中国科学: 生命科学 2022 年 第 52 卷 第 11 期: 1678 ~ 1691
SCIENTIA SINICA Vitae lifecn.scichina.com
《中国科学》杂志社 SCIENCE CHINA PRESS
评 述 中国知名大学及研究院所专栏 四川大学华西医院专辑

抑郁症病因学和治疗学的研究进展

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收稿日期: 2022-07-20; 接受日期: 2022-09-05; 网络版发表日期: 2022-09-29

摘要 抑郁症是一种常见的精神疾病, 因其高患病率、高致残率和高自杀率给个体、家庭和社会带来了严重损害, 一直是业界学者关注的重点. 大量的人力和物力投入到了抑郁症病因学和治疗学的研究中, 力图更好地认识其产生的原因和病理机制, 从而更好地打开改善治疗结局与康复的迷局. 近年来, 抑郁症在流行病学、分子遗传学、神经影像学、神经免疫学、肠道微生物和治疗等领域的研究取得了重要进展. 本文将从上述领域进行回顾, 同时也将介绍四川大学华西医院心理卫生中心所做的相关工作, 以期为精神科医师和抑郁症领域研究者提供参考.

关键词 抑郁症, 病因机制, 临床治疗, 研究进展

抑郁症作为最为重要的精神疾病之一, 对人类健康有着重要影响, 全球约3亿人受到该疾病的困扰[1]. 据最新的全球疾病负担研究显示, 由抑郁症导致的伤残调整生命年(disability adjusted life years, DALYs)数量占全球所有DALYs的1.85%[2]. 我国精神卫生调查(China Mental Health Survey, CMHS)项目在2012~2015年也对全国精神障碍的流行病学和精神卫生服务利用情况进行了调查, 该项目涉及我国31个省市的城市和农村人口, 数据显示抑郁症终身患病率女性为8.0%, 男性为5.7%[3]. 抑郁症的平均发病年龄在25岁左右, 约40%的人在20岁前经历第一次抑郁发作, 女性的发病率几乎是男性的2倍[4,5]. 抑郁症通常起病慢, 复发率高, 并且复发风险随着发作次数的增加而增加, 约80%的患者在其一生中至少有过1次复发[6,7]. 近年来, 抑郁症病因学和治疗等领域的研究受到广泛关注, 也取得了一些重要进展, 本文将对这些内容进行综述.

1 生物学标记的研究进展

1.1 遗传学研究

精神疾病的遗传因素很早就受到关注, 但直至19世纪, 人们观察到抑郁症发病具有家族聚集现象, 才认识到抑郁症也可能与基因遗传有关(图1).

早期的家系及双生子研究结果提示, 抑郁症的遗传度与不同的起病年龄、疾病发作次数等因素相关. 早发型抑郁症比晚发型抑郁症的遗传风险大[8,9], 复发性抑郁症比单发性抑郁症患者的遗传风险高[9], 抑郁症患者的一级亲属罹患抑郁症的风险为37.8%[10]. 进一步量化遗传因素对抑郁症的影响, 发现抑郁症估计

引用格式: 杨潇, 董再全, 王瑜, 等. 抑郁症病因学和治疗学的研究进展. 中国科学: 生命科学, 2022, 52: 1678–1691
Yang X, Dong Z Q, Wang Y, et al. Advances in the etiology and clinical treatment of depression (in Chinese). Sci Sin Vitae, 2022, 52: 1678–1691, doi: 10.1360/SSV-2022-0157

图 1　抑郁症的病因学研究
Figure 1　Etiology of depression

遗传度约为37%, 而压力性生活事件、父母的抚养方式和家庭贫困等个体特定的环境因素对抑郁症的影响可能高达63%, 如果同时存在发病年龄、疾病的严重程度和复发率等因素, 抑郁症的遗传度可高达70%[11~13].

