L, $\bar{x}\pm s$)	NA	5.98±1.10	–	–
HbA_{1c}(%, $\bar{x}\pm s$)	8.20±1.94	NA	–	–
TSH(mU/L, $\bar{x}\pm s$)	2.02±1.17	NA	–	–

T2DM. 2型糖尿病；BMI. 体重指数；MMSE. 简易精神状态检查量表；MoCA. 蒙特利尔认知评估量表；CDT. 画钟测验；HAMD-24. 汉密尔顿抑郁量表；HAMA. 汉密尔顿焦虑量表；FPG. 空腹血糖；RPG. 随机血糖；HbA_{1c}. 糖化血红蛋白；TSH. 促甲状腺激素；NA. 不适用；–. 无数据

2.2 两组FCS比较 全脑FCS分析结果显示，在控制年龄、性别、受教育年限和平均FD后，与对照组比较，T2DM组右侧颞中回FCS升高(GRF矫正，体素水平P<0.001，集簇水平P<0.05，表2、图1)。

2.3 两组基于种子点FC的比较 与对照组比较，T2DM组右侧颞中回-左侧前扣带皮质(RMTG-LACC)间FC降低(GRF矫正，体素水平P<0.001，集簇水平P<0.05，表2、图1)。

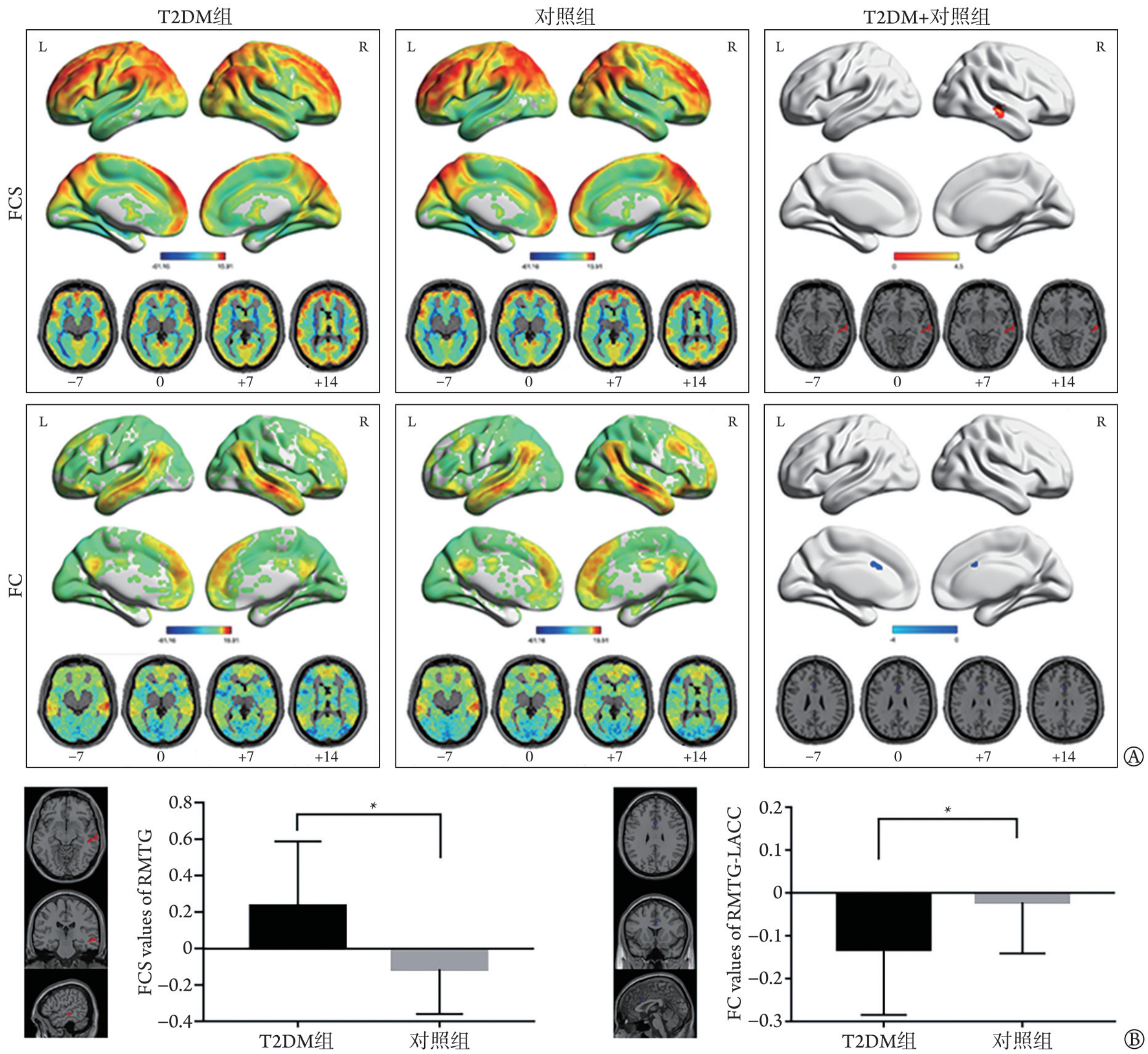
2.4 T2DM患者FC、FCS与神经心理评估结果及部分临床指标的相关性分析 T2DM患者RMTG-LACC FC值与HAMD-24评分(r=−0.395，P=0.003)、HbA_{1c}水平(r=−0.303，P=0.023)呈负相关，与TSH水平(r=0.324，P=0.017)呈正相关(图2)；而与MMSE、MoCA、CDT、HAMA评分及FPG水平无明显相关性(P>0.05)。

