Advances in Psychology 心理学进展, 2021, 11(7), 1759-1767
Published Online July 2021 in Hans. http://www.hanspub.org/journal/ap
https://doi.org/10.12677/ap.2021.117196

Hans汉斯

抑郁症神经生理机制研究进展

卢　玺，吴　燕

成都医学院，四川 成都
Email: mrluxi@outlook.com

收稿日期：2021年6月17日；录用日期：2021年7月13日；发布日期：2021年7月23日

摘　要

抑郁症是一种常见的精神障碍疾病，是以显著而持久的情绪低落为主要特征的精神障碍。其主要表现是以情感低落、思维迟缓和精神运动性抑制三大症状为基本特征。部分抑郁症患者伴有严重的焦虑症状，出现自杀观念及行为，给全球带来沉重的疾病负担。抑郁症的病因十分复杂，迄今仍未完全阐明。近年来，国内外对抑郁症的研究从未停止，在抑郁症发病机制的研究上取得了重要进展。文本文通过对以往基因遗传学研究，脑结构和功能研究，神经炎症以及神经内分泌的研究进行阐述，以拓展对抑郁症的认识。

关键词

抑郁症，神经生理机制，下丘脑，HPA

Progress in Neurophysiological Mechanisms of Depression

Xi Lu, Yan Wu

Chengdu Medical College, Chengdu Sichuan
Email: mrluxi@outlook.com

Received: Jun. 17th, 2021; accepted: Jul. 13th, 2021; published: Jul. 23rd, 2021

Abstract

Depression is a common mental disorder that is characterized by significant and persistent depressed mood. It is characterized by low emotion, slow thinking and psychomotor inhibition. Some patients with depression have serious anxiety symptoms, suicidal ideas and behaviors, which bring heavy disease burden to the world. The etiology of depression is very complex and has not yet been fully elucidated. In recent years, the research on depression has never stopped at

文章引用: 卢玺, 吴燕(2021). 抑郁症神经生理机制研究进展. *心理学进展, 11(7),* 1759-1767.
DOI: 10.12677/ap.2021.117196

home and abroad, and important progress has been made in the pathogenesis of depression. In this paper, the past genetic studies, brain structure and function studies, neuroinflammation and neuroendocrine studies are briefly described in order to expand the understanding of depression.

Keywords

Depression, Neurophysiological Mechanisms, Hypothalamic, HPA

1. 引言

抑郁症是最常见的精神疾病之一，主要表现为情绪低落、思维迟缓、活动减少，常同时伴有焦虑情绪，及饮食、睡眠等障碍。其不仅影响患者的正常工作和生活，严重者甚至导致患者自杀。2018 年 3 月，世界卫生组织(WHO)公布，全球约有 3 亿人遭受抑郁症的困扰，每年约有 80 万人因抑郁症而自杀身亡。抑郁症是自杀的头号杀手，其死亡率高达 15%~25% (Sokero et al., 2005)。随着抑郁症的发病率呈逐年上升趋势，不仅给患者和家属带来痛苦，也给社会带来巨大的负担。但令人遗憾的是，抑郁症的病因至今尚不完全清楚，并且对于抑郁症的诊断还是以临床表现及量表作为其主要的诊断依据，尚缺乏实验诊断等客观指标。但关于抑郁症生理机制的研究却不曾停止。本文列举了一些最近有关抑郁症的神经生理机制研究，包括基因遗传学研究，脑结构和功能研究，神经炎症以及神经内分泌的研究，以增进对抑郁症的了解。

2. 基因遗传研究与抑郁症

通过家庭和双胞胎的研究，发现遗传因素在抑郁症的致病过程中起着十分重要的作用(McGuffin et al., 2007)。与遗传力较高程度的自闭症，双相情感障碍和精神分裂症相比，抑郁症的遗传力更大，介于 31%和 42%之间(Sullivan et al., 2000)。

2.1. MDD 候选基因研究

候选基因的选取一般与疾病的病理生理机制和药物作用机制来确定。根据以往的研究，抑郁症的候选基因主要集中在神经递质系统，下丘脑－垂体－肾上腺轴(HPA)和脑源性神经营养因子(BDNF)上。

研究发现，承受压力和抑郁能力低的人的 5-羟色胺转运蛋白(5-HTT)基因，同时，这些人的单胺氧化酶 A (MAOA)基因，COMT 基因的表达水平有出现异常(Azadmarzabadi et al., 2018)，这些特质都与抑郁症的发病有关。Bustamante et al. (2018)发现，HPA 轴中涉及的 FKBP5 基因表达水平与抑郁症的发病史有关，存在抑郁症发病史的人 FKBP5 基因表达水平更高。Van Der Auwera (2018)通过荟萃分析得到，FKBP5、5-HTT 基因，色氨酸羟化酶 2 (TPH2)基因，多巴胺 D2 受体(DADR2)基因，BDNF 基因以及其他候选基因和抑郁症患者的儿童期创伤经历显著相关，具有儿童创伤经历的患者存在更高水平的该候选基因。通过药物的作用机制也能得出相似的结论，Fischer et al. (2018)对 HPA 轴的荟萃分析发现，促肾上腺皮质激素释放激素结合蛋白(CRHBP)基因，促肾上腺皮质激素释放激素受体 1 (CRHR1)基因和促黑素皮质激素(POMC)基因座可以预测抗抑郁药的治疗效果。另外，聂容荣等人通过对脑卒中后抑郁症患者针灸治疗也发现患者血清 5-HT、NE 和 BDNF 水平比对照组显著降低(聂容荣等，2017)。

