基于区域的抑郁症默认网络内部功能连接研究

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【摘要】 **目的：**探讨静息状态下首发重性抑郁症默认网络内部各节点间功能连接状况。**方法：**采集31例首发重性抑郁症患者、33例健康对照静息态功能磁共振数据，以后扣带回为种子点进行基于体素的时间相关分析，得到默认网络的关键节点。采用基于区域连接的方法分析默认网络内各节点间功能连接系数。**结果：**与正常对照组比较，抑郁症患者默认网络背内侧前额叶与后扣带回、右顶下小叶功能连接降低，左顶下小叶与右侧海马结构功能连接降低。**结论：**抑郁症默认网络内部各节点之间功能连接存在异常，这可能是抑郁症的核心病生理特征。

【关键词】 抑郁症；默认网络；基于区域的功能连接

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Default Mode Network in Depressive Patients Based on Region-wise Functional Connectivity

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【Abstract】 **Objective:** This paper was to study the functional connectivity(FC) among the regions within the default mode network(DMN) in patients with major depressive disorder at rest. **Methods:** We analyzed resting-state functional magnetic resonance imaging(fMRI) data obtained from 31 first-episode, treatment-naive young adults with MDD and from 33 matched healthy control subjects. Seed-based analysis with posterior cingulated cortex(PCC) was used to define DMN. Region-wise FC analysis was performed to inspect FC among the regions within the DMN. **Results:** Compared with the control group, patients with MDD showed significantly decreased FC of dmPFC(dorsal medial prefrontal cortex) with PCC and right inferior parietal cortex(IPL), as well as decreased FC between left IPL and right HF. **Conclusion:** The abnormal FC among the regions within DMN is the important in the pathophysiological mechanisms of MDD.

【Key words】 Major depressive disorder; Default mode network; Region-wise functional connectivity

尽管目前抑郁症神经病理学机制尚不明确，但大量研究发现抑郁症静息状态下脑网络存在异常[1]。抑郁症脑网络研究涉及默认网络（default mode network, DMN）[2]、中央执行网络[3]、凸显网络[4]和情感网络[5]等，其中以DMN的研究最为活跃。DMN的范围主要涉及内侧前额叶、后扣带回/楔前叶、双侧顶下小叶（包括角回）、双外侧颞叶、海马及海马旁回等大脑核心区域[6]。DMN被认为与自我反映/参照、外在环境及内省状态的监视等密切相关[7]。大量研究揭示，DMN是抑郁症重要的神经病理机制[8,9]，与抑郁情绪、自我异常、记忆损害等抑郁症典型临床特征密切相关。有关DMN的研究，传统上多采用种子点相关分析法和独立成分分析法，这两种方法无法揭示DMN内各脑区之间功能连接状况，存在一定的局限性。本研究在前期研究的基础上[9]，以首发未服药的重症抑郁症为研究对象，采用基于区域（Region-wise）[10]的功能连接分析方法，分析抑郁症DMN内各节点之间功能连接状况，以期从更细粒度上分析抑郁症DMN的异常特性。

1　对象与方法

1.1　对象

1.1.1　*抑郁症组*　在中南大学湘雅二医院心理门诊招募首发抑郁症患者。入组标准：①符合美国精神疾病诊断与统计手册第四版(DSM-IV)重性抑郁症的诊断标准；②流调中心用抑郁量表得分（CES-D）>29分；③首次发病，无服药史；④汉族，右利手；⑤文化程度为大学或以上。排除标准：①合并其它精神障碍或有酒精和药物滥用病史；②有明显内科疾病、脑疾病、外伤或其它躯体疾病；③有MRI扫描禁忌。共34例，3例因头动过大被排除，终入组31例（男14，女17），年龄20.54±1.75岁。

