·临床研究·

抑郁症静息态脑功能影像的脑区激活可能性分析

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[摘 要] **目的:**系统地研究抑郁症患者脑区激活特点。**方法:**在BrainMap和中国知网数据库中检索建库至2018年7月符合纳入标准的所有功能性磁共振成像(functional magnetic resonance imaging,fMRI)研究。使用Ginger-ALE2.3软件计算脑区激活可能性分布,使用Mango软件显示脑区图像结果。**结果:**将89篇文献共3 836例研究对象纳入研究范围。结果表明,抑郁症会导致边缘叶-丘脑-皮质网络、额叶和小脑的脑功能异常。**结论:**抑郁症患者相关脑功能区如边缘叶-丘脑-皮质系统和额叶被过度激活或受到损伤而导致相应症状。同时,枕叶和小脑出现异常,但症状与脑功能不完全对应,这可能是进一步研究的方向。

[关键词] 抑郁症;脑功能;ALE
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抑郁症又称抑郁障碍,其特征是持续的抑郁情绪、烦躁不安和焦虑、动机和社会行为的改变、心理运动的改变和睡眠异常。世界卫生组织统计,25%的普通人群在生活中会出现与重度抑郁发作相一致的症状[1]。

抑郁症的病理生理学机制尚不清楚。目前主要有两种理论,即单胺理论和神经源性假说[2]。单胺理论认为,抑郁症的病理生理学基础是由于中枢神经系统中单胺的缺陷,神经源性假说认为成人海马神经减少可能是抑郁症发病的基础。从以往研究中了解到,受影响的大脑区域位于边缘-丘脑-皮质网络中。在过去20年里,神经影像学研究促进了我们对大脑解剖、功能和精神病理学之间关系的理解。Bench等[3]通过正电子发射断层摄影技术发现前额叶皮质在抑郁症患者脑区中存在异常;利用核磁共振成像和脑功能磁共振成像技术,Soares等[5-6]研究表明前扣带皮质、基底神经节和其他边缘和旁边缘区在重度抑郁综合征中发挥作用。

为了进一步确定抑郁症与脑功能区变化的关系,探索抑郁症对大脑功能是否存在传统认知以外的影响,本文基于BrainMap数据库和中国知网数据库对抑郁症患者脑功能区域改变的研究进行整合和再分析。

1 资料和方法

1.1 资料

BrainMap是由德克萨斯大学圣安东尼奥健康科学中心影像研究所开发的存储已发表功能和结构神经影像学实验的数据库。Sleuth是一个基于Brainmap数据库的免费公开的搜索工具[7]。基于Sleuth可获得BrainMap数据库内所有符合检索条件文献的基本信息(包括第一作者、发表时间、研究方法、样本总数等)以及各个研究激活区峰值坐标(默认为Talairach坐标)。

本研究首先使用Sleuth 2.2对BrainMap数据库进行检索:实验对象被诊断为患有抑郁症结果(Subjects→Diagnosis→is→Depression),年龄、性别不限,文献中均包含Talairach坐标,语种设定为英文。下载抑郁症状态下功能异常的全脑坐标(72篇论文、2 657个位置、154个实验、2 311个实验对象)。再检索中国知网数据库,检索截止日期为2018年7月,检索式为“题名=抑郁症 并且 题名=fMRI 或者 题名=抑郁症 并且 题名=脑功能(精确匹配)”。

此外,还对原文及综述所列出的参考文献进行手工检索。

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1.2 方法

1.2.1 文献选择标准

纳入标准:①文献所纳入的病例均应符合中国精神疾病诊断与分类标准第3版(CCMD-3)抑郁症诊断标准或符合美国精神障碍诊断与统计学手册第4版(DSM-IV)抑郁诊断标准。②研究方法均涉及fMRI的脑功能成像。③研究结果呈现形式须为Talairach或蒙特利尔神经科学研究所(Montreal Neurological Institute,MNI)坐标。③研究结果包含抑郁症患者与正常对照fMRI的差异结果。