2.2. MDD 基因突变研究

常见突变在抑郁症的遗传力中所占的比例约为 4%，因此这种遗传变异吸引了大量学者进行相关研究。

对于大样本基因的分析表明，与抑郁症相关的变异基因与肥胖，HPA 轴的慢性过度激活，突触前分化，神经免疫，神经元钙通道，多巴胺能神经递质和谷氨酸能神经递质有关(Li et al., 2018)。分析还发现，这些突变位于大脑皮层，涉及神经元并且没有发生显著的子序列变化富集，这表明涉及外显子序列变化的遗传变异对抑郁的意义不大(Wray et al., 2018)。

具有不同抑郁特征或不同抑郁特征的人可能具有不同的遗传结构，减少异质性将有助于更好地揭示抑郁的遗传特征(Ostergaard et al., 2011)。Howard et al. (2018)根据表型将 322,580 例英国抑郁症患者分为三个亚组，发现 17 个位点与三种亚型显著相关，表明兴奋性突触可能与抑郁症有关。Peterson et al. (2017)针对汉族妇女严重抑郁症患者进行研究，不仅发现与抑郁症相关的常见 SNP (单核苷酸多态性)，而且还发现该选择位点已定位在蛋白质编码区中。Hall et al. (2018)发现 3p22.3 基因在苏格兰和英国的男性抑郁症患者中有一定的作用。这些发现不仅为抑郁症的现有假设提供了相关证据，而且为进一步了解抑郁症的生物学机制和后续研究提供了线索。

常见突变仍不能完全揭示抑郁症的遗传模型。因此，越来越多的学者将注意力转向稀有突变研究。Pirooznia et al. (2016)使用高通量测序技术对涉及突触的 1742 个基因进行测序和分析，提出抑郁症的病因可能与钙通道和树突的调节有关。此外，研究发现 NKPD1 基因的突变(Amin et al., 2017a)和 LIPG 基因 rs77960347 位点的错义突变(Amin et al., 2017b)与抑郁症状具有一定的关系。

2.3. MDD 的染色体结构变异研究

除了可以解释抑郁症遗传力的突变位点外，一些学者还把诸如短串联重复序列和重复数数变异(CNV)等结构突变视为抑郁症的来源之一。Yu et al. (2017)使用全基因组测序的研究发现 CNV 缺失突变与抑郁症相关。并发现墨西哥裔美国人抑郁症患者的 23 条染色体的短串联重复序列明显少于正常对照(Yu et al., 2018)。此外，Gillentine et al. (2018)对候选基因 CHRNA7 的 CNV 研究发现抑郁症和焦虑症患者中该基因的重复数增加，表明该基因调节的神经元烟碱型乙酰胆碱受体可用作治疗抑郁症的靶标。以上表明对染色体结构变异的进一步探索将有助于抑郁症遗传学研究的发展。

3. 神经结构功能异常研究与抑郁症

在过去的几十年中，大量的神经影像研究证明了抑郁症中的各种临床症状与特定大脑区域(尤其是那些支持情绪调节，认知控制和奖励的区域)的结构和功能异常改变有关，并进一步将发生异常的脑结构定位于“皮质–边缘系统”。

3.1. MDD 中神经结构异常

先前的结构神经影像学研究发现，抑郁的受试者在许多大脑区域都伴有结构异常，包括背阔肌前额叶皮层，眶额叶皮层，前扣带回皮层，海马，纹状体，杏仁核和尾状核(Zhang et al., 2019; Han et al., 2014; Pirnia et al., 2016)。MDD 患者大脑多个区域的皮质厚度和灰质体积减小，表明灰质体积的差异可能会成为 MDD 的鉴别诊断标记(Kambeitz et al., 2017)。Suh et al. (2019)对测量皮层厚度的神经影像学研究进行了全面系统的回顾表明，抑郁的受试者的左钙骨肌裂隙/舌状回，左近鳃肌和双侧额回的皮质厚度显着降低，而缘上回的皮质厚度显着增加。另外的一些荟萃分析研究显示，抑郁的受试者在右下纵筋膜，右额枕下部和右后丘脑辐射中显示出分数各向异性变化(Jiang et al., 2017; Wise et al., 2016)。

3.2. MDD 中神经功能异常

神经影像学技术的最新进展发现，抑郁症中功能性神经的拓扑特征受到破坏。研究表明，MDD 与许多局部脑区域发生改变有关(Qiu et al., 2018)。

大量的神经影像研究表明，MDD 患者在额叶前额叶，颞叶和边缘系统中观察到了明显的大脑异常(Sheline et al., 2010; Arnone, 2019; Tang et al., 2018)。Gong & He (2015)发现 MDD 患者存在大规模的异常脑连接组。抑郁症中的神经回路受到破坏，导致各种神经基质发生临床症状，包括前额皮层下回路，背外侧前额回路，眶额前额回路，前扣带回前额回路，前额海马回路和额丘脑回路(Zhang et al., 2018; Marchand, 2010; Tekin & Cummings, 2002; Wegener et al., 2015)。国内学者郁仁强等通过静息态功能磁共振研究发现，与对照组相比，观察组默认网络(DMN)在左内侧额上回脑区功能连接强度值显著减低(郁仁强等，2019)。此外，中央执行网络(CEN)和显着网络(SN)也和抑郁症的发病机制相关(Zhang et al., 2016)。这些异常的功能拓扑与诸如奖励处理，认知控制和情绪调节之类的认知功能相关联，因此有可能充当 MDD 的生物标记(Jie et al., 2015)。

