·专题·脑功能康复·

2型糖尿病合并轻度认知障碍患者脑葡萄糖代谢连接网络拓扑结构分析

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摘要 **目的:**分析2型糖尿病(T2DM)合并轻度认知障碍(MCI)(T2DM&MCI)患者脑葡萄糖代谢连接网络拓扑结构的改变情况。**方法:**选择阿尔茨海默病神经影像学倡议(ADNI)数据库收录的T2DM&MCI受试者(观察组)和健康受试者(对照组),每组35例。从数据库获取2组简易智能精神状态检查量表(MMSE)评分、患者报告日常认知量表的记忆评分(EcogPtMem)、患者亲属报告日常认知量表的记忆评分(EcogSPMem)以及氟代脱氧葡萄糖-电子发射断层扫描(FDG-PET)图像。利用SPM12将FDG-PET图像标准化到蒙特利尔神经病学研究所(MNI)空间脑模板上。以小脑作为参考区,提取每个受试者解剖自动标记法(AAL)模块脑区的标准摄取值比率(SUVR),构建葡萄糖代谢连接脑网络。采用GRETNA软件分析全局效率、度中心性、节点局部效率等脑网络拓扑属性;采用Spearman相关性分析差异脑区度中心性与EcogPtMem评分以及EcogSPMem评分的相关性、节点局部效率与EcogPtMem评分以及EcogSPMem评分的相关性。**结果:**与对照组比较,观察组MMSE评分明显更低,EcogPtMem和EcogSPMem评分均明显更高,差异具有统计学意义($P<0.05$)。与对照组比较,观察组的全局效率组间差异无统计学意义($P>0.05$)。与对照组比较,观察组左侧海马旁回($P=0.005$)、左侧海马($P=0.013$)、左侧顶下缘角回($P=0.031$)、左侧角回($P=0.034$)、右侧角回($P=0.013$)、右侧顶下缘角回($P=0.044$)、右侧海马旁回($P=0.024$)度中心性明显降低;左侧直回($P=0.028$)、左侧海马旁回($P=0.044$)、左侧海马($P=0.026$)、左侧顶下缘角回($P=0.031$)、左侧角回($P=0.024$)、右侧角回($P=0.004$)、右侧顶下缘角回($P=0.039$)节点局部效率明显降低。相关性分析结果显示,观察组左侧海马度中心性($r=-0.273$,$P=0.022$)和左侧海马旁回度中心性($r=-0.341$,$P=0.004$)与EcogPtMem评分呈负相关关系;左侧海马度中心性($r=-0.391$,$P=0.001$)、左侧海马旁回度中心性($r=-0.410$,$P<0.001$)、右侧海马旁回度中心性($r=-0.240$,$P=0.045$)与EcogSPMem评分呈负相关关系。观察组左侧海马节点局部效率($r=-0.257$,$P=0.032$)、左侧海马旁回节点局部效率($r=-0.251$,$P=0.036$)、右侧角回节点局部效率($r=-0.265$,$P=0.027$)与EcogPtMem评分呈负相关关系;左侧海马节点局部效率($r=-0.363$,$P=0.002$)和左侧海马旁回节点局部效率($r=-0.362$,$P=0.002$)与EcogSPMem评分呈负相关关系。**结论:**T2DM&MCI患者脑葡萄糖代谢连接网络拓扑结构异常可能是引起其记忆功能下降的原因之一,这可为探究T2DM&MCI神经机制提供参考。

关键词 2型糖尿病;轻度认知障碍;度中心性;节点局部效率;脑葡萄糖代谢;网络拓扑结构分析

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在过去50年里，2型糖尿病（type 2 diabetes mellitus，T2DM）的患病率在全球范围内不断上升[1]。T2DM会对中枢神经系统造成损害，加速患者脑组织变性，继而可能引发认知功能下降[2]。流行病学研究显示，T2DM是轻度认知障碍（mild cognitive impairment，MCI）的重要危险因素[3-4]。MCI是一种从正常衰老到痴呆的过渡阶段，以记忆障碍为特征的临床综合征[5-6]。T2DM合并MCI（T2DM&MCI）通常以记忆力减退为主要症状，涉及注意力和执行功能减退，常发生在糖尿病的并发症阶段[7]。在我国，老年T2DM患者中MCI患病率为45%，显著高于非T2DM老年人群的14.71%[8-9]。因此，进一步了解T2DM&MCI患者记忆功能减退的神经机制，能够为临床早期诊断和治疗提供重要的理论支撑。