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1.1.2　健康对照组　在湖南高校招募健康大学生志愿者。入组标准要求CES-D得分<18分，汉族、右利手，个人或直系亲属无精神疾病史，无明显内科疾病、脑疾病、外伤或其它躯体疾病、无酒精和药物滥用等病史。共35例，2例因头动过大被排除，终入组33例（男16，女17），年龄20.85±1.45岁。

1.2　方法

1.2.1　磁共振数据采集　使用美国Siemens1.5T磁共振扫描仪，标准八通道头部线圈进行数据扫描。扫描采用仰卧位，受试者头部固定、清醒闭眼、戴耳塞。所有扫描由同一名影像科医师完成。常规扫描包括轴位T1W、T2W和T2-FLAIR。静息态功能数据像采用基于梯度回波的平面回波序列（GradientRecalled Echo-Echo Planar Imaging，GRE-EPI）。脉冲重复时间/回波时间：2000ms/40ms；矩阵：64×64；层数：26层；层厚：5mm；层间隔：0mm；体素大小：5×3.85×3.85mm^3；时间点：150个；扫描时间：300s。

1.2.2　磁共振数据预处理　首先去除因磁场不均匀及受试者不适应的前10个时相，后续数据采用DPARSF软件（http://rfmri.org/DPARSF）进行预处理。主要步骤包括：时间校正，头动校正（头动方向不超过1.5mm，旋转角度超过1.5°），空间标准化（MNI模板），数据平滑（全宽半高=6mm）、滤波（0.01 Hz-0.08 Hz）、去线性漂移等。

1.2.3　提取DMN关键节点　以PCC为种子点（-5，-49，40）（Talairach坐标）[11]，提取PCC的平均时间序列，与全脑所有体素的时间序列进行相关分析，回归6个头动参数、全脑信号、脑白质信号及脑脊液信号，得到相关系数r。利用Fisher's z transformation将r转化为z，z代表脑区间的功能连接强度。为了确保提取DMN关键脑区的无偏性，将病人组、正常组的结果合为一组，利用SPM8软件（http://www.fil.ion.ucl.ac.uk/spm）进行组内单样本t检验（P<0.05，FDR校正，体素>20），得到与PCC正相关的脑区分布图，即DMN的关键脑区，共11个（见附表）。

附表　DMN关键脑区

脑区	Broadman分区	缩写	MNI*坐标	t值
背内侧前额叶皮层	9	dmPFC	0 48 30	12.87
腹内侧前额叶皮层	10	vmPFC	0 57 9	13.65
左侧额上回	8	sup_F R	-21 34 57	18.86
右侧额上回	8	sup_F L	19 36 54	13.24
左海马旁回	-	PH L	-24 -36 -15	10.98
右海马旁回	-	PH R	30 -33 -18	11.72
左颞中回	21	mid_T L	-51 -6 -27	15.46
右颞中回	21	mid_T R	60 -6 -18	14.66
左顶下小叶（含角回）	39	Inf_P L	-48 -69 33	17.67
右顶下小叶（含角回）	39	Inf_P R	50 -60 24	15.56
后扣带回	31	PCC	0 -52 30	27.32

注：*MNI为蒙特利尔神经研究所人脑坐标

1.2.4　DMN内部节点间功能连接　使用REST（http://rfmri.org/rest）软件，采用Region-wise功能连接方法，对每个被试的11个脑区两两进行相关分析，得到相关系数r。利用Fisher's z transformation将r转化为z，得到每个被试的11×11的功能连接矩阵。