4. 神经炎症研究与抑郁症

炎症激活被认为是一种自我保护的生存机制，它是人体对各种创伤刺激的自我防御反应。越来越多的临床证据表明，免疫分子和细胞都与 MDD 的病理生理持有关，与健康受试者相比，抑郁者的血浆细胞因子升高(Mao et al., 2018)。

4.1. 免疫细胞

免疫细胞主要包括小胶质细胞、星形细胞、T 细胞、B 细胞。

小胶质细胞是脑细胞的主要成分，参与许多病理和生理过程。在正常情况下，小胶质细胞的功能主要有助于大脑发育以及神经元的正常结构和功能过程。但是，在存在病原体和压力的情况下，小胶质细胞可以作为中枢神经系统的一种重要效应物和调节剂。最近的证据证实，过度激活和激活不足的小胶质细胞均可引起抑郁。Wohleb et al. (2018)发现，在前额叶皮层(PFC)中，压力使小胶质细胞激活并发生形态和功能变化，这导致突触缺陷并引发焦虑和抑郁行为。Tong et al. (2017)发现由慢性不可预测的压力(CUS)导致的严重抑郁小鼠，其海马小胶质细胞数量减少以及激活异常。还有研究表明小胶质细胞活化减少有可能助于 MDD 恢复(Juarez-Orozco et al., 2018)。

星形胶质细胞也被认为是大脑中的主要免疫介质，在动物模型和人脑中，星形胶质细胞功能障碍与 MDD 的发病机理有关。在抑郁症中，星形胶质细胞显示出退化的迹象并且数量减少，这可能导致神经传递失衡和突触连接异常。最近的一项研究发现，星形胶质细胞在抑制抑郁症神经炎症方面对脑膜蛋白具有独特的作用(Leng et al., 2018)。另一项研究发现在不服用抗抑郁药的抑郁受试者中，海马星形胶质细胞的密度显着降低(Cobb et al., 2016)。Monai & Hirase (2018)最近研究发现，星形胶质细胞钙信号被颅直流电刺激(tDCS)激活，tDCS 是治疗慢性束缚应激诱导的抑郁小鼠所必需的成分。

除此之外，调节性 T 细胞(Treg)也与抑郁症有关，某些药物如长期高剂量卡托普利的长期给药可能会通过 Treg 减少和小胶质细胞活化来诱导抑郁症样行为(Park et al., 2017)。T 淋巴细胞对 MDD 的抵抗力也至关重要。在抑郁过程中，T 淋巴细胞在平衡适应性和适应不良的免疫反应中，在神经免疫网络中起着至关重要的作用(Toben and Baune, 2015)。

4.2. 免疫分子

越来越多的证据证实，MDD 患者大脑中趋化因子和细胞因子被激活。

最近的研究表明，MDD 患者趋化因子水平和常人相比较高。一项研究表明，IL-1β (促炎细胞因子)与激活 CNS (中枢神经系统)炎症途径和行为改变有关，用 IL-4 进行治疗可以调节 IL-1β 诱导的抑郁样行为并增加社交活动能力(Park et al., 2015)。IL-1β 是脂多糖(LPS)产生的氧化和神经炎症反应所必需的，当海马中的IL-1β敲低可显着减轻 LPS 诱导的小鼠的记忆障碍以及焦虑和抑郁样行为时(Li et al., 2017)。IL-6 是一种可以被压力诱导的细胞因子。它可能通过其对 HPA 轴的影响而参与抑郁症的治疗(Girotti et al., 2013)。Kakeda et al. (2018)发现在未接受药物治疗的 MDD 患者的第一个抑郁发作期间，血清 IL-6 水平显着升高，并且在 MDD 早期阶段 PFC 的形态变化中起关键作用。Ng et al. (2018)对 34 项相关研究的荟萃分析显示，患有抑郁症的老年人中仅 IL-6 仍显着较高。研究发现 TNF-α 破坏了血脑屏障的完整性(Cheng et al., 2018)。抑郁症伴随着在 mRNA 和蛋白质水平上 TNF，TNFRSF1A 和 TNFRSF1B 基因的表达增加，并且 TNF-α，TNFRSF1A 和 TNFRSF1B 的表达升高与认知效率呈负相关(Bobinska et al., 2017)。TNF-α 拮抗剂有助于缓解抑郁症状和改善认知缺陷(Bortolato et al., 2015)。有证据表明干扰素 IFN-α 发现了抑郁症的病理生理学(Su, 2015)。IFN-α 可以诱发抑郁症，这种抑郁症具有更多的躯体症状，更少的情绪，焦虑和负面认知症状(Su et al., 2019)。

