科学通报 2017 年 第 62 卷 第 22 期: 2492 ~ 2499
评 述
《中国科学》杂志社
SCIENCE CHINA PRESS

抑郁症相关的认知与情绪系统脑网络异常

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2017-02-22 收稿, 2017-04-05 修回, 2017-04-06 接受, 2017-05-17 网络版发表
国家自然科学基金(31671169, 31530031)、深圳市高端人才科研启动基金(000099)和深圳大学新引进教师科研启动基金(201564)资助

摘要 对周围的情境有正常的认知及产生相应的情绪对于人类社会交往有重要意义. 与健康人群相比, 抑郁个体却对情境有着减弱的认知加工及过强的情绪加工, 这反映了大脑中认知及情绪网络功能上存在异常. 以脑功能磁共振成像为研究手段, 近年来对抑郁症脑机制的研究逐渐增多. 这些研究在认知、情绪以及二者交互作用3个方面集中显示了额叶-边缘系统的功能改变. 其中, 情绪网络异常主要体现在杏仁核和脑岛, 并涉及5-羟色胺转运体基因型与抑郁症之间的关系; 认知网络异常主要体现在执行控制和默认网络; 而抑郁症对二者交互作用的影响则主要体现在杏仁核和背外侧前额叶. 了解归纳与抑郁症相关的认知和情绪脑网络异常能够为将来进一步揭示抑郁症发生的神经机制奠定基础, 同时为更加深入的研究提供线索.

关键词 抑郁症, 功能性磁共振成像, 认知, 情绪, 脑功能网络

情感性加工(affective processing)对于社会性的人类来说是一项重要的大脑高级功能. 基本所有的行为和决策均处在情绪性的情境中. 因此, 人类大脑的认知与情绪系统两者之间息息相关. 一般地, 认知功能会受到自下而上(bottom-up)情绪状态的影响, 而理性认知也能够反过来自上而下(top-down)地调节情绪性反应[1]. 与健康人群相比, 抑郁症(major depressive disorder, MDD)患者却有着异常的认知-情绪交互. 例如, 他们通常表现出认知控制减弱, 注意力降低, 以及情绪低落. 这些外在表现出来的行为学改变具有与之对应的内在脑功能异常. 揭示这些内在的神经机制是有效诊断和治疗抑郁症的前提基础.

近年来, 功能性磁共振成像(functional magnetic resonance imaging, fMRI)大量地被用于对抑郁症神经机制的研究. 除了在大脑结构上的改变[2,3], 抑郁症个体更多地显示了功能网络上的缺陷[4]. 因为情绪和认知功能损伤在抑郁症中具有普遍性, 这两方面的脑成像研究较为集中. 目前的研究结果显示, 抑郁症主要体现在额叶(frontal lobe)和边缘系统(limbic system)网络功能上的异常, 其中涉及背外侧前额叶(dorsolateral prefrontal cortex, DLPFC)、杏仁核(amygdala)、前扣带回(anterior cingulate cortex, ACC)、内侧前额叶(medial prefrontal cortex, mPFC)、海马(hippocampus)等多个脑区[5]. 基于fMRI在抑郁症研究中所获得的近期成果, 从情绪、认知以及二者的交互这3个方面进行简单介绍.

1 抑郁个体的情绪网络异常

大量行为学数据表明, 抑郁个体存在着负性情绪加工偏向(negative emotional bias); 相应地, 脑功能成像揭示杏仁核对负性面孔刺激激活增强, 对正性面孔刺激激活偏中性, 而对中性面孔刺激的激活偏负性[6]. 另外, 除了情绪性面孔, 大多数的脑成像研究也发现, 抑郁个体在对其他情绪性刺激进行加工时, 杏仁核的激活强于正常人[7,8]. 具体地, Suslow等人[9]采用了后掩蔽(backward masking)范式, 将中

引用格式: 陈丹, 李至浩, 罗跃嘉. 抑郁症相关的认知与情绪系统脑网络异常. 科学通报, 2017, 62: 2492–2499
Chen D, Li Z H, Luo Y J. Alterations in cognitive and emotional brain networks related to depression (in Chinese). Chin Sci Bull, 2017, 62: 2492–2499, doi: 10.1360/N972016-00892

