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海马神经发生在精神分裂症中的研究进展

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摘　要

海马神经发生是海马齿状回颗粒下区形成新的神经元的过程，受到各种生理或病理因素的调控。精神分裂症是一种重性精神疾病，临床上主要表现为阳性症状、阴性症状和紊乱综合征，并伴随海马神经发生异常，提示精神分裂症相关风险因子作为病理刺激影响海马神经发生。反之，调控海马神经发生对精神分裂症的早期干预和治疗也有一定的意义。该文就精神分裂症相关因子对海马神经发生的影响及调控海马神经发生在精神分裂症中的作用进行综述。

关键词

海马神经发生，精神分裂症，易感基因，神经发育，认知缺陷

Research Progress on Hippocampal Neurogenesis in Schizophrenia

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Abstract

Hippocampal neurogenesis is the process of forming new neurons in the subgranular area of hippocampal dentate gyrus, which is regulated by various physiological or pathological factors. Schizophrenia is a serious neuropsychiatric disease characterized by the presence of positive symptoms, negative symptoms and disorganisation syndromes. Importantly, it is accompanied by abnormal hippocampal neurogenesis, suggesting that schizophrenia related risk factors may affect hippocampal neurogenesis. Additionally, the regulation of hippocampal neurogenesis is critical for the early intervention and treatment of schizophrenia. Therefore, here the article will review

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the recent progress on the effects of schizophrenia related factors on hippocampal neurogenesis and the roles of regulating hippocampal neurogenesis in schizophrenia.

Keywords

Hippocampal Neurogenesis, Schizophrenia, Susceptibility Gene, Neurodevelopment, Cognitive Deficits

1. 引言

精神分裂症常起病于青春期或成年早期，是遗传和环境因素共同作用的结果。该病的临床表现复杂多样，包括阳性症状、阴性症状和紊乱综合征，认知障碍现在被认为是该疾病的进一步临床特征[1]。需要指出的是，现有的抗精神分裂症药物对阳性症状改善效果较佳，却未能很好地干预阴性症状和紊乱综合征。研究发现，认知缺陷并不随抗精神病药物改善阳性症状而改善，却可能随着病程的迁延而加重，严重影响患者的生活质量及社会回归，具体可以表现为患者存在技能获取受限、教育程度降低、职业成功概率减少等困境[2] [3] [4]。认知缺陷的持续存在与患者所服用抗胆碱能药物存在相关性，药物负荷大大增加了患者的认知障碍及痴呆可能性，而其中的机制仍未阐明[5]。因此，阐明精神分裂症认知缺陷的调控机制具有重要意义。

精神分裂症患者大脑发育异常，其中与认知功能密切相关的海马是较早受到影响的脑区之一[6]。海马位于脑颞叶下部，具有很明显的分层结构，包括海马角(cornuammonis, CA)和齿状回(dentate gyrus, DG)。海马内存在两条重要的神经环路：1) CA3锥体神经元→Schaffer collateral神经元→CA1锥体神经元突触；2) 内嗅皮层→前穿质通路→齿状回颗粒细胞[7]。认知功能通常与神经环路结构和可塑性相关，海马DG区新产生的神经元参与神经环路的重塑，同认知功能的改变密切相关[8]。近来研究发现精神分裂症患者存在海马神经发生及环路异常，且提示神经干细胞在治疗精神分裂症中的潜在作用[9]。因此，理解精神分裂症成体神经发生异常的机制对治疗精神分裂症具有重要意义。

本文首先简要介绍海马神经发生的特点和功能，然后重点综述精神分裂症中海马神经发生的改变及精神分裂症相关风险因子对海马神经发生的调控作用，以及以海马新生神经元为靶点治疗精神分裂症的研究进展，从而有助于深入理解精神分裂症的发病机制，为疾病干预提供有效策略。