基于抑郁症的病因学假说, 人们开展了候选基因研究, 主要涉及经典的神经递质系统相关基因, 如发现*SLC6A4*基因(5-HTT基因)的STin2.9等位基因、5-羟色胺转运体基因启动子区(5-HTTLPR)中S等位基因可能增加抑郁症的患病风险, 而L等位基因可能是保护性因素[14~17]. 亚甲基四氢叶酸还原酶(5,10-methylenetetrahydrofolate reductase, MTHFR)基因C667T的TT纯合子、载脂蛋白E(apolipoprotein E, ApoE)的e4等位基因和e3/e4基因型、血管紧张素转化酶(angiotensin converting enzyme, ACE)基因的基因型DD变异体、BDNF基因66位的Met等位基因可能增加抑郁症的患病风险[18~21]. 此外, 谷氨酸受体亚型2(glutamate metabotropic receptor, GRM2)受体的基因表达增加和*SLC1A3*基因表达下降被认为与抑郁症及自杀关系密切[22,23]. 综上所述, 抑郁症候选基因研究取得了一定成果, 但在独立样本中的重复性有待提高.

随着测序技术的进展, 全基因组水平的关联分析(genome-wide association studies, GWAS)被广泛应用于精神疾病的遗传学研究中. Sullivan等人[24]于2009年对来自荷兰1738例抑郁症患者和1802个健康对照首次进行了GWAS分析, 未发现任何单核苷酸多态性(single nucleotide polymorphism, SNP)与抑郁症发生相关. 此后, 多项针对英国、德国、瑞士等欧洲病例进行的大样本GWAS分析结果提示, *DSEL*, *CCND2*, *BICC1*, *NLGN1*, *GRM7*, *ADCY3*, *GAL*, *HOMER1*, *CPM*, *SCL6A15*, *SETD6*, *LPCAT1*, *MS4A7*, *TROVE2*和*SLC25A37*等基因可能参与抑郁症的发生[25~37]. 鉴于抑郁症较高的临床异质性, 学者们对临床症状相似的中国汉族女性复发性抑郁症患者进行了GWAS分析, 发现位于10号染色体的两个基因位点与抑郁症发病密切相关, 即去乙酰化酶(sirtuin1, SIRT1)基因的rs12415800位点及无机焦磷酸化酶/无机焦磷酸酶(phospholysine phosphohistidine inorganic pyrophosphate phosphatase, LHPP)基因的rs35936514位点, 可能是抑郁症的风险位点[38]. 总之, GWAS研究为寻找抑郁症的风险基因提供了证据, 但检测到的每个遗传变异的贡献较小, 尚难以找到明确的遗传风险位点.

多基因风险评分(polygenic risk score, PRS)作为GWAS的补充方法逐渐被广泛应用, 其能在个体水平对遗传负荷进行度量, 可综合其他生物学和临床指标进行分析, 是未来精准医疗的重要工具之一, 可极大地促进遗传学的临床转化. 它的原理是通过结合多个已发现的疾病易感基因, 在早期预测个体未来患病的风险, 可用于疾病早期筛查和干预. 目前常用的预测模型是利用已知的疾病易感位点, 计算个体的PRS评分, 预测疾病的发病风险. 如先前研究发现, PRS能预测个体精神分裂症或者双相情感障碍的诊断[39,40]. 并且PRS有助于在精神疾病的前驱期之前预测个体未来出现疾病的可能性, 从而为高危人群筛查及预防干预提供依据, 有助于降低个体特别是高风险人群的发病率[41,42]. 近期的一项研究还发现, 基于个体水平的PRS能够有效地预测患者的临床疗效, PRS评分越高提示其疗效越差[43].

此外, 转录组学是一门在整体水平上研究细胞中所有基因转录情况及转录调控规律的科学, 能有效解释不同个体和不同细胞(或组织)在不同生理或病理状态下的基因差异表达信息, 有助于更全面地揭示疾病发生和发展的分子病理学机制[44]. 研究发现, mRNA(如BDNF mRNA, TNFA mRNA, SIRT1 mRNA和

GSK3B mRNA等)[45~49], miRNA(miR-16, miR-132, miR-1202和miR-9等)[50~53], lncRNA(TCONS_00019174和Cox-2-lncRNA等)[54~57], circRNA(circDYM和hsa_circRNA_103636等)[58,59]均与抑郁症的发病和症状严重程度有关, 可能是抑郁症潜在的分子生物学标记物.