性人脸作为启动和掩蔽刺激，情绪性人脸作为阈下目标刺激，研究抑郁患者杏仁核对阈下情绪性面孔的反应. 结果发现，抑郁个体的杏仁核在负性情绪加工时激活增强，在正性情绪加工时激活减弱. 这样的结果说明，在无意识加工水平上，抑郁患者对负性情绪刺激更加敏感，而对正性情绪刺激所分配的注意资源较少. Victor等人[10]采用类似的实验范式，但使用抑郁个体、抑郁状况康复的个体(remitted MDD, rMDD)和正常人3组作为被试，发现抑郁个体和抑郁康复个体两组被试与正常人相比，在对阈下悲伤面孔刺激加工时其杏仁核激活更强. 有研究者通过将抑郁个体杏仁核对阈下情绪加工的反应与其症状做相关分析，发现杏仁核激活与抑郁症的核心症状，即快感缺失(anhedonia)相关[11]. 即使采用抑郁康复的个体作为被试，研究者仍然发现他们存在着过多的负性情绪加工[12]. 既然抑郁症病人会出现杏仁激活异常的特性，那么是否可以利用在情绪面孔加工时杏仁核的活动作为抑郁症的生物学指标(biomarker)呢? Mattson等人[13]采用156名男性作为被试，将人脸图片在屏幕上下方分别呈现，上方呈现一张，下方呈现两张，在实验过程中让被试判断下方哪一张图片与屏幕的上方是匹配的，结果发现，杏仁核在对于人脸加工时的激活增强确实能够预测被试两年后抑郁症状的增多.

对应于杏仁核的激活异常，深层次的基因型研究主要发现5-羟色胺转运体(serotonin-transporter-linked polymorphic region, 5-HTTLPR)功能的变化[14]. 元分析(meta-analysis)结果表明，杏仁核活动强度与*5-HTTLPR*基因型相联系，杏仁核的激活归结于*5-HTTLPR*基因型的可能性达到10%以上[15]. 更具体地，Murphy等人[16]通过对涉及1402名被试的34项研究(包括了5项未发表的研究)进行了元分析，结果发现，*5-HTTLPR*的短型(S)基因表达主要与负性情绪条件下杏仁核活动的增强有关. 最早把基因表达和脑成像结合的研究也发现，短型基因携带者其杏仁核活动对情绪性面孔的增强主要存在于抑郁组中，并且该活动增强与患者的住院时长正相关[17]. 之后更多的研究也得出类似的结论[18]. 然而，也有其他的研究在考察负性情绪刺激条件下抑郁个体杏仁核活动与*5-HTTLPR*基因型关系的时候没有得出显著性结果[19]. 目前关于*5-HTTLPR*基因型与抑郁症的关系还有待进一步研究确认.

虽然大多数的研究结果认为，抑郁症病人在对情绪性刺激进行加工时，杏仁核激活会增强，但仍存在着另外一些研究发现，抑郁个体杏仁核在对情绪性刺激加工时，与正常人相比，没有表现出显著的激活差异[20]. 采用事件相关(event-related)实验设计，让被试观看3种情绪性人脸(惊恐、悲伤、高兴)，Almeida等人[21]研究发现，杏仁核激活增强更多的是与双相情感障碍(bipolar disorder)相关. 另外，现有研究结果的一致性可能还受被试药物使用的影响. 例如，舍曲林(sertraline)这种抗抑郁药可以使杏仁核在情绪性面孔加工条件下的激活减弱[10].

在情绪网络中，除了杏仁核，脑岛(insular)也同样受到了fMRI研究的关注. 有研究将诊断为早期抑郁症的病人作为被试，利用厌恶性面孔图片作为刺激，让被试去判断面孔的性别. 结果发现，抑郁个体在左侧脑岛上的激活比正常人强. 这一脑岛激活的增强可能反映了另一种情绪加工偏向，即厌恶情绪与抑郁症状也存在着高相关[22]. 与此相一致地，一项关于抑郁障碍的两年追踪研究也发现，随着个体的抑郁状态的缓解，其脑岛的激活也会下降[23]. 但是目前抑郁症研究中关注脑岛的还不太多，抑郁状态改变与脑岛激活改变这两者之间的因果关系尚不明确.