2. 海马神经发生

成体神经发生最初由 Altman 等报道发现[10]，成年哺乳动物大脑中神经发生主要在前脑侧脑室内侧壁的室下区(the subventricular zone, SVZ)和海马齿状回的颗粒细胞下层(the subgranular zone, SGZ) [11]。后者新生成的神经元迁移至海马齿状回的颗粒细胞层分化成熟并整合到神经环路中形成具有功能活性的新神经元，此过程称为海马神经发生。这些新生神经元的常用标记分子是 GFAP，Sox2，Nestin 和 DCX 等。据报道在小鼠海马齿状回每天新生成的神经元数目约有 800~1600 [12]。这些成活的神经元伸出树突结构到达海马齿状回分子层接收来自内嗅皮层的信号，并且进一步通过轴突结构把信号传递给 CA3 区，从而整合到现有的神经网络中[13]。这种新生神经元的形成、分化和整合到网络的过程涉及到大量的信号分子。其中 Notch，Shh，Wnts 和 BMPs 参与调控前体干细胞的增殖和分化等过程。神经递质，包括神经生长因

子、神经营养因子、细胞因子和激素参与调控神经发生的不同阶段[14] [15] [16] [17]。另外，细胞生长的内在因子，例如 miRNA、转录因子、细胞周期因子和表观遗传因子等也参与神经发生的增殖、分化和成活等过程[18]。因此，神经发生受控于一系列复杂的调节机制，任何环节发生异常，均有可能导致神经精神疾病的发生。

3. 海马神经发生在精神分裂症中的变化

研究表明，精神分裂症患者及模型动物中海马新生神经元异常。在精神分裂症患者中，海马齿状回体积变小[19]，通过检测患者和对照组死后海马组织中的 Ki67 标记的阳性细胞，发现精神分裂症患者 Ki67 阳性细胞的密度降低 50%~60%，提示增殖细胞显著减少[20]。精神分裂症的动物模型按其诱导策略大致可分为药物诱导、神经发育障碍和转基因动物三类。其中药物诱导模型，如在精神分裂症大鼠药物暴露模型中，反复注射 NMDA 受体拮抗剂 MK-801 后，海马齿状回的神经发生减少[21]。然而，也有研究报道，大鼠孕期慢性暴露苯环利定引起胎鼠早期发育异常，主要表现为海马齿状回新生神经元显著增加和旷场活动量的减少[22]。其中，海马齿状回新生神经元增加可能与胎鼠在孕期摄取胆碱导致胆碱能系统超敏相关[23]，此前研究已发现胆碱能系统参与调节齿状回新生神经元存活[24]。另一种可能的解释是细胞增殖的增加是一过性的，孕期应激可能导致胚胎发育细胞增殖减少，产后早期发生了反弹性的细胞增殖增加[25] [26]。旷场活动量的减少，可与大鼠对于慢性苯环利定暴露的耐受相联系[27]。此外，大鼠慢性应用亚麻醉剂量的氯胺酮同样增强海马神经发生[28]。

精神分裂症的神经发育障碍模型主要指动物早期大脑进行突触修剪、校正及神经发生调控的过程中，受到遗传或环境影响导致神经发育异常，出现精神症状[29]。常用的甲基氮氧基甲醇醋酸(Methylazoxymethanol acetate, MAM)模型在怀孕母鼠妊娠第 17 天注射 MAM，使胎鼠感染。实验发现，MAM 成年小鼠较正常小鼠的大脑体积与重量显著减小，尤其是海马体积缩小，背侧海马出现神经元异位现象，且齿状回细胞增殖和神经发生减少并伴随认知缺陷[30]。母体免疫激活(Maternal immune activation, MIA)是另一种神经发育模型，主要表现为前额叶皮质和海马的小清蛋白(Parvalbumin, PV)中间神经元及其相关的神经周围网(涉及结构和突触可塑性的细胞外基质结构)发生异常变化[31] [32] [33]，齿状回神经发生减少，树突发育异常，整体水平出现焦虑与空间学习能力障碍[34]。