表2 两组FCS和基于种子点FC的比较

Tab.2 Comparison of FCS and FC based on the seed points between the two groups

参数	脑区	体素数	峰值MNI坐标			T峰值
			X	Y	Z	
FCS T2DM组>对照组	RMTG	44	63	–21	–9	4.7180
FC T2DM组<对照组	RMTG-LACC	8	0	15	30	–3.9776

FCS. 功能连接强度；FC. 功能连接；T2DM. 2型糖尿病；MNI. 蒙特利尔神经学研究所；RMTG. 右侧颞中回；LACC. 左侧前扣带皮质



T2DM. 2型糖尿病；FCS. 功能连接强度；FC. 功能连接；L. 左；R. 右；RMTG. 右侧颞中回；LACC. 左侧前扣带皮质；A. 两组静息态脑功能MRI图像；B. 两组FCS和基于种子点FC水平比较；色柱示*t*值大小；$^*P<0.05$

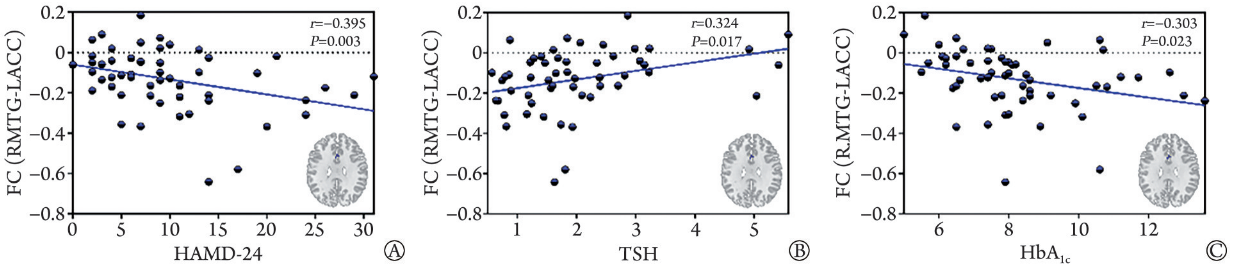
图1 两组FCS和基于种子点FC的组内与组间比较

Fig.1 Comparison of FCS and FC based on seed points in each group and between the two groups

3 讨　论

本研究基于FCS方法对T2DM患者脑功能改变进行探索，结果显示T2DM患者右侧颞中回FCS升高，RMTG-LACC间FC降低且与HbA_{1c}、HAMD-24评分呈负相关，与TSH水平呈正相关。这可能为从全脑功能连接异常的角度探索T2DM患者认知障碍及抑郁机制提供了新的视角。

FCS可用于识别全脑网络的“功能中枢”[27]。FCS值增高可能意味着从低耗能向高耗能连接的转变，也就是说大脑中枢等高耗能区域可通过连接成本和网络拓扑特征之间的协商来重新配置，以满足不同的、变化的认知需求[28-29]。本研究结果显示，T2DM患者存在认知功能受损且右侧颞中回FCS升高，颞中回与全脑功能连接增高，可能是支持认知任务的神经结构网络发生功能障碍后触发的代偿机



FC. 功能连接；HAMD-24. 汉密尔顿抑郁量表；TSH. 促甲状腺激素；HbA_{1c}. 糖化血红蛋白；RMTG. 右侧颞中回；LACC. 左侧前扣带皮质；A、C. MRTG-LACC与HAMD-24评分、HbA_{1c}水平呈负相关；B. 与TSH水平呈正相关