2 抑郁个体的认知网络异常

大量研究表明，与抑郁障碍相关的认知网络(cognitive network)改变主要来自于自传体记忆网络(autobiographic memory network, AMN)和认知控制网络(cognitive control network, CCN)[24~26]. 在没有外加实验任务的条件下，AMN也通常被称作默认网络(default mode network, DMN)[27]. AMN/DMN涉及的大脑区域主要有眶内前额叶(obitomesial prefrontal cortex, omPFC)、前喙扣带回(rostral anterior cingulate cortex, rACC)、扣带前回后部(posterior ACC)、压后皮质(retrospenial cortex)和楔前叶(precuneus).

正常个体在进行非自我参照(nonself-referential)加工时，其AMN/DMN激活会减弱[28]. 在Sheline等人[29]的研究中，他们让被试观看负性图片并进行认知重评，结果发现，在这个过程中，抑郁个体相比于正常人，AMN/DMN激活减弱失败. 也就是说抑郁个体在非自我参照任务下，AMN/DMN的激活比正常人强，并与抑郁的严重程度和抑郁表现——无望感(hopeless)正相关[30]. 在Rayner等人[27]总结的基础上，

本研究组画出了抑郁个体的认知网络改变示意图(图1), 其中黄色部分显示的是抑郁个体在AMN/DMN中相比于正常人激活增强的区域. 除了任务态fMRI, 针对抑郁症患者静息态fMRI (resting fMRI)的元分析也发现, AMN/DMN的功能连接在患者中增强, 而这一增强与抑郁症患者进行更多的自我加工相关[31]. 特别地, 有研究发现, 5周的经颅磁刺激(transcranial magnetic stimulation, TMS)治疗可以使抑郁个体AMN/DMN功能连接的增强趋于正常化[32]. 另外, Zhu等人[33]利用首次抑郁发作, 还未接受任何治疗的青少年作为被试进行静息态fMRI扫描, 发现在抑郁个体中, AMN/DMN的前部(anterior)与其后部(posterior)的功能连接改变并不一致, 有着分离的模式; 即前部功能连接增强, 而后部功能连接减弱, 特别是AMN/DMN前部功能连接的增强与抑郁个体的沉思(rumination)水平相关.

与AMN/DMN同样重要地, 个体的认知控制网络参与工作记忆、注意分配和任务切换, 认知控制网络涉及的大脑节点主要是背外侧前额叶. 从图1中可以看到, 抑郁个体的背外侧前额叶激活减弱; 也就是说, 抑郁个体的认知控制功能相对于正常人较差. 有研究针对第一次抑郁发作人群, 对涉及644名被试的15项研究进行元分析, 强调了抑郁症病人认知方面的缺陷, 包括在工作记忆、注意转换、语言流畅性等方面的功能减弱[34]. 抑郁症状越严重的个体其外侧前额叶(lateral prefrontal cortex)的激活会越弱[35]. 有研究者同时采用了认知负荷和无需认知负荷的情绪判断任务, 发现抑郁症患者的背外侧前额叶, 尤其是左侧激活的减弱与负性情绪判断相关[36]. 与此对应地, 也有研究表明, 经颅电刺激(transcranial direct current stimulation, tDCS)可以改善抑郁症被试背外侧前额叶的功能. 通过将阳极电极放置在背外侧前额叶的左侧, tDCS刺激该区域能够使抑郁症患者的工作记忆增强[37], 从而提升了抑郁个体在认知控制上的表现[38]. 在功能网络连接方面, 以背外侧前额叶作为种子点(seed)的功能连接分析发现, 抑郁患者的背外侧前额叶与扣带前回和左侧顶叶(parietal lobe)的连接较弱, 并且背外侧前额叶与扣带前回连接的强度与抑郁个体的执行功能具有正相关[39].