Disrupted-in-Schizophrenia-1 (*DISC1*)基因是一个与精神分裂症明确相关的基因，其参与编码影响神经元发育的支架蛋白[35]。抑制 *DISC1* 基因的表达减少神经干细胞的增殖，导致细胞周期的过早退出并诱导细胞分化[36]。*22q11.2* 基因是另一个精神分裂症相关的基因，*22q11.2* 基因缺失的小鼠模型表现出成体海马神经发生受损和空间工作记忆缺陷[37]。α7 烟碱型乙酰胆碱受体(α7 nicotinic acetylcholine receptor, CHRNA7)基因拷贝数与精神分裂症的发生密切相关，该基因拷贝数的变异改变通过调控海马中间抑制性神经元活性影响神经发生[38]。

4. 精神分裂症发病因素对海马神经发生的影响

4.1. 遗传因素

影响精神分裂症发生的因素中，遗传被认为是较主要的致病因素。过去几十年的研究已经在世界各地的许多人群中确定了数百个与精神分裂症相关的特定风险基因。这里，我们重点描述三个精神分裂症易感基因。

4.1.1. *DISC1* 及相关分子对海马神经发生的影响

DISC1 基因作为精神分裂症的重要风险因子，参与早期新生神经元的分化和成熟过程。研究发现，抑制 *DISC1* 基因表达导致神经前体细胞增殖减少[36]和新生神经元发育缺陷，后者包括胞体异常肥大、

定位错误和轴突靶向受损等[39]。进一步研究表明，抑制 *DISC1* 表达使新生神经元中 AKT/mTOR 信号通路过度激活，引起新生神经元过度兴奋而导致如上所述的神经元发育缺陷[39]，并且该异常与认知功能受损相关。星形胶质细胞特异性表达突变型 *DISC1* 同样抑制神经前体细胞的增殖并损害海马依赖的学习记忆能力，D-丝氨酸慢性给药可以减少异常的成体神经发生，增加神经前体细胞增殖，改善树突发育并提高 *DISC1* 突变小鼠的认知功能[40]。

4.1.2. *DTNBP1* 及相关分子对海马神经发生的影响

Dystrobrevin-binding protein 1 (*DTNBP1*)是精神分裂症另一个重要的风险因子，主要编码 dysbindin-1。该基因编码的 mRNA 在海马的神经元群(即下托和 CA1-3 的锥体神经元，DG 致密细胞层颗粒细胞和 DG 门区多形细胞)中均有显著表达[41]。而在精神分裂症患者中，dysbindin-1 表达减少了 20%~40%，尤其在齿状回颗粒细胞层、多形细胞层和 CA3 中，其表达显著降低[42]。dysbindin-1 有三种异构体，在精神分裂症患者中 dysbindin-1B 和 1C 表达量减少，但 1A 正常[43]。dysbindin-1C 特异性表达在 DG 门区的谷氨酸能神经元，其缺乏导致此类神经元数目减少，进而引起其投射的齿状回 γ-氨基丁酸(γ-aminobutyric acid, GABA)中间神经元的环磷腺苷效应元件结合蛋白(cAMP-response element binding protein, CREB)信号表达减弱，导致新生神经元成熟过程障碍，海马神经环路整合受到影响，认知行为发生改变[44]。

4.1.3. *NRG1* 基因及相关分子对海马神经发生的影响

Table 1. Major signaling molecules affecting adult neurogenesis in schizophrenia
表 1. 精神分裂症中影响成体神经发生的主要信号分子

EFFECT ON NEUROGENESIS	SIGNALING MOLECULES	REFERENCES
Proliferation	GABA	[52]
	Wnt	[53]
	Retinoid	[53]
	FOXG1	[54]
	TBR2	[54]
	PARP-1	[55]
	NR2E1	[56]
	bFGF	[57]
	IGF2	[37]
	5-HT	[58]
	BRINP1	[59]
	GSK3	[60]
	TNF-α	[61]
Differentiation	NGF	[62]
	Reelin	[53]
	Retinoid	[53]
	BDNF	[63]
	TGF-β	[63]