[^{18}F]-氟代脱氧葡萄糖（[^{18}F]-fluoro-2-deoxyglucose，[^{18}F]FDG）正电子发射断层扫描（positron emission tomography，PET）是一种常见的分子神经成像技术，用于研究人脑中的葡萄糖代谢，是了解大脑代谢网络功能的有效手段[10]。葡萄糖代谢连接网络分析能够提供功能性区域间连接信息，量化复杂脑网络的内部工作机制，探索网络拓扑属性，再现不同大脑区域之间的信息传递模式[11]。基于图论的代谢脑网络分析已被证明研究大脑活动变化的有效性，并被广泛应用于神经系统疾病成像[12-14]。既往研究发现，T2DM以及MCI患者都存在代谢功能以及网络拓扑结构等相关改变[15-17]。本研究通过构建T2DM&MCI患者的脑葡萄糖代谢连接网络，分析网络拓扑结构指标并与临床记忆量表做相关性分析，以探讨T2DM&MCI患者记忆功能下降的可能机制。

1 临床资料

1.1 诊断标准

1.1.1 T2DM诊断标准 符合2014年美国糖尿病协会有关T2DM的诊断标准，空腹血糖（fasting blood glucose，FBG）≥7.0 mmol/L[18]。

1.1.2 MCI诊断标准 简易智能精神状态检查量表（mini-mental state examination，MMSE）评分为24～30分（含30分），有记忆下降主诉，通过教育年限调整的韦氏记忆量表修订版（Wechsler memory scale-revised，WMS-R）逻辑记忆Ⅱ评分测量的客观记忆丧失，临床痴呆评定量表（clinical dementia rating，CDR）评分为0.5，其他认知领域没有明显的损伤，基本保留有日常生活活动能力[19]。

1.2 纳入标准

① 年龄55～90岁；② 会说英语或西班牙语，能够进行独立的功能评估；③ 愿意接受所有的测试程序（包括进行神经影像学检查），并同意进行纵向随访。其余纳入标准如下。

1.2.1 健康受试者 ① MMSE评分为24～30分；② CDR评分为0分；③ 老年抑郁量表（geriatric depression scale，GDS）评分＜6分。

1.2.2 T2DM&MCI受试者 同时符合T2DM和MCI的诊断标准。

1.3 排除标准

① 严重的神经系统疾病（如帕金森病、多发性梗死性痴呆、亨廷顿病、脑肿瘤、进行性核上性麻痹、癫痫发作性疾病、硬膜下血肿、多发性硬化症等）；② 严重的头部创伤史；③ 已知的脑结构异常。

1.4 一般资料

参照以往PET研究的文献，30例左右数据样本有较好的统计功效和可重复性[20]。选择阿尔茨海默病神经影像学倡议（Alzheimer's disease neuroimaging initiative，ADNI）数据库收录T2DM&MCI受试者（观察组）和健康受试者（对照组），每组35例。2组性别、年龄、教育程度差异无统计学意义（P＞0.05），观察组FBG水平明显高于对照组（P＜0.05）。见表1。

表1 2组一般资料比较

Table 1 Comparison of general data between two groups

组别	例数	性别		年龄/($\bar{x}\pm s$，岁)	教育程度/([$M(P_{25},P_{75})$]，年)	FBG/([$M(P_{25},P_{75})$]，mmol/L)
		男	女			
对照组	35	16	19	72.53±4.18	16(15,18)	6.59(6.16,6.73)
观察组	35	14	21	70.97±5.86	16(14,18)	7.25(7.15,7.38)[1)]
$t/Z/\chi^2$值		0.233		1.506	-2.864	7.196
P值		0.629		0.137	0.811	＜0.001

注：与对照组比较，1）P＜0.05。

Note: Compared with the control group, 1) P<0.05.