四川大学华西医院心理卫生中心一直致力于寻找抑郁症的潜在生物学标记, 基于全外显子测序和大脑结构性磁共振成像(structural magnetic resonance imaging, sMRI), 通过罕见变异负荷试验发现两个基因(*CSMD1*和*CNTNAP5*)和一条通路(neuroactive ligand receptor interactive)在负荷试验中有显著性; 进一步采用平行独立分量分析方法研究抑郁症患者脑灰质体积(grey matter volume, GMV)变化的遗传基础, 发现个体GMV的下降与智商有关, 并发现在智商的中介作用下, 遗传成分可能通过改变GMV和认知功能从而影响疾病的发生[60]. 通过转录组测序分析发现, 抑郁症外周血中一些miRNA表达量明显上调, 比如miR-132表达水平异常增加并且与个体大脑前额叶-边缘系统的结构和功能有关[61]; 而抑郁症患者外周血中表达上调的primR-chr11可能通过调控其靶基因BRPF1而影响个体的海马体积[62]. 此外, 外周血的全转录组测序分析显示, 多个lncRNA和circRNA可通过竞争性结合miRNA而参与相应靶基因的调控, 最终可能通过影响能量代谢及免疫炎症过程参与抑郁症的发病过程[63]. 这些发现有助于更好地从多视角理解抑郁症的病理生理机制.

综上所述, 家系研究、双生子研究、候选基因研究、GWAS研究、多基因风险评分及转录组学相关的研究, 为抑郁症病因学的探索提供了很多线索, 为抑郁症的诊疗提供了潜在生物学标记, 但目前对抑郁症的全面认识还有待加强.

1.2 影像学研究

抑郁症是一种脑病, 也是中国脑计划列为重点研究的疾病之一. 大脑是一个复杂的系统, 不同区域之间相互作用, 进而对个体情绪调节等发挥重要作用[64]. 目前影像学研究提示, 边缘-丘脑-皮层网络等神经环路可能在抑郁症的发生中具有重要作用[65], 相关脑区结构和脑网络功能与疾病有密切关系[66](图1). 增强影像遗传学研究联盟的抑郁症小组(enhancing neuroimaging genetics through meta-analysis, ENIGMA-MDD)是目前全球最大的抑郁症影像遗传研究团队, 该团队目前已收集了来自15个国家的40个研究队列, 在近10年的研究中, 他们通过整合多中心的大样本分析发现, 和正常对照相比, 抑郁症的大脑皮层下结构特别是海马灰质体积显著降低, 扣带回、脑岛皮层厚度更薄以及白质纤维分数各向异性值更低等变化[67~69]. 多项影像学研究都发现, 抑郁症海马体积明显降低并且和疾病发生有关, 提示这可能是抑郁症的一个特质[68,70,71]. 本中心的研究也验证了这一结果[71], 并且还发现一种新型的上调miRNA(pmiR-chr11)可能通过调控BRPF1影响个体海马体积[62].

同时, 在抑郁症这类高度异质性疾病的诊断和分类上, 神经影像也提供了重要依据. 比如, Drysdale等人[72]首次根据抑郁症患者边缘系统及额叶-纹状体网络功能连接的差异, 将患者从神经生理水平分为四种生物亚型. 这些不同亚型患者的脑影像学改变与其特定的临床症状相关, 更重要的是, 通过临床随访发现, 不同亚型的患者对重复经颅磁刺激治疗的反应存在差异, 这可能有助于临床医生在早期识别出能从这一治疗手段中获益的个体. 除了基于功能连接, 大脑结构的差异已逐渐被用于定义不同的生物亚型[73]. 本中心基于抑郁症脑结构共变网络的改变, 定义了两种抑郁症的生物亚型, 并发现不同亚型患者的认知功能存在显著差异[74]. 尽管影像学的研究有一些局限性需要关注[75], 但影像学技术的发展的确有助于更好地认识抑郁症这一高异质性疾病的病因及发病机制.