Continued

	Tcf4	[64]
	PARP-1	[55]
	NT-3	[62]
	GSK3	[60]
	Wnt	[53]
Survival	NGF	[62]
	Retinoid	[53]
	$Ca_v1.2$	[65]
	BDNF	[66]
	NT-3	[62]
Dendritic arborization	GABA	[52]
	Cyfip1	[67]
	GSK3	[60]
Synaptic plasticity	NGF	[62]
	Reelin	[53]
	BDNF	[68]
	NT-3	[62]
	Wnt	[53]
	TNF-α	[61]
Migration	Reelin	[53]
	BDNF	[63]
	PlxnA2	[69]
	Arp2/3	[67]
Fate specification	Wnt	[53]
	FOXG1	[54]
	TBR2	[54]
	TGF-β	[63]
	IL-1β	[61]
apoptosis	Cyfip1	[67]
	TNF-α	[61]

Neuregulin-1 (*NRG1*)及其受体 *ErbB4* 同是精神分裂症的易感基因，其表达异常与精神分裂症的发生密切相关。*NRG1* 促进细胞增殖，对髓鞘的形成有重要作用[45]。NRG-ErbB 信号通路参与调控神经干细胞的迁移、轴突引导、突触可塑性和少突胶质细胞发育[46]而且，该信号通路调控谷氨酸环路形成中锥体神经元辐射迁移、神经元突起生长和兴奋性突触形成等多个阶段，对 GABA 能神经元轴突和树突发育也有促进作用[45]。进一步研究发现，*NRG1* 的正确表达增加了抑制性神经元树突的复杂性，促进了抑制性神经元上谷氨酸能突触的形成，进而调控成体神经发生，并且这种效应在表达 *DISC1* 突变体或敲除 *DISC1*

后被阻断[47]。大多数尸检研究显示精神分裂症患者 NRG1-ErbB4 信号增加[48]，慢性(12 周)抗精神病药物治疗可以下调 NRG1-ErbB4 信号[49]。

除易感基因的变化与精神分裂症神经发生密切相关，一些信号分子也参与海马神经发生的调控。例如，细胞内在分子管道精确控制着神经前体细胞的自我更新和分化[50]；血管内皮生长因子(vascular endothelial growth factor, VEGF)信号作用于神经前体细胞存活、增殖，神经母细胞迁移、成熟等；GABA、谷氨酸及多巴胺等神经递质也对新神经元的产生起重要作用[51]。因此，我们整理了精神分裂症中影响成体神经发生的主要信号分子(表 1)。

4.2. 环境因素

生命早期的有害事件暴露与精神分裂症等精神疾病密切相关。首先，围产期不幸生活事件(如母体焦虑、应激、早产及难产)与更高的精神疾病发病风险相关[3]。胎儿直接接触风疹、人类巨细胞病毒、寨卡病毒等也容易引起神经精神障碍，表现出智力低下、学习障碍、感觉门控损伤和记忆能力减弱等症状[34]。其次，青春期也是神经发育过程中的重要阶段。流行病学调查显示人类青春期如果受到负向的外界刺激，比如大麻使用、种族歧视或城市生活压力，会增加精神分裂症的发病率。有研究表明，出生时间在冬季或春季以及出生地点在城市的人患精神分裂症的风险更大[70]。这或许与季节交替和城市农村地点的转换增加宫内感染概率相关。由宫内感染所引起的慢性神经炎症可进一步诱导过度的氧化应激反应，从而使神经发生受到抑制[61]，导致患病风险增加。

研究表明，环境应激导致哺乳动物海马成体神经发生异常。通过声学惊吓范式对怀孕的恒河猴施加早期和晚期应激，可引起 2.5~3 岁的后代海马齿状回神经发生显著减少[71]。孕鼠胚胎期长时间受到强光照射刺激会导致子代成年后海马新生神经元数量明显减少[72]。络丝蛋白(reelin)是精神分裂症相关的一种重要蛋白，母鼠孕中期感染人流感病毒会导致新生小鼠海马中的 reelin 阳性细胞数量显著减少，新皮质和海马厚度变薄，神经细胞发育异常[73]。同时产前感染影响新生儿大脑中神经元型一氧化氮合酶(neuronal nitric oxide synthase, nNOS)水平的变化，而 nNOS 是参与突触发生和兴奋毒性的重要分子[73]。这些结果提示，产前病毒感染可能通过减少新生儿大脑中络丝蛋白的产生和影响 nNOS 水平导致新生神经元发育和迁移异常。