2 方 法

2.1 数据提取与处理方法

2.1.1 FDG-PET数据获取 从ADNI数据库提取所有受试者的PET图像。PET数据采集协议的细节可以在ADNI的官方网站(https://adni.loni.usc.edu/)上获取。

2.1.2 PET数据处理 采用SPM 12软件进行PET图像数据处理。

2.1.2.1 构建标准摄取值比率矩阵 将PET图像标准化到蒙特利尔神经病学研究所(Montreal neurological institute,MNI)空间FDG模板上。以小脑作为参考区,选取解剖自动标记法(anatomical automatic labeling,AAL)模板大脑脑区作为网络节点,AAL模板包括90个感兴趣区域,提取每个受试者AAL模板各感兴趣区的标准摄取值比率(standard uptake value ratio,SUVR),以构建大小为1×90的SUVR数据矩阵。

2.1.2.2 从组水平脑网络构建个体脑网络 ① 建立对照组的相关系数矩阵;② 计算对照组SUVR图像的平均值和标准差,基于对照组FDG图像,计算效应量(effect size,ES)。应用Fisher变换得到的相关系数,计算权重矩阵得到最终的个体相关系数矩阵[12]。

2.2 观察指标

采用GRETNA软件(https://www.nitrc.org/projects/gretna/)进行网络分析指标(全局效率、度中心性、节点局部效率等脑网络拓扑属性)计算。

2.2.1 认知功能 采用MMSE评分评价受试者的整体认知功能;采用患者报告日常认知量表的记忆(everyday cognition:the patient-reported memory,EcogPtMem)评分以及患者亲属报告日常认知量表的记忆(everyday cognition:the study partner-reported memory,EcogSPMem)评分评价受试者的记忆功能。

2.2.2 全局效率 全局效率是指网络最短平均路径的倒数,反映了网络信息的全局传输能力[21-22]。网络全局效率越高,表示网络节点间传递信息的速率越快。

2.2.3 度中心性 度中心性是一种基于功能网络分析的图论指标,通常用于测量给定节点的直接连接数量,并在大脑的综合连接矩阵(即功能连接体)中量化每个节点与大脑其余部分之间的连接强度;这种测量表明该节点对整个大脑的影响程度,并整合跨功能分离的大脑区域的信息[23-24]。度中心性越高,表示该节点在网络中就越重要。

2.2.4 节点局部效率 节点局部效率定义为由节点及其相邻节点组成的最短平均路径长度的倒数,反映了网络局部信息传输能力[25-27]。节点局部效率越高,表示该节点受损后对于该网络的信息传递能力的影响越大。

2.3 统计学方法

采用SPSS 24.0软件进行数据分析。计量资料服从正态分布采用($\bar{x}\pm s$)进行表示,组间比较采用两独立样本t检验;计量资料不服从正态分布采用M(P_{25},P_{75})表示,组间比较采用Mann-Whitney U检验。计数资料采用χ^2检验。不符合正态分布、线性关系的连续变量采用Spearman相关性分析。$P<0.05$为差异有统计学意义。

3 结 果

3.1 2组MMSE、EcogPtMem和EcogSPMem评分比较

与对照组比较,观察组MMSE评分明显更低,EcogPtMem和EcogSPMem评分均明显更高,差异具有统计学意义($P<0.05$)。见表2。

表2 2组MMSE、EcogPtMem和EcogSPMem评分比较[M(P_{25},P_{75})] 分

Table 2 Comparison of MMSE,EcogPtMem and EcogSPMem scores between two groups [M(P_{25},P_{75})] Scores

组 别	例数	MMSE评分	EcogPtMem评分	EcogSPMem评分
对照组	35	29.00(28.00,29.00)	1.46(1.16,1.69)	1.13(1.00,1.47)
观察组	35	27.00(27.00,29.00)[1)]	2.13(1.63,2.88)[1)]	1.50(1.25,2.25)[1)]
Z值		-3.269	4.277	4.346
P值		0.001	<0.001	<0.001

注:与对照组比较,1) $P<0.05$。

Note: Compared with the control group, 1) $P<0.05$.

3.2　2组全局效率比较

与对照组比较，观察组全局效率差异无统计学意义（$P>0.05$）。见表3。

表3　2组全局效率比较[$M(P_{25},P_{75})$]

Table 3　Comparison of global efficiency between two groups [$M(P_{25},P_{75})$]