3 抑郁个体的认知与情绪交互异常

Diener等人[40]对抑郁症相关的认知和情绪研究做了元分析, 其报告中强调了前脑岛(anterior insular)和前喙扣带回(rostral anterior cingulate cortex)的作用. 抑郁症个体前喙扣带回在情绪性刺激、记忆编码、情绪性转换条件下激活减弱, 这与外在行为上所体现出的认知控制减弱相关. 另外, 抑郁症个体前脑岛在情绪性判断和情绪性转换条件下的激活也减弱, 这与他们外在行为中的负性情绪偏向相关.

大脑结构中认知网络的主要代表节点是背外侧前额叶, 情绪网络的主要代表节点是杏仁核. 大部分研究发现, 在对负性情绪加工时, 抑郁个体相比于正

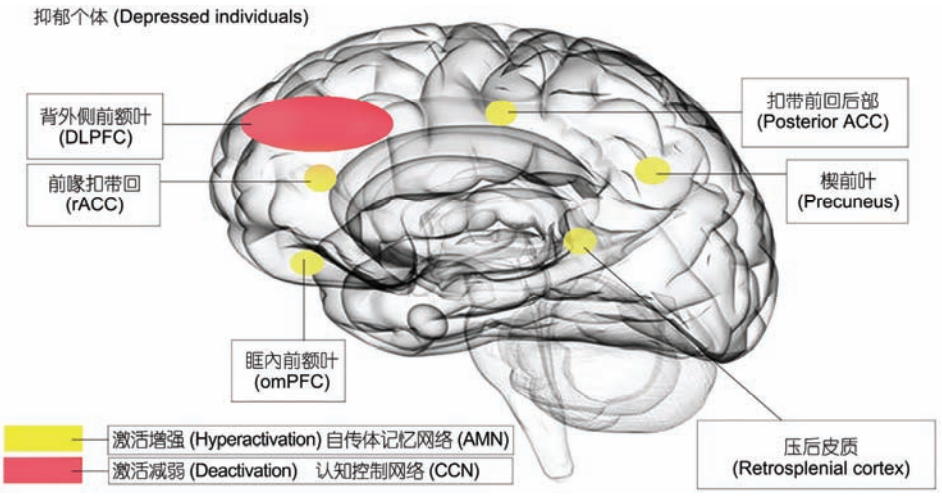

图 1 抑郁个体认知网络激活改变示意图. 黄色意味着激活增加, 红色意味着激活减弱. 本示意图改编自文献[27]

Figure 1 Alterations of the cognitive network during a nonself-referential task in depression showing hyperactivation (yellow) and deactivation (red). (Adapted from ref. [27])

常人，其背外侧前额叶激活减弱，杏仁核激活增强[41,42]，即抑郁个体的认知系统减弱，情绪系统活动增强. 抑郁个体的自上而下加工减弱，自下而上加工增强. Siegle等人[43]采用数字排序任务测量被试的认知系统，从而观察背外侧前额叶的活动. 采用“自我相关评定”任务来检测被试的情绪系统，让被试对屏幕中出现的正性、负性和中性情绪词汇进行与自身相关性程度的评定，以此来观察杏仁核的活动. 在这样的实验范式下，发现相比于正常被试，抑郁个体在数字排序任务中背外侧前额叶活动减弱，在情绪任务条件下杏仁核活动增强. 但是，Fales等人[44]认为，Siegle等人[43]的研究中认知与情绪的任务是分开的，无法说明认知与情绪的相互作用. 所以，Fales等人[44]采用了另一种实验范式，即在认知任务中加上情绪性面孔干扰. 具体来说，他们的实验材料为房子和情绪性人脸图片，当一对房子图片和一对人脸图片呈现在屏幕中时，被试需要忽视人脸并判断房子图片是相同的还是不同的. 结果显示，在需要忽视人脸图片干扰时，与正常人相比，抑郁个体杏仁核激活增强. 在同样的条件下，相比于抑郁个体，正常人的背外侧前额叶激活增强. 结果表明，与正常人相比，抑郁个体对非注意条件下的负性情绪比较敏感. 在后续的研究中，Fales等人[45]还发现，使用抗抑郁治疗能够让抑郁个体背外侧前额叶的激活减少趋于正常化. 这样的结果同样支持了在对负性情绪加工时，抑郁个体相比于正常人，其背外侧前额叶激活减弱，杏仁核激活增强的结论.