排除标准:①文献信息不完整或数据有误(如:缺少对照组)。②重复文献、文摘、综述及讲评类文献。

1.2.2 资料提取

根据上述纳入及排除标准对检索的文献进行筛选,提取资料中的临床信息及数据,包括文献第一作者、发表时间、研究对象样本含量、坐标类型、各个研究激活区峰值坐标。

1.3 统计学方法

激活可能性估计法(activation likelihood estimation,ALE)是一种由Turkeltaub等[8]提出的基于体素坐标的功能脑区定位分析方法,通过对纳入文献的相关坐标进行三维高斯函数平滑和排列检验,达到定位脑区的目的。为了减少研究结果的假阳性率,Eickhoff等[9]对统计学算法进行了补充,引入一种基于错误发现率(false discovery rate,FDR)的检验方法,通过控制拒绝假设检验中出现误判的比例来确定阈值,避免假阳性率发生。Eickhoff等[9]改进了原有的统计学模型,把固定效应模型变为随机效应模型,使得分析结果更加客观准确。

具体方法:①首先运用Icbm2tal软件(Ginger-ALE2.3内置插件)将所有空间坐标统一为Talairach坐标,依据ALE手册中坐标录入方法将坐标数据导入Ginger-ALE2.3软件进行分析。②使用Ginger-ALE2.3软件计算得出脑区的ALE分布图。根据最大激活坐标峰值,按三维高斯分布建模,具体参数如下:FDR为0.05,像素簇阈值>200 mm^3,经过软件运算后得出脑区ALE分布图。③使用mango软件以及BrainMap网站提供的标准脑解剖模板显示脑区图像结果。

2 结 果

2.1 文献检索结果与纳入文献的基本特征

检索BrainMap数据库和中国知网数据库中自建库至2018年7月符合纳入标准的所有fMRI研究,初步检索到文献268篇;通过阅读文章题目、摘要、全文,排除重复文献、非相关文献以及其他不满足纳入标准的文献等,最终共纳入89篇文献。纳入文献的基本特征详见表1。

2.2 分析结果

如表2所示,结果提供了抑郁症患者ALE脑功能区异常区域及其坐标和ALE值,表明89篇论文、3 299个位置、220个实验、3 836个实验对象所得的脑功能区坐标中存在着共性区域。抑郁症患者在左右半球前扣带、左右半球海马旁回和杏仁体、左右半球额中回、左右半球豆状核、丘脑、左右半球岛叶、左右半球尾状核、左半球胼胝体、左半球额内侧回、左半球额下回、右半球小脑山顶表现出脑功能异常。

再根据布罗德曼分区绘制出具体的异常区域,如图1所示。布罗德曼分区最初由德国解剖学家Korbinian Brodmann定义并编号,其依据是用Nissl染色法观察到的大脑皮层神经元细胞结构组织。

3 讨 论

在社区样本中,女性的抑郁症终生患病率为10%~20%,男性为5%~12%。过去研究一直认为抑郁症与边缘叶-丘脑-皮质网络的大脑功能区域有关,本研究发现抑郁症不但影响以上区域的大脑功能,还对额叶和小脑功能存在影响。

3.1 边缘叶-丘脑-皮质网络

边缘叶由隔区、扣带回、海马回、海马旁回和钩回构成。边缘叶与杏仁核、丘脑前核、下丘脑、中脑被盖、岛叶前部、额叶眶面等结构共同组成边缘系统。边缘系统与网状结构和大脑皮质有广泛联系,参与高级神经、精神(情绪和记忆等)和内脏的活动。边缘系统损害时可出现情绪及记忆障碍、行为异常、幻觉、反应迟钝等精神障碍及内脏活动障碍。丘脑是各种感觉传导的皮质下中枢和中继站,其对运动系统、感觉系统、边缘系统、上行网状系统和大脑皮质的活动发生着重要作用。丘脑受损主要为对侧感觉缺失和刺激征并可有情感和记忆障碍。杏仁核是产生情绪、识别和调节情绪、控制学习和记忆的脑部组织。海马体主要负责长时记忆的存储转换和定向等功能。