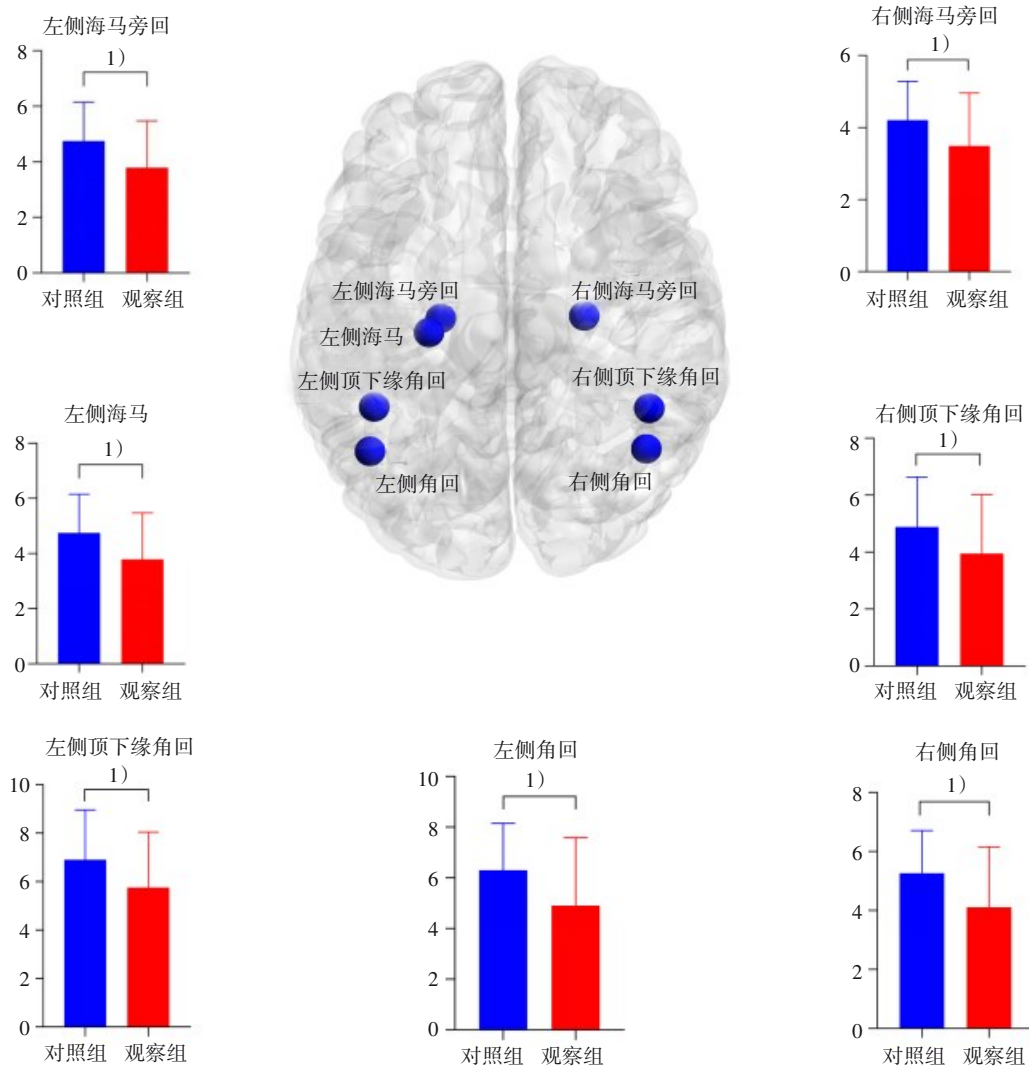
组 别	例数	全局效率
对照组	35	0.122(0.115,0.127)
观察组	35	0.117(0.110,0.125)

3.3　2组度中心性比较

与对照组比较，观察组左侧海马旁回（$P=0.005$）、左侧海马（$P=0.013$）、左侧顶下缘角回（$P=0.031$）、左侧角回（$P=0.034$）、右侧角回（$P=0.013$）、右侧顶下缘角回（$P=0.044$）、右侧海马旁回（$P=0.024$）的度中心性明显更低。见图1。

3.4　2组节点局部效率比较

与对照组相比，观察组左侧直回（$P=0.028$）、左侧海马旁回（$P=0.044$）、左侧海马（$P=0.026$）、左侧顶下缘角回（$P=0.031$）、左侧角回（$P=0.024$）、右侧角回（$P=0.004$）、右侧顶下缘角回（$P=0.039$）的节点局部效率明显更低。见图2。