总而言之，了解神经免疫系统的作用和 MDD 中的炎症机制可能有助于解释抑郁症的症状，识别诊断的生物标志物以及探索新的治疗方法。

5. 神经内分泌研究与抑郁症

5.1. 下丘脑－垂体－肾上腺素轴(HPA)与抑郁症

以往研究发现 HPA 参与抑郁症的发病机制，大脑边缘系统与下丘脑之间神经信息传递障碍是抑郁症发病的重要原因之一(龚绍麟，2010)。

以往研究显示，HPA 轴过度活动对抑郁症的形成和发展起到了重要的影响(Barden, 2004; Holsboer and Ising, 2008)。以往发现高达80%的抑郁症患者存在下丘脑－垂体－肾上腺轴功能亢进的现象(汪道文，何健，2010)。有研究表明，抑郁症患者的唾液、血浆及尿液中皮质激素水平和垂体和肾上腺的体积成显著正相关，与海马体积成显著负相关；抑郁症患者的唾液、血浆及尿液中皮质激素水平增高，垂体和肾上腺的体积增大(Nemeroff and Vale, 2005)、海马的体积缩小(Colla et al., 2007)；Ge 通过对小鼠不可预见性温和攻击(CUMS)，发现每当大鼠有 HPA 轴过度活动时，会产生抑郁样行为(Ge et al., 2013)。近年来发现，通过对伴有精神病性症状的抑郁患者研究，发现也存在 HPA 功能轴的活动显著增加的情况(Schatzberg, 2015)。

5.2. 下丘脑－垂体－甲状腺轴(HPT)与抑郁症

HPT 轴功能紊乱也可能与抑郁的相关症状有关。研究发现，抑郁症患者血浆甲状腺激素(T3、T4)显著降低(于璟，2013)。一些研究发现甲状腺功能标记物的变化与产后抑郁症相关(Plaza et al., 2010)。还有研究者更进一步认识到甲状腺功能和抑郁症之间的关系，发现患有甲状腺功能减退的患者通常表现出抑郁症状(Kvetny et al., 2015)。也有研究发现甲状腺过氧化物酶自身抗体(TPO-Ab)与抑郁症的特征标记存在正相关，TPO-Ab 的出现可能是抑郁症易感性的标志物(Van de Ven et al., 2012)。

5.3. 下丘脑－垂体－性腺轴(HPG)与抑郁症

当 HPG 功能轴紊乱时，性激素水平也随之下降，进而可致机体生理周期紊乱，性欲减退，从而产生焦虑、抑郁等症状。Bloch et al. (2011)的研究发现，对处在体外受精转移周期的女性使用促性腺激素释放激素(GnRH)受体激动剂可以导致她们产生抑郁和焦虑症状；此外，研究发现低水平的睾丸酮(testosterone, T)与抑郁症间的因果关系本质虽然不确定，但是许多性腺机能减退的男性患有抑郁症，反之有些抑郁症

病人同时患有性腺机能减退(Amore et al., 2012)。还有研究提示，对某些围绝经期的抑郁症患者进行抗抑郁药治疗，使用雌激素替代疗法有抗抑郁的效果(Rasgon et al., 2001)。以上这些结果提示抑郁症患者可能存在 HPG 功能轴紊乱。

6. 结语

以上研究提供众多证据，从不同角度说明抑郁症的神经生理机制。然而，有关抑郁症生理机制的研究仍有很长的路要走，未来可以从以下三个方面进行研究。首先，要扩大样本量，大样本可以克服某些抑郁症的异质性干扰。其次，为了减少异质性，具有不同抑郁特征或不同抑郁特征的人可能具有不同的遗传结构，减少异质性将有助于更好地揭示抑郁的遗传特征。最后，需要寻求新技术和分析方法。新的分析方法和新的计算方法是可能的并为抑郁症的基因研究带来新的线索。综上所述，抑郁症发病机制复杂。明确抑郁症的发病机制，对于抑郁症的诊治至关重要。随着样本量的不断积累和技术的进步，抑郁症的发病机制有望取得突破性进展，以进一步了解抑郁症，为寻求新的治疗方法提供线索。

基金项目

四川省应用心理学研究中心重点项目 CSXL-171002；成都医学院研究生创新基金项目 519-2020020。

参考文献

龚绍麟(2010). *抑郁症*(pp. 158-160). 北京: 人民卫生出版社.

聂容荣, 莫碧文, 曾伟星, 等(2017). 针灸对脑卒中后抑郁症患者血清 5-HT、NE 和 BDNF 水平的影响. *西部医学, 29(6),* 808-812+816.

汪道文, 何健(2010). *唾液皮质醇检测在抑郁症诊断中的应用探讨*. 硕士学位论文, 北京: 北京协和医学院.

于璟(2013). *甲状腺功能与抑郁障碍关系的研究*. 博士学位论文, 大连: 大连理工大学.

郁仁强, 张志伟, 吕发金, 等(2019). 静息态功能磁共振研究未治疗首次发作重症抑郁症患者默认网络功能连接. *西部医学, 31(4),* 608-613.