通过测量抑郁症患者的局部脑血流量(regional cerebral blood flow,rCBF),Park等[99]发现抑郁症患者双侧楔叶、梭状回/海马旁回、小脑、枕下回rCBF显著下降。Dougherty等[100-101]发现抑郁症患者前扣

表1 纳入文献的基本特征

第一作者	发表年份	坐标类型	样本含量	第一作者	发表年份	坐标类型	样本含量
Mayberg H S[10]	1999	Talairach	8	Krausz Y[55]	2007	Talairach	20
Mitterschiffthaler M T[11]	2003	Talairach	7	Bremner J D[56]	2007	Talairach	18
Okada G[12]	2003	Talairach	10	Epstein J[57]	2006	Talairach	10
Yatham L N[13]	2000	Talairach	20	Fu C H[58]	2007	Talairach	19
Holmes A J[14]	2005	Talairach	17	Mitterschiffthaler M T[59]	2008	Talairach	17
Bench C J[15]	1992	Talairach	33	Elliott R[60]	1998	Talairach	6
Bonte F J[16]	2001	Talairach	21	Chen C H[61]	2007	Talairach	17
Dolan R J[17]	1992	Talairach	20	Knutson B[62]	2008	Talairach	14
Drevets W C[18]	1992	Talairach	23	Fales C L[63]	2008	Talairach	27
Oda K[19]	2003	Talairach	23	Fales C L[64]	2009	Talairach	23
Machale S M[20]	2000	Talairach	42	Fu C H[65]	2008	Talairach	35
Videbech P[21]	2001	Talairach	42	Grimm S[66]	2008	Talairach	19
Kennedy S H[22]	2001	Talairach	13	Johnstone T[67]	2007	Talairach	21
Perico C A M[23]	2005	Talairach	15	Tavares J V[68]	2008	Talairach	25
Skaf C R[24]	2002	Talairach	21	Wang L[69]	2008	Talairach	19
Goldapple K[25]	2004	Talairach	27	Yang T T[70]	2009	Talairach	13
Mayberg H S[26]	2002	Talairach	4	Bertocci M A[71]	2012	Talairach	41
Mayberg H S[27]	2000	Talairach	14	Fernandez-Corcuera P[72]	2013	Talairach	41
Smith G S[28]	2002	Talairach	6	Garrett A[73]	2011	Talairach	15
Smith G S[29]	1999	Talairach	6	Vizueta N[74]	2012	Talairach	21
Brody A L[30]	1999	Talairach	9	Walter H[75]	2007	Talairach	27
Vlassenko A[31]	2004	Talairach	19	Almeida J R C[76]	2010	Talairach	45
Canli T[32]	2004	Talairach	15	Hulvershorn L A[77]	2012	Talairach	30
Gotlib I H[33]	2005	Talairach	18	Kemp A H[78]	2007	Talairach	16
Keedwell P A[34]	2005	Talairach	12	Whalley M G[79]	2009	Talairach	32
Kumari V[35]	2003	Talairach	6	Keedwell P[80]	2009	Talairach	12
Lawrence N S[36]	2004	Talairach	21	Segarra N[81]	2016	Talairach	35
Surguladze S[37]	2005	Talairach	16	李夏黍[82]	2013	MNI	30
Anand A[38]	2005	Talairach	15	王丽[83]	2008	Talairach	22
Audenaert K[39]	2002	Talairach	20	王晓霞[84]	2011	Talairach	10
Elliott R[40]	2002	Talairach	10	朱俊娟[85]	2014	MNI	16
Fu C H[41]	2004	Talairach	19	姚志剑[86]	2008	Talairach	15
Harvey P O[42]	2005	Talairach	10	王晓霞[87]	2015	MNI	14
Liotti M[43]	2002	Talairach	17	谭俊华[88]	2009	Talairach	20
Tremblay L K[44]	2005	Talairach	12	王晓霞[89]	2014	MNI	10
Schaefer H S[45]	2006	Talairach	9	邱天爽[90]	2015	MNI	5
Beauregard M[46]	2006	Talairach	12	牟君[91]	2007	Talairach	20
Yang J C[47]	2004	Talairach	10	马宁[92]	2007	MNI	22
Pizzagalli D[48]	2001	Talairach	9	陈宇[93]	2009	MNI	11
Wu J C[49]	1999	Talairach	36	李卓琳[94]	2007	Talairach	19
Wagner G[50]	2006	Talairach	16	王丽[95]	2009	Talairach	48
Abler B[51]	2007	Talairach	12	袁辉[96]	2008	Talairach	30
Matsuo K[52]	2007	Talairach	15	黄国权[97]	2013	MNI	39
Walter H[53]	2007	Talairach	12	范洪峰[98]	2009	MNI	10
Fitzgerald P B[54]	2008	Talairach	13				