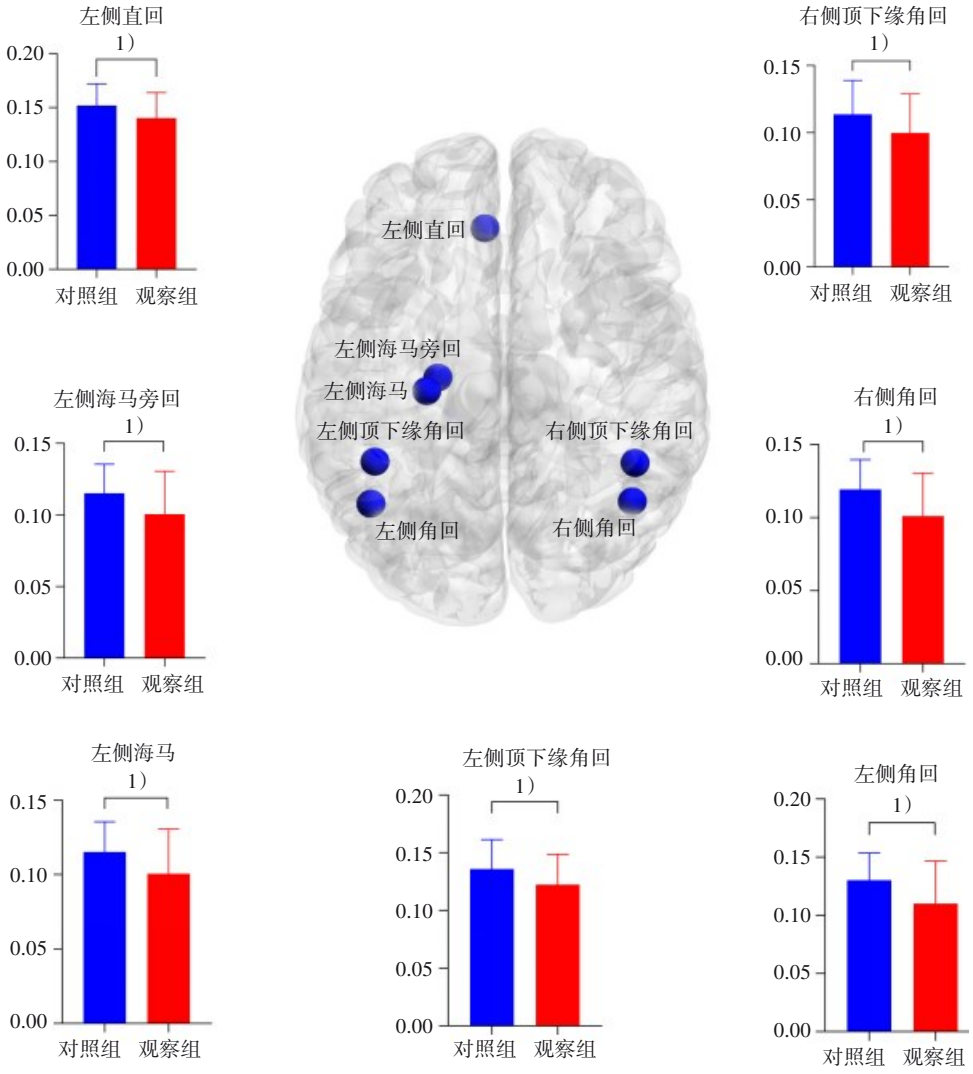


注：与对照组比较，1）$P<0.05$。

Note: Compared with the control group, 1) $P<0.05$.

图1　2组度中心性比较

Figure 1　Comparison of degree centrality between two groups



注:与对照组比较,1) $P<0.05$。

Note: Compared with the control group, 1) $P<0.05$.

图2 2组节点局部效率比较

Figure 2 Comparison of node local efficiency between two groups

3.5 观察组差异脑区度中心性、节点局部效率与EcogPtMem和EcogSPMem评分相关性分析

3.5.1 度中心性与EcogPtMem和EcogSPMem相关性分析 在性别、年龄、教育程度组间比较差异无统计学意义的前提下,相关性分析结果显示观察组左侧海马度中心性($r=-0.273$, $P=0.022$)、左侧海马旁回度中心性($r=-0.341$, $P=0.004$)与EcogPtMem评分呈负相关关系;左侧海马度中心性($r=-0.391$, $P=0.001$)、左侧海马旁回度中心性($r=-0.410$, $P<0.001$)、右侧海马旁回度中心性($r=-0.240$, $P=0.045$)与EcogSPMem评分呈负相关关系。见图3。

3.5.2 节点局部效率与EcogPtMem和EcogSPMem评分相关性分析 观察组左侧海马节点局部效率($r=-0.257$, $P=0.032$)、左侧海马旁回节点局部效率($r=-0.251$, $P=0.036$)、右侧角回节点局部效率($r=-0.265$, $P=0.027$)与EcogPtMem评分呈负相关关系;左侧海马节点局部效率($r=-0.363$, $P=0.002$)、左侧海马旁回节点局部效率($r=-0.362$, $P=0.002$)与EcogSPMem评分呈负相关关系。见图4。