此外, 脑区的异常不仅与抑郁症病因有关, 也与其疗效有关[76]. 研究者发现, 个体海马体积的异常降低, 可能与其抗抑郁药物治疗反应较差相关[77,78]; 而个体扣带回等区域体积的增加以及脑区之间功能连接的变化, 则可能与其治疗有效[76,79]、早期起效有关[80,81]. 本中心的研究也验证了影像学在疗效预测中的作用[82], 发现海马亚区的体积以及功能连接的改变可能与其抗抑郁药物疗效[83]和早期起效有关[84]. 此外, 前额叶、前扣带皮层、海马、杏仁核和脑岛等脑区体积以及脑区之间的功能连接也可作为认知行为治疗(cognitive behavioral therapy, CBT)和电休克治疗(electroconvulsive therapy, ECT)的疗效预测指标[76,85]. 比如杏仁核与左侧背外侧前额叶之间更强的功能连接, 与个体CBT治疗后症状的改善相关[86]. 而个体杏仁核体积更大[87],

额下回和外侧颞叶体积降低，则可能与个体经过ECT治疗的快速起效有关[88].

总体上，神经影像学作为一种非侵入性的检查手段，帮助人们发现了一些与情感、认知和奖赏等功能相关的脑区，比如前额边缘区及其神经环路等. 更重要的是，抑郁症作为一种临床异质性高的疾病，神经影像学为重新认识抑郁症的病因及发病机制，探索不同的疾病亚型提供了新的机会，也提高了对抑郁症治疗效果的生物学机制的认识，并确定一些脑区可作为刺激靶点以优化抑郁症的临床治疗[89,90].

然而抑郁症的病理生理也可能是高度异质性的，不同的病理生理机制可能导致不同的个体出现相似的症状，而相同的潜在生物风险因素也可能导致某种疾病在个体出现不同表现，未来还需要进一步识别抑郁症潜在的生物遗传和环境等多因素与大脑改变的相互作用, 以及更具有临床转化潜力的测量或预测方法.

1.3　肠道微生物与抑郁症

肠道菌群被称为“第二大脑”，其自身组成及代谢产物变化可以通过迷走神经、下丘脑-垂体-肾上腺轴、神经免疫系统以及各种代谢过程影响机体大脑功能和心理状态，进而与各种神经精神疾病产生关联[91~93](图1).

近年来, 大量研究发现, 肠道菌群构成及其代谢物与抑郁症发病、临床表型、疗效[94]以及大脑的结构有关[95]. 比如，抑郁症患者肠道菌群的定植可以导致正常小鼠出现抑郁样行为[96,97]，益生菌、运动和饮食等可以通过影响肠道菌群而显示出抗抑郁的潜力[98]. 有学者综述了不同分类水平上多种与抑郁症发病相关的肠道菌群[99]，详见表1. 同时人们开始探索独特肠道菌群特征是否能作为抑郁症诊断的生物学标记[93]. Yang等人[100]通过分析确定了一个“组合标记面板”，该方法可以有效地区分抑郁症和健康对照. 他们还设计了一种肠道微生物的“分类器”，并验证了其对抑郁症和双相情感障碍的诊断和鉴别作用[101]. 除了抑郁症, 微生物代谢产物的功能分析也被尝试用于多种精神疾病的诊断和病因机制探索[102]. 比如, 研究发现, 双相情感障碍患者的神经活性微生物和代谢物与个体脑功能的异常相关, 从而提示潜在的肠道和大脑的微生物群, 可能在双相情感障碍的病理生理学中起作用[91]. 同时, 研究也发现肠道微生物的重要代谢产物——丁酸盐和不饱和脂肪酸，在抑郁症与健康对照中的水平存在显著差异，提示这些肠道微生物群失调的特征可能是潜在的抑郁表型的生物标志物[103].

肠道微生物标记物不仅可能作为诊断标记物，同样也可以用于预测疗效. Hu等人[104,105]研究发现, 肠道微生物还可以预测双相抑郁患者的短期治疗效果，提示肠道微生物组成和代谢功能的改变可能与个体对抗抑郁药的不同反应有关.