带回皮层存在rCBF的下降，Kameno等[102-103]的研究发现丘脑存在rCBF的下降。Dougherty等[100]的研究发现抑郁症患者rCBF纹状体和苍白球存在异常，Zheng等[104]通过fMRI发现抑郁症患者纹状体功能显著减退，提示抑郁症患者的边缘叶-丘脑-皮质网络和丘脑皮层纹状体通路可能受到了损伤。Drevets等[105]的研究采用正电子发射断层扫描技术对重度抑郁症的神经功能进行了研究，测量脑血流量的差异，发现从左腹外侧前额皮质延伸到内侧前额皮质表面的区域脑血流量增加，进一步发现抑郁症患者杏仁核和前额叶皮质活动增强，Kim等[101]研究通过测量rCBF进一步证明了抑郁症患者的杏仁核确实

表2　抑郁症患者ALE脑功能异常区域及坐标

脑叶	脑区	布罗德曼分区	x	y	z	ALE值
边缘叶	左前扣带灰质	32	−4	40	−2	0.079
			−10	46	0	0.070
			−4	26	28	0.052
			−4	40	16	0.050
		24	−4	22	−6	0.059
	右前扣带灰质	32	10	36	14	0.058
		24	2	12	30	0.060
			2	28	18	0.071
		25	2	16	−6	0.055
	左海马旁回杏仁体		−18	−4	−18	0.056
	右海马旁回杏仁体		22	−6	−12	0.094
额叶	左额内侧回灰质	10	−6	54	8	0.062
			−10	44	12	0.054
	左扣带回灰质	32	−12	24	36	0.061
	左额下回灰质	9	−44	10	28	0.076
	左额中回灰质	46	−38	34	20	0.065
		9	−38	24	28	0.057
		8	−34	16	40	0.053
			−26	24	42	0.052
			−22	30	42	0.048
	右额中回灰质	46	44	26	18	0.052
			44	26	24	0.050
		9	36	26	30	0.065
	左胼胝体	25	−6	14	−10	0.059
下叶	左豆状核壳核		−24	−4	10	0.085
			−28	8	−2	0.070
	左豆状核侧苍白球		−18	−2	−8	0.067
	右豆状核壳核		24	10	6	0.065
			22	10	0	0.064
	右豆状核侧苍白球		18	−8	8	0.072
	左屏状核灰质		−30	20	2	0.051
			−38	−8	−4	0.049
	右尾状核体		14	10	6	0.059
	右尾状核头		8	18	0	0.052
	左丘脑灰质		−6	−8	−2	0.055
	右丘脑灰质		14	−20	4	0.057
	左岛叶灰质	13	−42	0	0	0.052
	右岛叶灰质		42	8	−2	0.053
			−40	8	12	0.055
小脑前叶	右小脑山顶灰质		6	−40	−6	0.062

存在血流分布的异常，Loureiro等[106]用电休克疗法（electroconvulsive therap，ECT）和氯胺酮治疗调节杏仁核的反应起到抗抑郁反应和治疗焦虑的效果，提示杏仁核与抑郁症患者情绪不稳定和动荡多变密切相关。Kim等[101]和张向荣等[107]研究发现抑郁症患者海马旁回的rCBF下降，表明抑郁症患者海马可能受损，与抑郁症患者认知功能损伤和记忆力损伤有关[107]。