也有研究表明，在对情绪性刺激加工时，抑郁个体背外侧前额叶激活比正常人强[46]，而抑郁个体与正常人在杏仁核激活上却没有表现出显著差异[20]. 虽然有关认知与情绪交互作用脑功能成像的研究很多，但目前关于杏仁核或背外侧前额叶激活在抑郁个体上的激活是增强还是减弱还未得到一致性的结论. 这些结果的不一致可能是抑郁个体的临床症状表现不一致、被试用药不同、或研究者使用不同的实验范式所导致.

4 展望

基于上述已有的研究和一些存在争议的研究结果，关于抑郁症个体认知和情绪系统未来的研究主要关注在两个大方面：脑机制层面上的基础研究和应用层面上的治疗探索. 对于脑机制层面上的基础研究，可以关注以下4个方面. (ⅰ) 为了取得一致性的结果，在研究方法上可以采取更加细致的实验前措施. 因为抑郁症的症状个体差异较大，发作阶段不同，未来的研究可能需要根据相关症状量表匹配好需要进行比较的抑郁症人群. 因为采用不同的抗抑郁药物，如米氮平(mirtazapine)和文拉法辛(venlafaxine)会在患者大脑中产生不同的激活效应[47]，所以在实验过程中可以考虑尽量采用未经历过任何临床治疗的抑郁患者作为被试. 因为不同的实验范式会涉及不同的功能，尽量考虑选取统一的实验范式(如研究持续性注意的可以采用oddball，探讨抑制加工过程的可以采用go-nogo)也能提高不同研究之间的可比性[48]. (ⅱ) 当前大部分的研究只关注在认知控制(即认知任务下的正激活)和情绪加工这两大网络上，或只单独考察了抑郁症患者默认网络与正常人的差异. 未来进一步的探索可以在认知控制和情绪网络的基础上再增加默认网络，进行三大网络之间的交互研究，考察这三大信息加工资源在抑郁症病人的大脑中是如何分配的. (ⅲ) 在方法学上，过去的研究主要采取节点激活分析，而目前的连接组(connectome)分析发现，抑郁症同时在节点和通路这两个方面均发生改变[49,50]. 今后在脑成像分析方法上可以采取基于节点激活和基于图论(graph theory)的脑网络分析同时进行比较的策略，通过多种分析方法和多模态影像指标来发现抑郁症患者的生物学标记. (ⅳ) 脑成像揭示的是抑郁症病人不同脑区的功能改变以及相对宏观层面的神经机制. 如何将宏观改变和与之对应的微观生理生化机制联系起来也是未来研究的方向之一. 目前有研究发现，大部分抑郁患者同时伴有炎症反应，生理层面上表征为体内与炎症相关的C-反应蛋白(C-reactive protein, CRP)浓度增加[51]. 而在奖赏系统功能网络层面上，抑郁症患者腹侧纹状体(ventral striatum)和腹内侧前额叶(ventromedial prefrontal cortex, vmPFC)之间功能连接减弱[52]. 生理层面的炎症反应可能通过系统层面的功能连接来最终影响抑郁症的外在表现(快感缺失).

对于抑郁症的治疗，未来的研究可以关注以下3个方面. (ⅰ) 将脑成像数据与临床治疗方法相结合，提升效果评价. 以往在临床心理治疗上，无法精确考察或没有相对可靠的证据来评估心理咨询疗法是否对个体的认知提升或情绪控制有效. 通过比较脑成像数据在治疗前后的差异来评价治疗的效果，可以