但是，环境并不是只对机体产生有害的影响，积极的活动对于成体海马神经发生有促进作用，比如自发性的运动[74] [75] [76]、海马依赖性的联想学习训练[77]、丰富的环境[21]等。

5. 调控成体海马神经发生对精神分裂症的影响

5.1. 基因调控

基因的遗传变异是影响精神分裂症的关键因素。全基因组关联研究已经明确了超过 180 个与精神分裂症高度关联的基因座，其中很多基因参与调控成体神经发生，研究进一步发现大多数的精神分裂症风险变异体位于非编码区[78]，这意味着我们可以通过改变基因表达的方式来调控风险基因的功能，从而达到治疗疾病的目的。表观遗传修饰就是这样一种调控方式，它通过修饰非编码区实现对致病基因表达和功能的调节，从而影响海马神经发生等一系列表型，并且该方法可能通过使用生物标记物的表观遗传干预来推进个体化治疗[79]。

2006 年，Takahashi 和 Yamanaka 通过给已经分化的人体细胞导入特定的转录因子，使体细胞再次编程成为多能干细胞，即诱导性多能干细胞(inducedpluripotent stem cells, iPSCs) [80]。iPSCs 可分化成为各种神经细胞，功能类似于成体神经干细胞，这为研究神经发育过程奠定了基础。目前发现的与精神分裂症相关的风险基因多在产前或早期就已经表达，iPSC 技术有助于培养疾病相关的发育组织，这使得研究

与精神分裂症患者具有完全相同遗传背景的组织发育异常成为可能[81]。因此，iPSCs 也被用于建立精神分裂症模型，并且在研究精神分裂症的发病机制、诊断和治疗中具有广阔的应用空间。

精神分裂症易感基因调控机制的发现与深入研究，特别是调控易感基因对成体神经发生的影响以及诱导多能干细胞用于精神分裂症模型的深入研究，有助于为精神分裂症的基因疗法提供潜在的靶点和可行方案。

5.2. 药物调控

目前，临床上使用的一些抗精神病药物对海马神经发生也有影响。例如，奥氮平是治疗精神分裂症最有效和最常用的第二代抗精神病药物之一。研究发现，奥氮平能够部分改善精神分裂症患者的症状，增加神经可塑性、神经发生，发挥神经保护作用[82]。在动物模型中，使用 BrdU 标记增殖细胞后，由 MK-801 诱导的精神分裂症小鼠因奥氮平诱导产生的神经元显著增加[83]。利培酮是新一代的抗精神病药物之一，在近二十年的时间内一直被用于治疗精神分裂症和相关的精神障碍疾病。在 NTera2/CloneD1 细胞系诱导的人类神经元样细胞中，利培酮显著上调了神经发生相关基因的表达[84]。其慢性治疗增加了成年小鼠海马区的神经发生[85]。在 MK-801 诱导的精神分裂症小鼠中，利培酮用药显著促进神经发生，增加小鼠在 Y 迷宫的自发交替次数，改善其认知功能[86]。

5.3. 其他调控

5.3.1. 电休克治疗

电休克治疗(electroconvulsive therapy, ECT)是一种重要的精神疾病治疗方式，已使用超 80 年。ECT 对精神分裂症特别是耐药性患者或者需要快速缓解的患者治疗效果较好。已有研究表明，在急诊治疗重症精神分裂症患者时，维持 ECT 对患者阳性及阴性症状均有所改善[87]。在疾病动物模型中，使用电休克治疗可以有效刺激海马区的神经再生[88]。单次治疗即可显著地增加新生神经元的数量，重复治疗 10 天(保持每天一次的频率)增加的新生神经元数量最多[89]。关于 ECT 的作用机制，有研究认为 VEGF 信号是介导 ECT 促进新生神经元增殖的主要因素，因为 VEGF 在神经发生和神经保护机制中起重要作用[88]。这些结果表明，ECT 极可能通过促进神经发生发挥对精神分裂症的治疗作用。