Amin, N., Belonogova, N. M., Jovanova, O. et al. (2017a). Nonsynonymous Variation in NKPD1 Increases Depressive Symptoms in European Populations. *Biological Psychiatry, 81,* 702-707. https://doi.org/10.1016/j.biopsych.2016.08.008

Amin, N., Jovanova, O., Adams, H. H. et al. (2017b). Exome-Sequencing in a Large Population-Based Study Reveals a Rare Asn396ser Variant in the LIPG Gene Associated with Depressive Symptoms. *Molecular Psychiatry, 22,* 537-543. https://doi.org/10.1038/mp.2016.101

Amore, M., Innamorati, M., Costi, S., Sher, L., Girardi, P., & Pompili, M. (2012). Partial Androgen Deficiency, Depression, and Testosterone Supplementation in Aging Men. *International Journal of Endocrinology, 2012,* Article ID: 280724. https://doi.org/10.1155/2012/280724

Arnone, D. (2019). Functional MRI Findings, Pharmacological Treatment in Major Depression and Clinical Response. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 91,* 28-37. https://doi.org/10.1016/j.pnpbp.2018.08.004

Azadmarzabadi, E., Haghighatfard, A., & Mohammadi, A. (2018). Low Resilience to Stress Is Associated with Candidate Gene Expression Alterations in the Dopaminergic Signaling Pathway. *Psychogeriatrics, 18,* 190-201. https://doi.org/10.1111/psyg.12312

Barden, N. (2004). Implication of the Hypothalamic-Pituitary-Adrenal Axis in the Physiopathology of Depression. *Journal of Psychiatry and Neuroscience, 29,* 185-193.

Bloch, M., Azem, F., Aharonov, I., Ben Avi, I., Yagil, Y., Schreiber, S., Weizman, A. et al. (2011). GnRH-Agonist Induced Depressive and Anxiety Symptoms during *in Vitro* Fertilization-Embryo Transfer Cycles. *Fertility and Sterility, 95,* 307-309. https://doi.org/10.1016/j.fertnstert.2010.07.1073

Bobinska, K., Galecka, E., Szemraj, J., Galecki, P., & Talarowska, M. (2017). Is There a Link between TNF Gene Expression and Cognitive Deficits in Depression? *Acta Biochimica Polonica, 64,* 65-73. https://doi.org/10.18388/abp.2016_1276

Bortolato, B., Carvalho, A. F., Soczynska, J. K., Perini, G. I., & McIntyre, R. S. (2015). The Involvement of TNF-α in Cognitive Dysfunction Associated with Major Depressive Disorder: An Opportunity for Domain Specific Treatments. *Current Neuropharmacology, 13,* 558-576. https://doi.org/10.2174/1570159X13666150630171433

Bustamante, A. C., Aiello, A. E., Guffanti, G. et al. (2018). Fkbp5 DNA Methylation Does Not Mediate the Association between Childhood Maltreatment and Depression Symptom Severity in the Detroit Neighborhood Health Study. *Journal of Psychiatric Research, 96,* 39-48. https://doi.org/10.1016/j.jpsychires.2017.09.016

Cheng, Y., Desse, S., Martinez, A., Worthen, R. J., Jope, R. S., & Beurel, E. (2018). TNFα Disrupts Blood Brain Barrier Integrity to Maintain Prolonged Depressive-Like Behavior in Mice. *Brain, Behavior, and Immunity, 69,* 556-567. https://doi.org/10.1016/j.bbi.2018.02.003

Cobb, J. A., O'Neill, K., Milner, J., Mahajan, G. J., Lawrence, T. J., May, W. L., Miguel-Hidalgo, J., Rajkowska, G., & Stockmeier, C. A. (2016). Density of GFAP-Immunoreactive Astrocytes Is Decreased in Left Hip-Pocampi in Major Depressive Disorder. *Neuroscience, 316,* 209-220. https://doi.org/10.1016/j.neuroscience.2015.12.044

Colla, M., Kronenberg, G., Deuschle, M., Meichel, K., Hagen, T., Bohrer, M., & Heuser, I. (2007). Hippocampal Volume Reduction and HPA-System Activity in Major Depression. *Journal of Psychiatric Research, 41,* 553-560. https://doi.org/10.1016/j.jpsychires.2006.06.011

Fischer, S., Gardini, E. S., Haas, F. et al. (2018). Polymorphisms in Genes Related to the Hypothalamic-Pituitary-Adrenal Axis and Antidepressant Response-Systematic Review. *Neuroscience & Biobehavioral Reviews, 96,* 182-196. https://doi.org/10.1016/j.neubiorev.2018.11.009

Ge, J. F., Qi, C. C., & Zhou, J. N. (2013). Imbalance of Leptin Pathway and Hypothalamus Synaptic Plasticity Markers Are Associated with Stress-Induced Depression in Rats. *Behavioural Brain Research, 249,* 38-43. https://doi.org/10.1016/j.bbr.2013.04.020

Gillentine, M. A., Lozoya, R., Yin, J. et al. (2018). CHRNA7 Copy Number Gains Are Enriched in Adolescents with Major Depressive and Anxiety Disorders. *The Journal of Affective Disorders, 239,* 247-252. https://doi.org/10.1016/j.jad.2018.07.017

Girotti, M., Donegan, J. J., & Morilak, D. A. (2013). Influence of Hypothalamic IL-6/gp130 Receptor Signaling on the HPA Axis Response to Chronic Stress. *Psychoneuroendocrinology, 38,* 1158-1169. https://doi.org/10.1016/j.psyneuen.2012.11.004

Gong, Q., & He, Y. (2015). Depression, Neuroimaging and Connectomics: A Selective Overview. *Biological Psychiatry, 77,* 223-235. https://doi.org/10.1016/j.biopsych.2014.08.009