微生物群的复杂性使得寻找其与疾病之间明确的因果关系极富挑战，且确定肠道细菌的高分类分辨率对于准确分析非常重要[99]，既往大多是小样本的研究, 未来高同质性大样本的研究对明确肠道微生物在抑郁症诊治中的作用具有重要意义.

1.4　神经免疫

越来越多的证据表明，神经免疫在抑郁症的发病机制和病理生理过程中也发挥重要作用[106]. 中枢神经系统和炎症通路的相互作用与抑郁症的发生有关[107,108](图1). 中枢神经系统中的免疫活性细胞, 尤其是小胶质细胞在抑郁症的发生发展中起着重要作用. 小胶质细胞在大脑中释放各种促炎因子，如肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、白细胞介素-1β(interleukin 1bet, IL-1β)和抗炎因子(如白细胞介素-1(interleukin-1, IL-1)、白细胞介素-10(IL-10)). 大量研究发现，抑郁症患者的C反应蛋白(C-reactive protein, CRP)、前列腺素和其他花生四烯酸衍生物以及白细胞介素-6(IL-6)、IL-1β、TNF-α、干扰素-α(interferon-α, INF-α)等因子的水平明显升高[109~113]. 另外还有研究发现，炎症因子可以直接导致抑郁症状的发展[114]，这提示抑郁症与神经免疫间可能存在双向因果的关系.

此外，细胞因子也是抑郁症诊断的潜在生物学标记物[115,116]. 多项研究发现，抑郁症患者外周血中促炎因子的水平升高[117]. Chang等人[118]研究发现，无论在抑郁发作期或缓解期，血浆CRP水平是区别重性抑郁症和双相II型抑郁发作患者的重要标记物. 另外, 神经免疫的生物学标记物在抑郁症分型中也可能发挥重要作用. 比如, Lamers等人[114]的研究发现, 与典型抑郁症相比，非典型抑郁症患者的急性期蛋白以及促炎因子CRP, IL-6和TNF-α的水平升高更为显著.

神经免疫生物学标记物不仅与抑郁症诊断、鉴别有关, 还能预测抗抑郁药物的疗效. Uher等人[119]发现,

表 1 不同分类水平上与抑郁症最相关的细菌

Table 1 Bacteria associated with MDD at different taxonomic levels

Higher in MDD (抑郁症患者中含量较高)	Lower in MDD (抑郁症患者中含量较低)
Actinobacteria (门水平)	Christensenellaceae和*Christensenella* (科和属水平)
Alistipes (属水平)	*Coprococcus* (属水平)
Bacteroides (属水平)	*Eubacterium* and *E. rectale* (属和种水平)
Bifidobacteriaceae和*Bifidobacterium* (科和属水平)	*Faecalibacterium*和*F. prausnitzii* (属和种水平)
Flavonifractor (属水平)	*Roseburia* (属水平)
Parabacteroides (属水平)	Ruminococcaceae (科水平)
Streptococcus (属水平)	Sutterellaceae和*Sutterella* (科和属水平)

CRP可作为抑郁症临床治疗效果的差异预测因子. 在一个多中心的临床试验中, 重性抑郁症患者随机接受12周的艾司西酞普兰或去甲替林治疗, 发现个体基线CRP的水平可以预测其治疗效果, 提示CRP水平可能有助于选择对个体更有效的抗抑郁药物. 最近的研究还发现, 血清中IL-6可能是氯胺酮治疗难治性抑郁症的临床疗效的预测因子[120]. Yang等人[121]在氯胺酮治疗难治性抑郁的研究中也发现, 反应组基线血清IL-6的水平明显高于对照组和无反应组.

总之, 神经免疫可能在抑郁症的发病机制和病理生理过程中发挥重要作用, 但作为抑郁症诊断和鉴别的生物学标志物以及预测抗抑郁药物疗效的机制还需要深入研究.