5.3.2. 重复经颅磁刺激

重复经颅磁刺激(repeat transcranial magnetic stimulation, rTMS)也是临床使用的一种物理治疗方式。高频 TMS (≥ 5 Hz)可增强皮质活动，而低频 TMS (≤ 1 Hz)降低皮质活动。对不同部位进行刺激会产生不一样的治疗效果，低频 rTMS 刺激左侧颞顶区治疗阳性症状(主要为幻觉)远比刺激右侧颞顶叶和前额有效，高频 rTMS 刺激左侧背外侧前额叶有助于改善精神分裂症阴性症状[90]。就认知功能而言，低频 rTMS 刺激能够选择性改善阳性症状和某些社会认知障碍[91]。此外，将 rTMS 与其他已知的认知增强疗法相结合，可能会产生双重的治疗效果[92]。在动物模型中，用 5 Hz 的 rTMS 持续刺激大鼠海马 14 天诱导 BDNF 水平升高，增加海马突触可塑性，改善空间记忆的损伤[68]；同时，实验显示 14 天慢性 rTMS 能够促进成年大鼠 DG 区神经发生，DG 颗粒下祖细胞数量明显增多[93]。以上均提示 rTMS 可能通过升高 BDNF 水平，增强海马神经发生，改善精神分裂症的认知损伤。

5.3.3. 自发运动

研究报道，健康人群的有氧运动可以集中注意力，提高阅读速度，增强记忆力和执行功能等[74]，而其改善认知功能的机制可能与增加 BDNF 促进成体神经发生有关[94]。在健康小鼠中，亦存在有氧运动影响成体海马神经发生，促进细胞增殖的现象[95]。且有氧运动可以减少精神分裂症患者的海马齿状回体积丢失[96]并改善症状，例如，瑜伽增强精神分裂症患者的长期记忆[97]。运动能够减缓精神分裂症相关

的行为表型，如减轻阳性症状、阴性症状，改善认知功能[98]，从而提高生活质量。在 MK-801 诱导的精神分裂症样动物模型中，跑步增加成体海马新生神经元的树突复杂性和树突棘的数量，同时增加 DG 区 PV 阳性中间神经元的数量，而这些 PV 阳性中间神经元进一步调控成体神经发生，改善认知功能[75]。

5.3.4. 丰富环境

丰富环境(enriched environment, EE)是一种结合感官刺激、体育锻炼和社会交互的实验范式[21]。相较于生活在贫乏环境下，生活在丰富复杂环境下的啮齿类动物成体海马的新生神经元显著增加，且拥有更大体积的颗粒细胞层，颗粒细胞层的增加帮助海马新生神经元在复杂的环境中更好地存活[99]。EE 增加了存活的新生神经元数量[95]。此外，研究发现 MK-801 模型大鼠在 EE 后 BDNF 水平升高，突触可塑性增加，海马 PV 阳性中间神经元显著增加，进而成体海马神经发生增加，认知损伤改善，空间学习记忆能力有所提高[21]。

5.3.5. 热量限制

高脂饮食(high-fat diet, HFD)影响海马齿状回神经发生。研究报道，高脂饮食喂养的肥胖动物模型齿状回神经干细胞增殖与分化显著降低。这可能与过多高脂食物的摄入降低了海马 BDNF 含量和突触可塑性有关，进而导致认知功能下降[100]。在大鼠模型中，降低动物的卡路里摄入量增加了 SGZ 中新生成的神经元数量，提高了 BDNF 的水平，缓解了因年龄增长而导致的学习和记忆缺陷。饮食限制(dietary restriction, DR)通过增加存活细胞数量使得新生神经元增加[101]。研究发现，良好的饮食习惯及生酮饮食对改善精神分裂症的阳性、阴性症状及认知功能均具有正向作用[102]。此外，限时饮食对于精神分裂症的症状改善亦有干预作用[103]。