Hall, L. S., Adams, M. J., Arnau-Soler, A. et al. (2018). Genome-Wide Meta-Analyses of Stratified Depression in Generation Scotland and UK Biobank. *Translational Psychiatry, 8,* 9. https://doi.org/10.1038/s41398-017-0034-1

Han, K. M. et al. (2014). Cortical Thickness, Cortical and Subcortical Volume, and White Matter Integrity in Patients with Their First Episode of Major Depression. *The Journal of Affective Disorders, 155,* 42-48. https://doi.org/10.1016/j.jad.2013.10.021

Holsboer, F., & Ising, M. (2008). Central CRH System in Depression and Anxiety—Evidence from Clinical Studies with CRH1 Receptor Antagonists. *European Journal of Pharmacology, 583,* 350-357. https://doi.org/10.1016/j.ejphar.2007.12.032

Howard, D. M., Adams, M. J., Shirali, M. et al. (2018). Genome-Wide Association Study of Depression Phenotypes in UK Biobank Identifies Variants in Excitatory Synaptic Pathways. *Nature Communications, 9,* 1470.

Jiang, J. et al. (2017). Microstructural Brain Abnormalities in Medication-Free Patients with Major Depressive Disorder: A Systematic Review and Meta-Analysis of Diffusion Tensor Imaging. *Journal of Psychiatry & Neuroscience, 42,* 150-163. https://doi.org/10.1503/jpn.150341

Jie, N. F. et al. (2015). Discriminating Bipolar Disorder from Major Depression Based on SVM-FoBa: Efficient Feature Selection with Multimodal Brain Imaging Data. *IEEE Transactions on Autonomous Mental Development, 7,* 320-331. https://doi.org/10.1109/TAMD.2015.2440298

Juarez-Orozco, L. E., Kurtys, E., Dierckx, R. A., Moriguchi-Jeckel, C. M., Doorduin, J., Li, H., Sagar, A. P., & Keri, S. (2018). Translocator Protein (18 kDa TSPO) Binding, a Marker of Microglia, Is Reduced in Major Depression during Cognitive-Behavioral Therapy. *The Journal of Cerebral Blood Flow & Metabolism, 83,* 1-7. https://doi.org/10.1016/j.pnpbp.2017.12.011

Kakeda, S., Watanabe, K., Katsuki, A., Sugimoto, K., Igata, N., Ueda, I., Igata, R., Abe, O., Yoshimura, R., & Korogi, Y. (2018). Relationship between Interleukin (IL)-6 and Brain Morphology in Drug-Naive, First-Episode Major Depressive Disorder Using Surface-Based Morphometry. *Scientific Reports, 8,* Article No. 10054. https://doi.org/10.1038/s41598-018-28300-5

Kambeitz, J. et al. (2017). Detecting Neuroimaging Biomarkers for Depression: A Meta-Analysis of Multivariate Pattern Recognition Studies. *Biological Psychiatry, 82,* 330-338. https://doi.org/10.1016/j.biopsych.2016.10.028

Kvetny, J., Ellervik, C., & Bech, P. (2015). Is Suppressed Thyroid-Stimulating Hormone (TSH) Associated with Subclinical Depression in the Danish General Suburban Population Study? *Nordic Journal of Psychiatry, 69,* 282-286. https://doi.org/10.3109/08039488.2014.972454

Leng, L., Zhuang, K., Liu, Z., Huang, C., Gao, Y., Chen, G., Lin, H., Hu, Y., Wu, D., Shi, M., Xie, W., Sun, H., Shao, Z., Li, H., Zhang, K., Mo, W., Huang, T. Y., Xue, M., Yuan, Z., Zhang, X., Bu, G., Xu, H., Xu, Q., & Zhang, J. (2018). Menin Deficiency Leads to Depressive-Like Behaviors in Mice by Modulating Astrocyte-Mediated Neuroinflammation. *Neuron, 100,* 551-563.E7. https://doi.org/10.1016/j.neuron.2018.08.031

Li, M., Li, C., Yu, H., Cai, X., Shen, X., Sun, X., Wang, J., Zhang, Y., & Wang, C. (2017). Lentivirus-Mediated Interleukin-1beta (IL-1beta) Knock-Down in the Hippocampus Alleviates Lipopolysac-Charide (LPS)-Induced Memory Deficits and Anxiety- and Depression-Like Behaviors in Mice. *Journal of Neuroinflammation, 14,* 190. https://doi.org/10.1186/s12974-017-0964-9

Li, X., Luo, Z., Gu, C. et al. (2018). Common Variants on 6q16.2, 12q24.31 and 16p13.3 Are Associated with Major Depressive Disorder. *Neuropsychopharmacology, 43,* 2146-2153. https://doi.org/10.1038/s41386-018-0078-9

Mao, R., Zhang, C., Chen, J., Zhao, G., Zhou, R., Wang, F. et al. (2018). Different Levels of Pro- and Anti-Inflammatory Cytokines in Patients with Unipolar and Bipolar Depression. *Journal of Affective Disorders, 237,* 65-72. https://doi.org/10.1016/j.jad.2018.04.115

Marchand, W. R. (2010). Cortico-Basal Ganglia Circuitry: A Review of Key Research and Implications for Functional Connectivity Studies of Mood and Anxiety Disorders. *Brain Structure and Function, 215,* 73-96. https://doi.org/10.1007/s00429-010-0280-y

McGuffin, P., Cohen, S., & Knight, J. (2007). Homing in on Depression Genes. *The American Journal of Psychiatry, 164,* 195-197. https://doi.org/10.1176/ajp.2007.164.2.195

Monai, H., & Hirase, H. (2018). Astrocytes as a Target of Transcranial Direct Current Stimulation (tDCS) to Treat Depression. *Neuroscience Research, 126,* 15-21. https://doi.org/10.1016/j.neures.2017.08.012

Nemeroff, C. B., & Vale, W. W. (2005). The Neurobiology of Depression: Inroads to Treatment and New Drug Discovery. *Journal of Clinical Psychiatry, 66,* 5-13.