为临床治疗的有效性提供评价依据. 已有研究开始利用fMRI来评估临床咨询上采取的认知行为疗法(cognitive behavioral therapy, CBT)对治疗女性青少年抑郁个体是否有效[53]. 结果发现, 治疗后被试大脑对于情绪性刺激的不正常反应减少, 从而提供了认知疗法对抑郁治疗有效性的证据. (ⅱ) 将脑成像与脑刺激相结合来提升个体水平上的精准医疗. 临床抑郁症的治疗会用到TMS刺激患者左边的DLPFC区域, 但刺激不同的靶点会带来不同的治疗功效. 有研究将fMRI与TMS相结合, 发现与膝下扣带回(subgenual cingulate, sgACC)负相关越强的DLPFC靶点能为抑郁症患者带来更好的治疗效果[54]. 因此, 如果把体现情绪异常的杏仁核/sgACC等区域作为感兴趣区, 用基于静息态fMRI的功能连接在皮层上定位TMS靶点将有可能提升TMS的治疗效果. (ⅲ) 未来的研究可以考虑利用实时fMRI (real-time fMRI, rt-fMRI)来对抑郁症患者进行神经反馈(neurofeedback)训练, 让病人实时观看自身疾病相关区域的活动并通过自主调节来改变该脑区的活动. 例如, 已有研究开始通过使用实时神经反馈来调节杏仁核的活动, 从而帮助抑郁病人克服负性情绪[55]. 另外, Sherwood等人[56]也尝试使用rt-fMRI让被试有意识地调节自身背外侧前额叶的活动, 结果发现, 这样的训练能够提高被试的工作记忆成绩. 实时反馈机制同时也能够用来训练上面提到的DLPFC-sgACC神经通路. 实时fMRI在治疗疾病方面的运用已有10多年的历史[57], 但由于治疗花费高或长期效果尚未明确等因素, 这方面的运用还处于探索阶段.

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Summary for “抑郁症相关的认知与情绪系统脑网络异常”

Alterations in cognitive and emotional brain networks related to depression

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It is essential for social interactions if one can process the perceived external world with appropriate cognitive control and well-regulated emotion. However, compared with healthy individuals, patients with major depression disorder (MDD) usually exhibit compromised cognitive and enhanced emotional processes, respectively; and these behavioral changes have been shown to be associated with alterations in functional brain networks. Recent advances of MDD research have been increasingly involving functional magnetic resonance imaging (fMRI) and focusing on brain networks of cognition and emotion, as well as the interaction of these two networks. While inconsistencies and debates noted, the present paper attempts to review and provide a summarized finding for these recent fMRI studies. Converging results have shown that MDD is associated with significant alterations in the fronto-limbic system. Specifically, compared with healthy controls, individuals with MDD usually show hyperactivation to negative facial stimuli in the amygdala, reflecting increased withdrawal, the core syndrome of depression. Some studies have also attempted to use hyperactivities of amygdala as the biomarker and reported its predictive value for MDD. Besides amygdala, increased insula response to disgusting faces was also reported in literature, emphasizing the role of disgust in emotional dysregulation. Cognitive abnormalities in depression mainly concern the default mode and executive control networks. In addition to alterations of regional activation in task state, individuals with MDD exhibit increased functional connectivity of the default mode network in resting state, suggesting enhanced self-referential processes. In particular, higher functional connectivity in the anterior default mode network corresponds with higher level of rumination. In the executive control network, many previous studies observed a decreased activation of dorsolateral prefrontal cortex in depression, indicating impaired ability of cognitive control. At the same time, recent research found that transcranial direct current stimulation in the left dorsolateral prefrontal cortex was helpful for working memory enhancement in individuals with MDD. While alterations were reported in the emotional and cognitive networks separately, interactive changes of these 2 modules have also been examined when they are simultaneously probed. Most studies have noted that when challenged with negative emotion, individuals with depression show increased activation in amygdala and decreased activation in dorsolateral prefrontal cortex, indicating a biased processing resource allocation towards the emotional system. Based on the aforementioned fMRI studies of MDD, we suggest that future improvements may consider aspects of (i) matching depressive syndromes for optimized confounding factor control; (ii) incorporating multimodal approaches for both brain imaging and stimulation; as well as (iii) applying neuroimaging together with psychological therapies either for prognosis evaluation or neurofeedback training.

major depression disorder (MDD), functional magnetic resonance imaging (fMRI), cognition, emotion, functional network

doi: 10.1360/N972016-00892