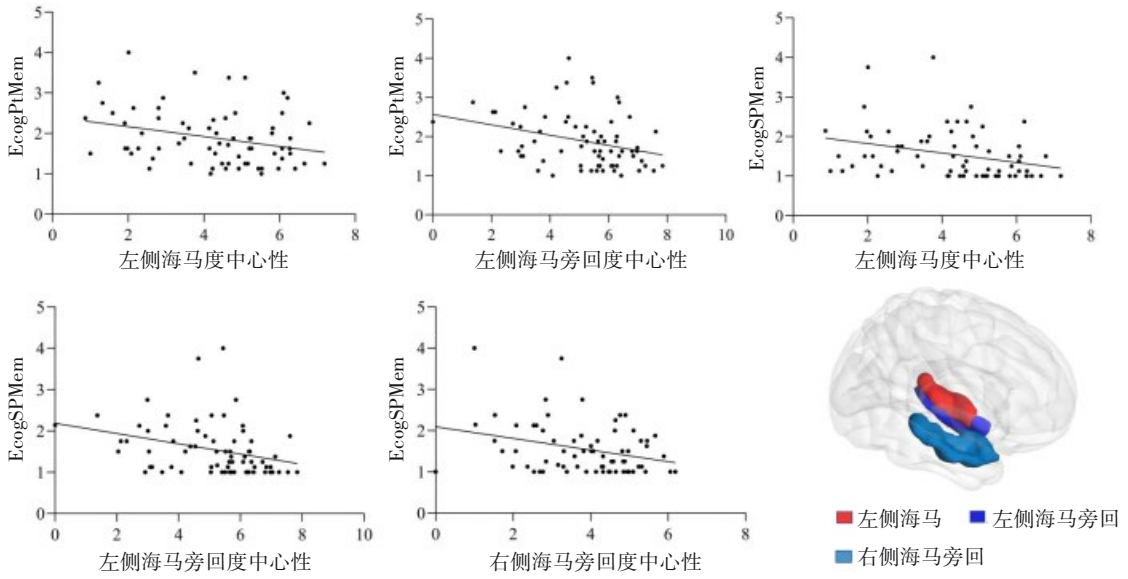


图3　差异脑区度中心性与日常认知量表评分相关性分析

Figure 3　Correlation analysis between degree centrality of different brain regions and daily cognitive scale score

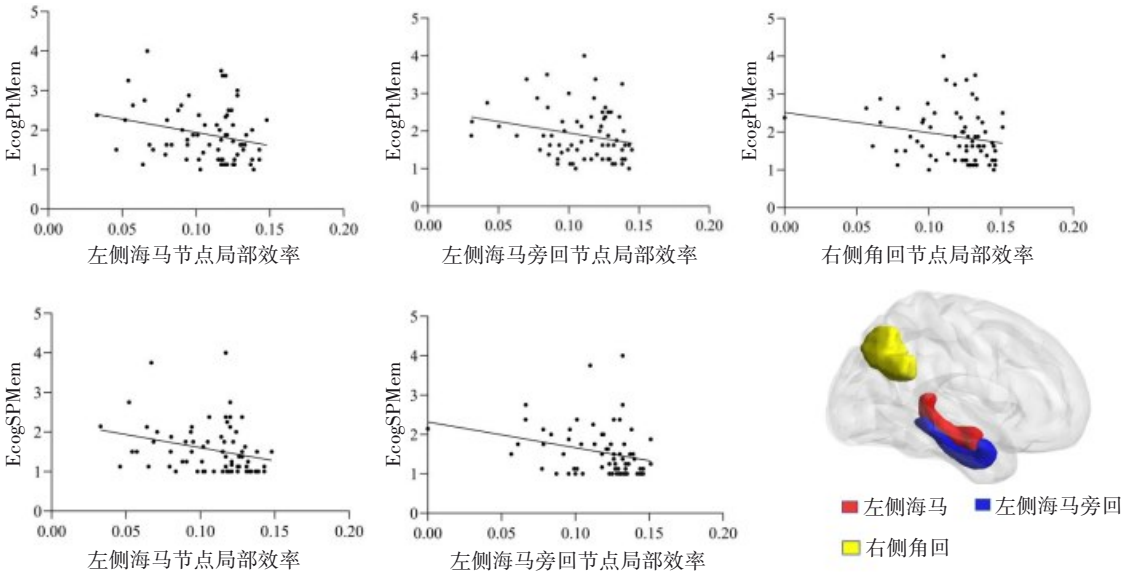


图4　差异脑区节点局部效率与日常认知量表评分相关性分析

Figure 4　Correlation analysis between nodal local efficiency of different brain regions and daily cognitive scale score