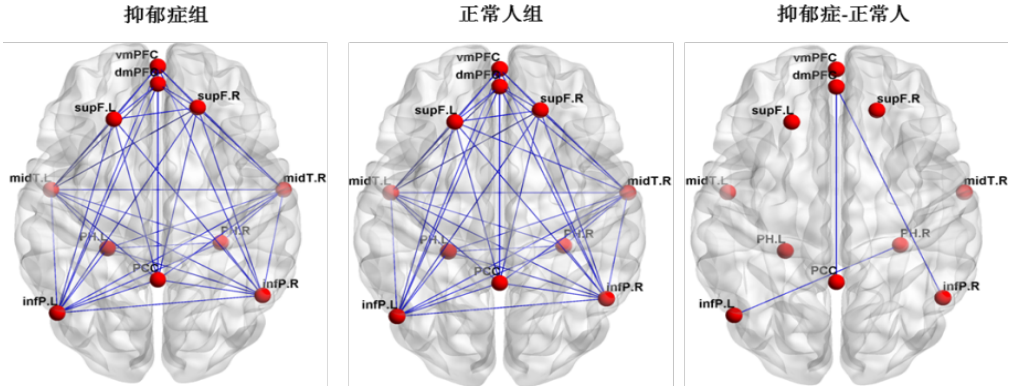
1.3　统计学分析

采用Matlab2014软件（The MathWorks，Inc，Natick，MA，USA）对抑郁组、正常组的功能连接矩阵进行组间双样本t检验（P<0.01，Alphasim校正）。运用SPSS17.0软件对两组人口统计学资料进行独立样本t检验或χ^2检验，显著水平为P<0.05。

2　结　　果

2.1　一般资料和行为数据比较

两组被试在男女性别比例、年龄及受教育程度组间均无显著差异（P>0.05），在CES-D抑郁症状总分组间存在显著差异（t=13.28，P<0.001）。



注：P<0.01，Alphasim校正

附图　DMN内各节点功能连接网络图

2.2　功能连接组分析结果

与健康对照组相比，首发重性抑郁症背内侧前额叶与后扣带回、右顶下小叶功能连接降低，左顶下小叶与右侧海马旁回功能连接降低，未发现功能连接升高的区域（见附图）。

3　讨　　论

多项研究发现，DMN是一个完整但异构的大脑系统[12,13]，内部至少分化成中枢系统和2个亚系统。以往基于独立成分分析的研究多从大脑全局性的角度关注DMN的活动特性，无法探析DMN内部更深层次的功能特性。本研究采用基于区域的功能连接，着重关注DMN内各节点间的功能连接状况。研究结果发现，与正常对照相比，抑郁症DMN内部的内侧前额皮质与后扣带、顶下小叶与海马旁回之间的功能连接紊乱。

内侧前额叶、后扣带回是DMN的中枢系统，是自我或自我相关加工的主要神经基础[14]。内侧前额叶皮质几乎参与所有与自我相关的加工，其中vmPFC主要参与自我表征，dmPFC主要与自我评定、自我决策相关[15]。后扣带回主要参与自我相关的情景记忆提取[16]。研究发现，抑郁症患者自我聚焦增强、负性自我归因、自动思维等自我异常特征都与DMN的中枢系统密切相关[17,18]。本研究发现内侧前额叶与后扣带回功能连接降低，说明抑郁症自我加工的神经机制出现紊乱，这或许是抑郁症临床表现出的自责自罪、无价值感的病生基础。

顶下小叶、海马旁回连同腹内侧前额叶构成DMN内部的子系统—“内侧颞叶子系统”[19]。该子系统在大脑从事回忆过去和想象未来的任务时明显激活。回忆过去和想象未来均以情景记忆为基础，这说明“内侧颞叶子系统”与情境记忆关系密切[20]。本研究发现顶下小叶与海马旁回的功能连接降低，说明抑郁症情景记忆加工的神经机制受损，这或许与抑郁症临床表现的记忆功能减退相对应。

DMN的正常机能来自于DMN与外部节点或网络之间、DMN内各节点之间、DMN内各子系统之间三者的相互作用相互协调。以往的研究[9]和本研究分别从大脑“全局”性、局部性的角度分别揭示了抑郁症DMN功能连接异常的特性。今后的研究可进一步从DMN内子系统之间功能整合的角度，深入挖据抑郁症DMN的特性，加深对抑郁症脑网络机制的认识。

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