Ng, A., Tam, W. W., Zhang, M. W., Ho, C. S., Husain, S. F., McIntyre, R. S., & Ho, R. C. (2018). IL-1beta, IL-6, TNF-Alpha and CRP in Elderly Patients with Depression or Alzheimer's Disease: Systematic Review and Meta-Analysis. *Scientific Reports, 8,* Article No. 12050. https://doi.org/10.1038/s41598-018-30487-6

Ostergaard, S. D., Jensen, S. O., & Bech, P. (2011). The Heterogeneity of the Depressive Syndrome: When Numbers Get Serious. *Acta Psychiatrica Scandinavica, 124,* 495-496. https://doi.org/10.1111/j.1600-0447.2011.01744.x

Park, H. J., Shim, H. S., An, K., Starkweather, A., Kim, K. S., & Shim, I. (2015). IL-4 Inhibits IL-1beta-Induced Depressive-Like Behavior and Central Neurotransmitter Alterations. *Mediators of Inflammation, 2015,* Article ID: 941413. https://doi.org/10.1155/2015/941413

Park, H. S., Han, A., Yeo, H. L., Park, M. J., You, M. J., Choi, H. J., Hong, C. W., Lee, S. H., Kim, S. H., Kim, B., & Kwon, M. S. (2017). Chronic High Dose of Captopril Induces Depressive-Like Behaviors in Mice: Possible Mechanism of Regulatory T Cell in Depression. *Oncotarget, 8,* 72528-72543. https://doi.org/10.18632/oncotarget.19879

Peterson, R. E., Cai, N., Bigdeli, T. B. et al. (2017). The Genetic Architecture of Major Depressive Disorder in Han Chinese Women. *JAMA Psychiatry, 74,* 162-168. https://doi.org/10.1001/jamapsychiatry.2016.3578

Pirnia, T. et al. (2016). Electroconvulsive Therapy and Structural Neuroplasticity in Neocortical, Limbic and Paralimbic Cortex. *Translational Psychiatry, 6,* e832. https://doi.org/10.1038/tp.2016.102

Pirooznia, M., Wang, T., Avramopoulos, D. et al. (2016). High-Throughput Sequencing of the Synaptome in Major Depressive Disorder. *Molecular Psychiatry, 21,* 650-655. https://doi.org/10.1038/mp.2015.98

Plaza, A., Garcia-Esteve, L., Ascaso, C., Navarro, P., Gelabert, E., Halperin, I. et al. (2010). Childhood Sexual Abuse and Hypothalamus-Pituitary-Thyroid Axis in Postpartum Major Depression. *Journal of Affective Disorders, 122,* 159-163. https://doi.org/10.1016/j.jad.2009.07.021

Qiu, M. et al. (2018). Aberrant Neural Activity in Patients with Bipolar Depressive Disorder Distinguishing to the Unipolar Depressive Disorder: A Resting-State Functional Magnetic Resonance Imaging Study. *Frontiers in Psychiatry, 9,* 238. https://doi.org/10.3389/fpsyt.2018.00238

Rasgon, N. L., Altshuler, L. L., & Fairbanks, L. (2001). Estrogen-Replacement Therapy for Depression. *American Journal of Psychiatry, 158,* 1738-1738. https://doi.org/10.1176/appi.ajp.158.10.1738

Schatzberg, A. F. (2015). Anna-Monika Award Lecture, DGPPN Kongress, 2013: The Role of the Hypothalamic-Pituitary-Adrenal (HPA) Axis in the Pathogenesis of Psychotic Major Depression. *The World Journal of Biological Psychiatry, 16,* 2-11. https://doi.org/10.3109/15622975.2014.916414

Sheline, Y. I. et al. (2010). Resting-State Functional MRI in Depression Unmasks Increased Connectivity between Networks via the Dorsal Nexus. *Proceedings of the National Academy of Sciences of the United States of America, 107,* 11020-11025. https://doi.org/10.1073/pnas.1000446107

Sokero, T. P., Melartin, T. K., Rytsala, H. J. et al. (2005). Prospective Study of Risk Factors for Attempted Suicide among

Patients with DSM-IV Major Depressive Disorder. *British Journal of Psychiatry, 186,* 314-318. https://doi.org/10.1192/bjp.186.4.314

Su, K. P. (2015). Nutrition, Psychoneuroimmunology and Depression: The Therapeutic Implications of Omega-3 Fatty Acids in Interferon-Alpha-Induced Depression. *BioMedicine, 5,* 21. https://doi.org/10.7603/s40681-015-0021-x