4　讨　论

4.1　度中心性变化可能是 T2DM&MCI 患者记忆功能下降的潜在生物标志物

本研究结果显示，与对照组比较，观察组左侧海马旁回、左侧海马、左侧顶下缘角回、左侧角回、右侧角回、右侧顶下缘角回、右侧海马旁回的度中心性明显降低，提示海马、海马旁回以及角回的度中心性变化可能是 T2DM&MCI 患者记忆功能下降的潜在生物标志物。这可能与以下因素有关，① 海马旁回与认知功能密切相关：海马旁回作为边缘系统的重要组成部分，是一个与认知功能密切相关的结构，从海马收集记忆，在学习、视觉空间任务和长时记忆的编码、提取过程发挥关键作用[28-29]。有研究发现，MCI 患者海马旁回功能连接出现异常，MMSE 评分明显降低[30]，与本研究发现 T2DM&MCI 患者海马旁回与大脑其他区域的功能联系减弱的结果一致。② 海马对记忆功能整合的重要作用：海马在记忆功能中起着关键作用，负责存储和提取情

景记忆[31]。有研究显示,MCI患者在记忆提取过程中,海马功能连接模式发生改变[32];分割后的几个海马区体积与记忆分数相关,突显了海马区在记忆衰退中的关键作用[33],与本研究结果显示T2DM&MCI患者海马度中心性降低的结果相互佐证。③ 角回在记忆整合过程中发挥重要作用:角回是默认模式网络的重要组成部分,在情景记忆和语义记忆的多模式整合中发挥重要作用[34]。LIU等[35]研究发现MCI患者角回局部一致性显著减弱,角回功能活动水平降低,与本研究发现一致,T2DM&MCI患者角回度中心性降低,角回在记忆整合过程中的作用下降。

4.2 节点局部效率降低可能反映T2DM&MCI患者脑区白质结构连接被破坏

本研究结果显示,与对照组比较,观察组左侧直回、左侧海马旁回、左侧海马、左侧顶下缘角回、左侧角回、右侧角回、右侧顶下缘角回的节点局部效率明显降低,提示节点局部效率降低可能反映T2DM&MCI患者脑区白质结构连接被破坏。节点局部效率的降低反映了不同区域的信息传输能力受损,可能是由于T2DM&MCI患者的短程连接的白质退化所致,与既往研究结果显示T2DM患者和MCI患者均存在白质病变的结果一致[36-39]。脑区白质结构连接被破坏,可能与髓鞘完整性被破坏和轴突密度降低有关。直回是额叶的重要组成部分,与认知和记忆功能有关,切除直回会对记忆回忆以及语言功能产生影响[40]。既往T2DM&MCI脑白质网络研究发现,与健康对照组比较,T2DM&MCI患者皮质-边缘相关结构白质纤维连接受损,海马、海马旁回、直回等脑区节点效率也明显下降,与本研究结果相一致[41]。

4.3 脑葡萄糖代谢连接网络拓扑结构异常可能与T2DM&MCI患者记忆功能下降有关

本研究结果显示,观察组海马旁回、角回脑代谢网络度中心性和节点局部效率明显降低,与Ecog-PtMem、EcogSPMem评分均呈负相关关系,提示脑葡萄糖代谢连接网络拓扑结构异常可能与T2DM&MCI患者记忆功能下降有关。可能与T2DM患者海马旁回、角回葡萄糖代谢减弱或功能障碍有关,但目前尚无证据证明与海马代谢功能改变有关。这与GARCÍA-CASARES等[15]和LI等[42]研究结果一致。