3.2　额叶

Kim等[101]和Wang等[108]发现患者大脑额叶

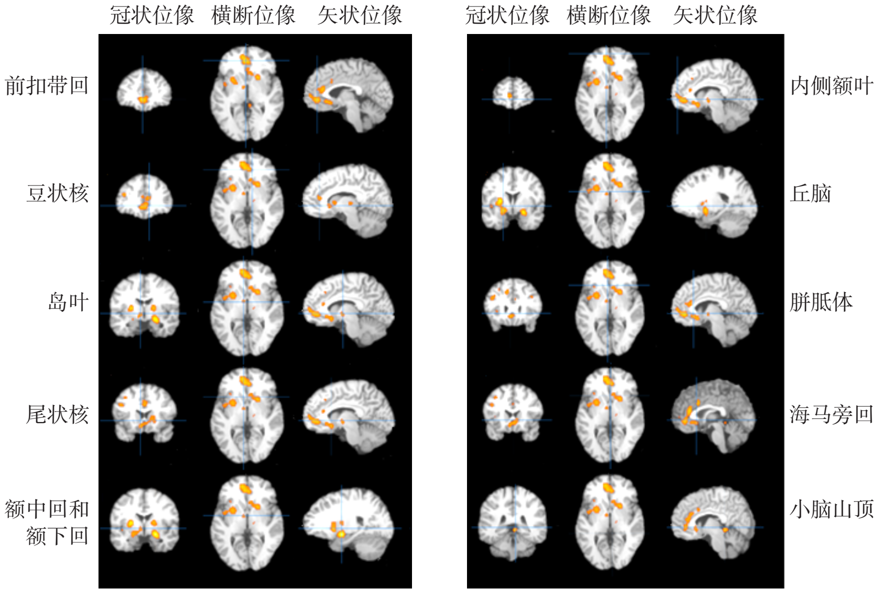

图1　抑郁症患者脑功能异常布罗德曼分区

rCBF降低，Zheng等[109]研究表明患者前额叶功能连接网络减少，提示抑郁症患者存在额叶损伤，可能与患者认知功能受损相关。Zheng等[104]和Che等[110]研究发现抑郁症患者大脑前额叶代谢显著增强，存在相对激活过度，可能是导致抑郁症患者情绪异常和动荡多变的另一原因。Yang等[111]发现抑郁症患者存在异常的额前-海马抑制通路，可能是患者记忆控制过程失败的原因。研究发现抑郁症患者的大脑功能在额旁回[112]、中央前后回[113]和额上回[114]存在异常，提示抑郁症可能还影响到患者额叶的其他功能区。

3.3　颞叶、枕叶

颞叶的主要功能区包括感觉性语言中枢、听觉中枢、嗅觉中枢，颞叶前部与记忆、联想、比较等高级神经活动有关，颞叶内侧面属边缘系统，与记忆、精神、行为和内脏功能有关。枕叶主要与视觉有关。研究发现颞叶[101]和枕叶[115]rCBF降低，提示抑郁症患者存在颞叶和枕叶损伤。

3.4　其他

此外还有研究发现抑郁症患者的rCBF在岛叶出现下降[108]，岛叶与控制网络间的连接减弱[116]，可能与患者处理不愉快刺激的能力减弱相关[117]。Depping等[118]研究还发现抑郁症的大脑功能在小脑后叶存在异常，研究发现尾状核、豆状核[119]和胼胝体的功能连接[120]存在异常。以及本研究中显示小脑山峰存在功能异常，这些都提示抑郁症可能不只影响传统认为的边缘叶-丘脑-皮质网络，还在其他方面对大脑功能造成伤害。

通过对既往研究的分析，认为抑郁症患者的边缘叶-丘脑-皮质系统和额叶、小脑的脑功能区存在异常，反映出抑郁症患者在这些功能区的大脑功能可能受到损害，提示人们在诊断与治疗抑郁症时，可参考脑功能影像的区域改变。

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