精神分裂症患者存在异常的海马神经发生，影响精神分裂症的遗传和环境因素参与调控海马神经发生的不同阶段(如图 1 所示)，疾病风险因素的异常改变导致海马神经发生受损，调控海马神经发生则有助于改善精神分裂症的各个症状，提示影响海马神经发生的相关分子可能成为精神分裂症的早期干预和治疗的潜在靶点。

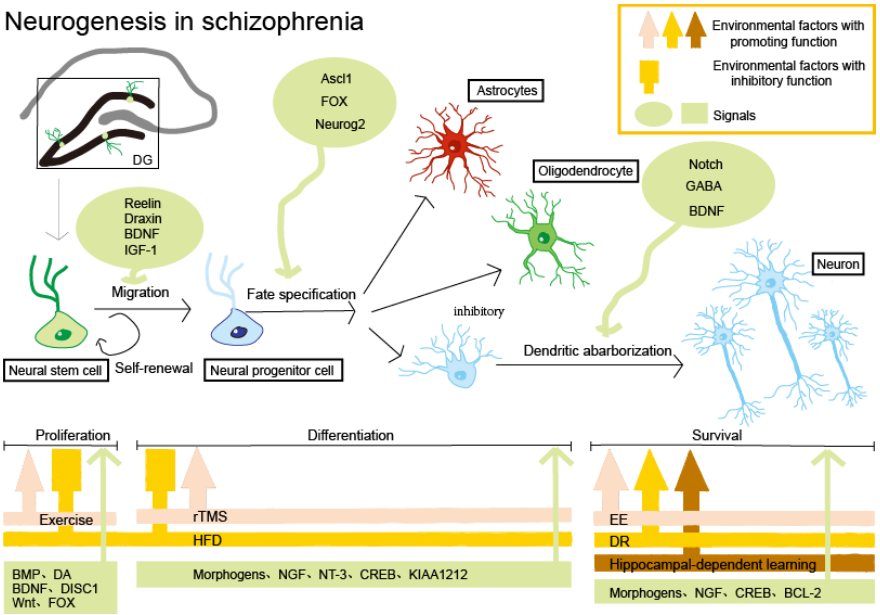

Figure 1. Factors affecting hippocampal neurogenesis in schizophrenia
图 1. 影响精神分裂症海马神经发生的因素

6. 成体神经发生与精神分裂症其他相关症状

6.1. 成体神经发生与感觉门控功能

成体神经发生异常，如新神经元的产生减少和神经回路的畸形，可能在动物模型的分子和细胞水平上代表精神分裂症的表型。然而，该表型不容易用作生物标志物。因此，我们关注感觉门控功能，它可以通过前脉冲抑制(pre-pulse inhibition, PPI)测试进行评分。PPI 受损被认为是精神障碍(如精神分裂症、孤独症和其他神经发育障碍)的重要内表型(生物标记物)之一。由于 PPI 的神经回路涉及海马，且与成体海马神经发生密切相关，因此通过丰富环境增加新生神经元可以改善精神分裂症模型小鼠的感觉门控功能缺陷[104]。

精神分裂症患者的外周免疫状态异常，小胶质细胞作为大脑固有的免疫活性细胞，成为精神分裂症治疗的潜在靶点。研究发现，小胶质细胞白细胞介素-1β (IL-1β)和肿瘤坏死因子 α (TNF-α)的增加介导母体免疫激活模型的海马神经发生减少和感觉门控功能损伤。抗生素米诺环素(3 mg/kg/天)治疗可调控海马小胶质细胞相关因子，并改善海马神经发生和感觉门控功能[105]，而在另一些研究中发现，米诺环素治疗对于精神分裂症治疗无效。于此而言，米诺环素的给药时间及剂量或许是影响其作用的关键因素[3]。