2 治疗的研究进展

2.1 药物治疗

截至目前, 药物治疗仍然是抑郁症治疗的主流方法. 即使经过充分的药物治疗, 仍有约1/3的患者不能达到临床痊愈, 且这些药物往往具有起效慢、不良反应多、停药易复发等不足. 研究更好的抗抑郁药物是亟待解决的问题.

近年来, 随着抑郁症发病机制相关研究的不断深入, 一些基于新的作用机制的药物被逐渐开发. 比如*N*-甲基-D-天冬氨酸(*N*-methyl-D-aspartate, NMDA)受体拮抗剂艾司氯胺酮, 该药物的鼻用喷雾剂已经被美国食品药品监督管理局(Food and Drug Administration, FDA)批准上市, 用于治疗成人难治性抑郁症, 国内生产的艾司氯胺酮也进入了临床试验阶段. 它的主要作用在于抑制外侧缰核的簇状放电活动. 外侧缰核位于海马体下方, 下游脑区是负责制造多巴胺等奖赏物质的中脑单胺核团. 而外侧缰核始终向下游发射抑制信息, 引发抑郁, 因此它又被称为是大脑的负面情绪中枢[122]. 而氯胺酮能阻断外侧缰核的簇状放电活动, 最终产生快速抗抑郁的疗效. 它的出现不仅颠覆了传统抑郁症的“单胺假说”, 还促进研究者们鉴定出了Kir4.1钾通道、NMDAR等快速产生抗抑郁效应的分子靶点, 为研发早期快速起效、更好的抗抑郁药物及干预措施提供了新思路, 对降低抑郁症自杀风险, 最终战胜抑郁症具有重大意义[123,124]. 此外, 作用于褪黑素受体的药物阿戈美拉汀, 目前也是抑郁症治疗的一线用药; 5-HT_{1A}受体部分激动和选择性5-HT再摄取抑制剂维拉佐酮(Vilazodone)、丁螺环酮(Buspirone)和坦度螺酮(Tandospirone)等被发现具有改善抑郁症状的作用[125~128].

另外, 一些具有免疫靶点的药物可以改善个体的抑郁症状[129]. 比如, 抗细胞因子抗体英夫利昔单抗、非甾体抗炎药塞来昔布、四环素抗生素米诺环素等被应用抑郁症或双相抑郁的增效治疗, 且显示出了对某些抑郁症亚群有效[130]. 但这些研究大多观察的是对原发性免疫疾病患者合并抑郁症状的改善作用, 很少有研究观察免疫调节药物的单一使用能否治疗抑郁症. 尽管研究结果还需进一步验证, 但目前的发现提示, 基于免疫机制设计的抗抑郁药物仍然具有广阔的前景.

此外, 一些致幻剂在抑郁症治疗方面也取得了进展. 研究显示, 其可促进个体神经可塑性、机体免疫状态的调节以及神经递质的释放. 欧洲药品管理局已批准赛洛西宾治疗重度抑郁症的III期临床研究, 其在抗抑郁治疗中具有不良反应小、起效快和效果持久等优势[131]. 而下丘脑-垂体-肾上腺轴(hypothalamic-pitui-

tary-adrenal axis, HPA axis)的功能亢进也是介导抑郁症发生的重要原因, 抑制HPA轴亢进的药物, 如糖皮质激素受体拮抗剂米非司酮也显示出抗抑郁作用[132].

近年来, 非典型抗精神病药物在抑郁症治疗中的作用也逐渐被发现. 一方面, 基础研究发现, 非典型抗精神病药物具有改变5-HT神经元的兴奋性, 增加去甲肾上腺素(norepinephrine, NE)神经元的活性, 促进神经元再生, 减少氧化应激等作用[133], 从而具有抗抑郁的潜力. 另一方面, 临床研究也证实联用非典型抗精神病药物可以更好地改善患者的抑郁症状[134,135]. 2016年更新的加拿大心境与焦虑治疗网络指南和2020年世界生物精神病学会联合会, 都推荐使用喹硫平、阿立哌唑等非典型抗精神病药物作为联用药物来治疗抑郁症[136,137].