图 2 T2DM患者MRTG-LACC FC与HAMD-24评分、HbA_{1c}及TSH水平的相关性分析

Fig. 2 Correlation analysis of FC in right middle temporal gyrus-left anterior cingulate cortex (MRTG-LACC) of T2DM patients with HAMD-24 scores, HbA_{1c}, and TSH

制[30-31]。颞中回参与语言、动作观察、逻辑推理、动态面部表情识别等功能[32-35]。T2DM患者的颞中回不仅存在局部神经元丢失、血管异常、微梗死、代谢降低、脑血流量减少等神经退行性改变[36]，还存在灰质体积萎缩，低频振幅、局部一致性和比率低频振幅降低等结构与功能改变[37-41]，提示T2DM患者颞中回存在神经退行性改变及局部脑功能活动降低，也支持T2DM患者颞中回FCS升高是一种代偿机制。

就T2DM患者情绪改变的机制来说，脑白质高信号与血脑屏障破坏、低灌注、血管内皮损伤等有关[42]，T2DM患者可能通过脑血流受损[43]导致脑白质高信号，而脑白质高信号可造成白质纤维束的结构连接降低，从而导致参与情绪调节的额-边缘情感网络、默认网络、皮质-纹状体网络中断，进而引起情绪障碍[44]。此外，本课题组前期研究显示，T2DM共病抑郁的发生与下丘脑-垂体-肾上腺轴功能紊乱、免疫炎症系统激活及胰岛素抵抗有关[9]。本研究未显示颞中回FCS异常与T2DM患者情绪改变的相关性，但颞中回具有情绪调节功能[45]，其局部损伤会导致情绪感知和情绪管理水平降低[46]，基于文献报道的T2DM患者颞中回存在神经退行性改变及局部脑功能活动降低[36-41]，T2DM患者颞中回FCS增高可能反映了一种情绪调节的代偿性功能改变。

本研究发现，T2DM患者RMTG-LACC间FC较健康对照者降低。颞中回和前扣带皮质是默认网络的关键脑区[47]，多项研究显示T2DM患者默认网络内部以及默认网络与其他脑区之间存在功能异常[48-49]且与认知障碍相关，尤其是前扣带皮质[50]，支持本研究结果。本研究中，T2DM患者RMTG-LACC间FC与HbA_{1c}呈负相关，与TSH水平呈正相关。HbA_{1c}可反映过去2~3个月的平均血糖水平，持续高血糖会通过增高谷氨酸盐水平，导致神经元损伤，也可通过氧化应激使线粒体功能受损并促进细胞凋亡[51]。由此可见，T2DM患者可能因HbA_{1c}升高造成脑损伤而导致脑功能异常。TSH是一种垂体前叶分泌的糖蛋白激素，许多糖尿病患者瘦素水平升高，进而经Janus激活激酶-2信号转导和转录激活因子3影响下丘脑-垂体-甲状腺轴，从而刺激TSH的合成[52-53]。甲状腺激素在中枢神经系统生长和发育中起重要作用，我们推测，T2DM患者TSH升高可能是脑功能受损后的一种代偿。此外，该异常FC与HAMD-24评分呈负相关，提示T2DM患者的抑郁情绪与RMTG-LACC间FC降低相关。颞中回具有情绪调节功能[45]，重度抑郁症患者颞中回存在皮质厚度减少[54]，比率低频振幅[55]、低频振幅[56]及FC[57]异常等改变，抑郁症患者前扣带皮质存在FC异常[58-59]、谷氨酸盐/谷氨酰胺和谷氨酸水平升高及γ-氨基丁酸水平降低[60]，提示颞中回及前扣带皮质与抑郁密切相关，均支持本研究结果。

本研究存在一些不足。首先，本研究未监测T2DM患者认知功能障碍和抑郁状态的动态变化；其次，T2DM患者降糖药物的使用及药物的种类可能对大脑有不同程度的影响，本研究中未予评价。因此今后需采用前瞻性大样本随机对照研究结合纵向设计进行进一步深入探讨。

综上所述，本研究结果显示，T2DM患者右侧颞中回FCS升高，且颞中回与前扣带皮质之间FC降低可能是T2DM脑损害的关键神经影像学特征之一。本研究可能为探索T2DM患者认知障碍及抑郁机制提供了新的视角。

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