5 小 结

T2DM&MCI患者脑代谢网络发生异常改变,网络拓扑指标如度中心性以及节点局部效率有多个记忆相关脑区出现异常,与患者的记忆功能改变密切相关,这为进一步研究T2DM&MCI神经机制提供参考。但本研究仍存在一些局限性:如本研究是横断面研究,无法评估疾病在进展过程中的大脑代谢网络的动态变化;主要聚焦于T2DM&MCI患者,并未分别探讨MCI、T2DM患者脑代谢网络改变以及其与认知表现的关系。未来研究将进一步观察MCI和T2DM患者的脑代谢网络变化情况,并细化健康对照组、T2DM组、MCI组和T2DM&MCI组之间的比较,以期对T2DM与MCI之间的关系有更深入的认识。此外,开展纵向研究以更好地理解T2DM&MCI疾病进程中脑代谢网络的动态变化情况。

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Topological Analysis of Brain Glucose Metabolic Connectivity Networks of Patients with Type 2 Diabetes Mellitus Combined with Mild Cognitive Impairment

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ABSTRACT **Objective:** To analyze the changes in the topology of the brain glucose metabolic connectivity networks of patients with type 2 diabetes mellitus (T2DM) combined with mild cognitive impairment (MCI). **Methods:** A total of 35 T2DM&MCI subjects (observation group) and 35 healthy subjects (control group) were included from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Mini-mental state examination (MMSE) score, everyday cognition: the patient-reported memory (EcogPtMem) score, everyday cognition: the study partner-reported memory (EcogSPMem) score, and fluoro-2-deoxyglucose (FDG)-positron emission tomography (PET) images of both groups were included from the ANDI database. FDG-PET images were normalised to the Montreal neurological institute (MNI) spatial brain template by SPM 12 software. Using the cerebellum as reference area, standardized uptake value ratio (SUVR) of the anatomical automatic labeling (AAL) module brain regions of each subject was extracted to construct the glucose metabolism connectivity brain network. GRETNA software was used to analyze the topological properties of the brain network, including global efficiency, degree centrality, and node local efficiency. Spearman's correlation analysis was used to analyze the correlation of differential brain area degree centrality with EcogPtMem score as well as EcogSPMem score, and the correlation of node local efficiency with EcogPtMem score as well as EcogSPMem score. **Results:** Compared with the control group, MMSE score of the observation group was significantly lower, EcogPtMem and EcogSPMem scores were significantly higher, and the differences were statistically significant ($P<0.05$). There was no statistically significant difference of the global efficiency between the control group and the observation group ($P>0.05$). Compared with the control group, the degree centralities of the left parahippocampal gyrus ($P=0.005$), left hippocampus ($P=0.013$), left subparietal marginal angular gyrus ($P=0.031$), left angular gyrus ($P=0.034$), right angular gyrus ($P=0.013$), right subparietal marginal angular gyrus ($P=0.044$), and right parahippocampal gyrus ($P=0.024$) of the observation group were significantly lower. The nodal local efficiencies of the left straight gyrus ($P=0.028$), left parahippocampal gyrus ($P=0.044$), left hippocampus ($P=0.026$), left subparietal angular gyrus ($P=0.031$), left angular gyrus ($P=0.024$), right angular gyrus ($P=0.004$), right subparietal angular gyrus ($P=0.039$) decreased significantly. Correlation analyses showed that, degree centrality of left hippocampal ($r=-0.273$, $P=0.022$) and left hippocampal parahippocampal gyrus ($r=-0.341$, $P=0.004$) were negatively correlated with EcogPtMem score. The degree centrality of left hippocampal ($r=-0.391$, $P=0.001$), left hippocampal parahippocampal gyrus ($r=-0.410$, $P<0.001$), and right hippocampal parahippocampal gyrus ($r=-0.240$, $P=0.045$) were negatively correlated with EcogSPMem score. The nodal local efficiencies of the left hippocampal ($r=-0.257$, $P=0.032$), left parahippocampal gyrus ($r=-0.251$, $P=0.036$), and right angular gyrus ($r=-0.265$, $P=0.027$) were negatively correlated with the EcogPtMem score. The nodal local efficiencies of left hippocampal ($r=-0.363$, $P=0.002$) and left parahippocampal gyrus ($r=-0.362$, $P=0.002$) were negatively correlated with EcogSPMem score. **Conclusion:** The abnormal topological structure of brain glucose metabolic connectivity network in patients with T2DM&MCI might be one of the reasons for the decline in memory, which could provide a reference for the exploring of the neural mechanism of patients with T2DM&MCI.

KEY WORDS type 2 diabetes mellitus; mild cognitive impairment; degree centrality; nodal local efficiency; brain glucose metabolism; network topology analysis
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