总体上, 针对抑郁症的药物治疗机制和作用靶点的研究一定程度上都取得了突破性的进展, 对未来快速抗抑郁药物或者干预技术的研发提供了重要的思路.

2.2　物理治疗

传统的物理治疗方法, 如电休克治疗(electroconvulsive therapy, ECT), 特别适用于伴有精神病性症状的抑郁患者以及难治性抑郁症(treatment-resistant depression, TRD)[138,139]. 近年来, 随着技术的不断发展, 越来越多的物理方法被应用于抑郁症的治疗. 比如, 重复经颅磁刺激(repetitive transcranial magnetic stimulation, rTMS)、经颅直流电刺激(transcranial direct-current stimulation, tDCS)等. 经颅电刺激(transcranial electrical stimulation, TES), 特别是tDCS是一种常用的治疗抑郁症的物理方法. 它通过传输电流至大脑特定区域, 通常是背外侧前额叶(dorsolateral prefrontal cortex, DLPFC), 引起相应大脑皮层兴奋性改变, 进而发挥改善个体临床症状的作用. tDCS操作方便、简单可行并且没有明显的认知受损等副作用. 个体经过tDCS治疗后, 症状改善持续的时间更长[140]. 但tDCS方法也有副作用, 比如个体接受刺激的部位可能会出现皮肤红肿、发热、瘙痒等症状, 但这些不良反应通常随着治疗的结束能较快缓解, 对个体不会产生严重影响[141].

此外, 经颅磁刺激(transcranial magnetic stimulation, TMS)也越来越多地被应用到抑郁症的临床治疗中, 尤其是rTMS技术. 它主要是通过将一定场强的磁场经颅骨作用于大脑中枢神经系统, 形成一定的感应电流, 调节大脑神经细胞的代谢和电活动, 从而发挥抗抑郁的治疗作用. 目前是TMS中最常用的, 且被FDA批准用于难治性抑郁治疗的方法[142]. 相比ECT, rTMS不会造成个体意识丧失, 整个过程中患者一直处于清醒状态. 除了改善抑郁症状的作用, 它对于抑郁症的复发也有一定的预防作用[143].

以上提到的这些物理治疗均为无创治疗手段, 临床上还有一些有创的治疗技术, 也能有效地改善个体的临床症状. 比如, 深部脑刺激(deep brain stimulation, DBS)和迷走神经刺激(vagus nerve stimulation, VNS)均为侵入性治疗方法. DBS又被称为脑起搏器治疗手术, 它主要是在MRI引导下, 通过脑立体定向技术在脑内特定神经核团位置植入电极, 同时在皮下植入脉冲发生器, 再利用外接设备控制大脑电极的放电, 调节大脑神经元的电活动, 进而改善个体的症状. 研究发现, 利用DBS刺激TRD患者的大脑前脑内侧束, 能快速改善个体抑郁症状, 且有效率超过50%[144]. 类似的, VNS也是一种侵入性的治疗方法, 它将迷走神经刺激器植入体内, 激活并刺激电极发射电流, 通过刺激迷走神经, 引起大脑各区域的脑电活动变化, 以达到调节神经元兴奋性并改善症状的作用. 研究发现, 它也可以改善患者抑郁症状并且延长其抗抑郁效果[145]. VNS已被美国FDA批准应用于难治性抑郁的治疗, 目前在国内尚无相应适应证. 本中心于近期发起了一项VNS治疗难治性抑郁症的临床研究, 以期进一步验证其在中国抑郁症人群的治疗效果.

总体上, 不同的物理治疗方法作用原理、靶向大脑部位以及参数的设置不同, 疗效可能存在一定的差异. 除了以上提到的这些物理治疗方案以外, 还有一些新型的方法, 如磁休克(magnetic seizure therapy, MST)等, 随着临床研究的深入, 未来将有更多该治疗方法临床应用的证据.

2.3　心理治疗

对于抑郁症的治疗, 实践指南建议对抑郁症进行药物和心理干预, 尽管药物治疗的可获得性较高, 但更多的患者都愿意接受心理治疗. 心理治疗也可以有效地帮助个体解决一生中各阶段出现的心理问题.