Su, K. P., Lai, H. C., Peng, C. Y., Su, W. P., Chang, J. P., & Pariante, C. M. (2019). Interferon-Alpha-Induced Depression: Comparisons between Early- and Late-Onset Subgroups and with Patients with Major Depressive Disorder. *Brain, Behavior, and Immunity, 80,* 512-518. https://doi.org/10.1016/j.bbi.2019.04.032

Suh, J. S. et al. (2019). Cortical Thickness in Major Depressive Disorder: A Systematic Review and Meta-Analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 88,* 287-302. https://doi.org/10.1016/j.pnpbp.2018.08.008

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic Epidemiology of Major Depression: Review and Meta-Analysis. *The American Journal of Psychiatry, 157,* 1552-1562. https://doi.org/10.1176/appi.ajp.157.10.1552

Tang, S. et al. (2018). Abnormal Amygdala Resting-State Functional Connectivity in Adults and Adolescents with Major Depressive Disorder: A Comparative Meta-Analysis. *EBioMedicine, 36,* 436-445. https://doi.org/10.1016/j.ebiom.2018.09.010

Tekin, S., & Cummings, J. L. (2002). Frontal-Subcortical Neuronal Circuits and Clinical Neuropsychiatry: An Update. *Journal of Psychosomatic Research, 53,* 647-654. https://doi.org/10.1016/S0022-3999(02)00428-2

Toben, C., & Baune, B. T. (2015). An Act of Balance between Adaptive and Maladaptive Immunity in Depression: A Role for T Lymphocytes. *Journal of Neuroimmune Pharmacology, 10,* 595-609. https://doi.org/10.1007/s11481-015-9620-2

Tong, L., Gong, Y., Wang, P., Hu, W., Wang, J., Chen, Z., Zhang, W., & Huang, C. (2017). Microglia Loss Contributes to the Development of Major Depression Induced by Different Types of Chronic Stresses. *Neurochemical Research, 42,* 2698-2711. https://doi.org/10.1007/s11064-017-2270-4

Van de Ven, A. C., Muntjewerff, J. W., Netea-Maier, R. T., de Vegt, F., Ross, H. A., Sweep, F. C. G. J., Janzing, J. G. E. et al. (2012). Association between Thyroid Function, Thyroid Autoimmunity, and State and Trait Factors of Depression. *Acta Psychiatrica Scandinavica, 126,* 377-384. https://doi.org/10.1111/j.1600-0447.2012.01870.x

Van Der Auwera, S., Peyrot, W. J., Milaneschi, Y. et al. (2018). Genome-Wide Gene-Environment Interaction in Depression: A Systematic Evaluation of Candidate Genes: The Childhood Trauma Working-Group of PGC-MDD. *Neuropsychiatric Genetics, Part B of the American Journal of Medical Genetics, 177,* 40-49. https://doi.org/10.1002/ajmg.b.32593

Wegener, I. et al. (2015). Changes of Explicitly and Implicitly Measured Self-Esteem in the Treatment of Major Depression: Evidence for Implicit Self-Esteem Compensation. *Comprehensive Psychiatry, 58,* 57-67. https://doi.org/10.1016/j.comppsych.2014.12.001

Wise, T. et al. (2016). Voxel-Based Meta-Analytical Evidence of Structural Disconnectivity in Major Depression and Bipolar Disorder. *Biological Psychiatry, 79,* 293-302. https://doi.org/10.1016/j.biopsych.2015.03.004

Wohleb, E. S., Terwilliger, R., Duman, C. H., & Duman, R. S. (2018). Stress-Induced Neuronal Colony Stimulating Factor 1 Provokes Microglia-Mediated Neuronal Remodeling and Depressive-Like Behavior. *Biological Psychiatry, 83,* 38-49. https://doi.org/10.1016/j.biopsych.2017.05.026

Wray, N. R., Ripke, S., Mattheisen, M. et al. (2018). Genome-Wide Association Analyses Identify 44 Risk Variants and Refine the Genetic Architecture of Major Depression. *Nature Genetics, 50,* 668-681. https://doi.org/10.1038/s41588-018-0090-3

Yu, C., Baune, B. T., Wong, M. L. et al. (2017). Investigation of Copy Number Variation in Subjects with Major Depression Based on Whole-Genome Sequencing Data. *The Journal of Affective Disorders, 220,* 38-42. https://doi.org/10.1016/j.jad.2017.05.044

Yu, C., Baune, B. T., Wong, M. L. et al. (2018). Investigation of Short Tandem Repeats in Major Depression Using Whole-Genome Sequencing Data. *The Journal of Affective Disorders, 232,* 305-309. https://doi.org/10.1016/j.jad.2018.02.046

Zhang, F. F. et al. (2018). Brain Structure Alterations in Depression: Psychoradiological Evidence. *CNS Neuroscience & Therapeutics, 24,* 994-1003. https://doi.org/10.1111/cns.12835

Zhang, H. et al. (2019). Intrinsic Gray-Matter Connectivity of the Brain in Major Depressive Disorder. *The Journal of Affective Disorders, 251,* 78-85. https://doi.org/10.1016/j.jad.2019.01.048

Zhang, K. et al. (2016). Molecular, Functional, and Structural Imaging of Major Depressive Disorder. *Neuroscience Bulletin, 32,* 273-285. https://doi.org/10.1007/s12264-016-0030-0