抑郁症的心理治疗主要是基于疾病特点和个体持

续存在的一些心理因素. 通常抑郁症急性期的心理治疗包括: 常用的认知行为疗法、人际关系疗法和行为激活疗法, 以及其他有一定疗效的心理治疗形式, 包括行为婚姻治疗、以解决问题为中心的治疗和短期心理动力学治疗. 这些疗法都是短期的、有教育意义和指导性的. 虽然认知行为治疗的使用较广泛, 但在具体实践中采用哪种治疗方法, 通常需要综合治疗师的能力、治疗师的可用性、婚姻状况和患者的偏好等因素来决定.

同时, 目前越来越多的治疗师通过互联网和移动设备远程提供心理治疗, 不同类型的治疗形式包括互联网、个人、团体、电话或引导式自助式的干预方法, 部分效果与面对面治疗的效果相当[146]. 并且一项调查发现, 远程提供心理治疗也能有效减轻个体抑郁症状严重程度, 并且参与者在远程心理治疗与面对面这两种干预措施的满意度方面没有统计学差异[147].

尽管根据以往的研究, 抗抑郁药物和心理治疗的联合治疗比单独治疗效果更好[146], 但关键挑战是要确定哪些个体需要联合治疗, 以及寻找能预测个体最佳治疗方式的指标, 这将有助于医生制定个体化的临床决策. 本中心在心理治疗的循证证据的探索和基于互联网的心理治疗上都有不同程度的探索, 并在地震灾害和新冠肺炎疫情的心理干预中都发挥了重要作用[148,149].

除了上述提到的治疗方案, 近年来, 一些其他治疗手段也逐渐被应用到抑郁症的治疗中, 包括光照治疗、运动疗法、益生菌以及神经营养调节剂等, 都被发现有助于改善个体的抑郁症状[98,150~153].

3 研究展望

抑郁症相关领域的研究进展无疑是可喜的, 但距离真正认识和治愈抑郁症尚有很长的距离. 随着测序技术的突飞猛进, 全基因组测序促使分子遗传的研究产生质的飞跃, 从根本上解决了遗传度缺失的问题. 7T MRI等技术的逐步普及, 也将极大提高结构和功能影像的分辨率, 提高图像的信噪比. 人们将会更加精准地破解抑郁症这一复杂的脑病, 发现其病因学和治疗学相关的神经环路, 将极大改善抑郁症诊断和疗效评估缺乏神经生物学标记的现状. 在肠道微生物的研究中, 肠道细菌之外的病毒组学的研究将会填补新的空白, 严谨的纵向设计将会助力抑郁症和肠道微生物因果关系的明晰. 此外, 华西医院生物医学大数据中心基于大样本人群队列的抑郁症疾病轨迹研究以及决策支持智能诊疗模型的建立, 也为促进抑郁症患者的全面健康提供了方向[154,155]. 在高质量的大数据建设和挖掘的助力下, 整合各领域的成果, 以生物学标记为主导的诊断系统和治疗评估体系也将会极大地改善抑郁症的研究和治疗现状. 同时, 积极探索对抑郁症危险因素的预测干预, 以期阻断或者延缓疾病或并发症的发生发展. 未来十年, 在脑科学框架下, 整合生物学机制和环境的研究, 抑郁症的病因学研究有望取得进一步的突破, 从而为抑郁症患者的治疗带来革命性的变革.

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Advances in the etiology and clinical treatment of depression

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Depression is a common mental illness with high disability and suicide rates. Its etiology and mechanism are still unclear, and its clinical treatment has raised concerns among researchers. To better understand the etiology and improve the treatment outcomes of depression, we have invested in various resources. Recently, significant progress has been achieved in the fields of genetics, neuroimaging, gut microbiota, and neuroimmunity in depression. Moreover, many important findings have been identified in the antidepressant treatment, physical therapy, and psychological treatment of depression. This review mainly focuses on the progress of the etiology and clinical treatment of depression to provide evidence for psychiatrists.

depression, etiology, clinical treatment, research progress

doi: 10.1360/SSV-2022-0157