6.2. 成体神经发生与阳性及阴性症状

研究发现，小鼠妊娠晚期 MAM 暴露引起成体神经发生异常，并进一步导致阳性和阴性症状[30]。临床试验报告，辅助性使用孕烯醇酮除提高注意力和工作记忆表现外也显著减少阳性症状和锥体外系副作用[106]。孕烯醇酮是一种神经甾体，对啮齿动物具有多重作用，包括增强学习记忆，促进髓鞘形成。服用孕烯醇酮会引起下游神经甾体(如别孕烯醇酮)升高，别孕烯醇酮是一种具有神经保护作用的分子，它能增加神经发生，减少细胞凋亡和炎症，调节下丘脑–垂体–肾上腺轴，并显著增加 GABA 受体反应。此外，服用孕烯醇酮还能提高硫酸孕烯醇酮水平，这是一种正向调控 NMDA 受体的神经甾体。因此，孕烯醇酮作为一种潜在的精神分裂症治疗药物可能存在多种机制，例如改善 NMDA 受体功能低下(通过代谢为孕烯醇酮硫酸盐)和缓解 GABA 失调(通过代谢为别孕烯醇酮) [107]。喹硫平是一种非典型抗精神病药物，对精神分裂症患者的阳性、阴性和认知症状有效。进一步研究发现，喹硫平(10 mg/kg)给药 7 或 21 天可逆转由应激诱导的海马神经发生抑制[108]，提示喹硫平可能通过增强海马神经发生改善精神分裂症患者的阳性、阴性和认知症状。

7. 总结

本文回顾了成体海马神经发生的历程，综述了精神分裂症患者及动物模型中海马神经发生的特点，同时分析疾病相关风险分子对成体海马神经发生的影响。最后，从基因、药物和物理因素等方面阐述了调控海马神经发生对精神分裂症的治疗作用。

目前精神分裂症的发病机制尚不明确，研究认为发育早期和青春期对精神分裂症相关致病因素敏感。虽然发育早期风险因子暴露可能不会直接导致精神疾病的发生，但会引起早期神经发育障碍而造成神经生物学的脆弱性。这种脆弱性使个体在青春期暴露于压力应激或其他负性事件时更容易产生神经功能紊乱，这也是精神分裂症通常在青春期末、成年期初发病的主要原因。

神经发生作为生命早期极易受到影响的精神分裂症风险因素，对疾病的发生发展具有重要意义。那么海马神经发生主要受到什么因素的调控？是以遗传为主的发育早期风险因子暴露，还是以环境为主的压力应激？结合细胞、网络和系统层面的理论和实验方法，如何阐明海马中相对少量的新神经元的增加却得以调节整个海马或大脑功能？精神分裂症中神经干细胞数量减少与以 PV 阳性神经元为代表的抑制性中间神经元缺乏是如何相互影响的？精神分裂症成体海马神经发生受损是病因还是疾病进程或药物干

预或其他共病的结果？精神分裂症患者海马神经发生的缺陷，在多大程度上导致了认知障碍？早期干预海马神经发生是否可以有效逆转认知损伤？这些问题在本文做了一定程度的综述，但仍不够清晰明确。因此，尝试阐明不同阶段的海马新生神经元在精神分裂症中的潜在机制和作用权重是未来研究的重要方向。

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参考文献

[1] Jauhar, S., Johnstone, M. and Mckenna, P.J. (2022) Schizophrenia. *The Lancet*, **399**, 473-486. https://doi.org/10.1016/S0140-6736(21)01730-X

[2] Vita, A., Minelli, A., Barlati, S., *et al*. (2019) Treatment-Resistant Schizophrenia: Genetic and Neuroimaging Correlates. *Frontiers in Pharmacology*, **10**, 402. https://doi.org/10.3389/fphar.2019.00402

[3] Wegrzyn, D., Juckel, G. and Faissner, A. (2022) Structural and Functional Deviations of the Hippocampus in Schizophrenia and Schizophrenia Animal Models. *International Journal of Molecular Sciences*, **23**, 5482. https://doi.org/10.3390/ijms23105482

[4] Thomas, M.L., Green, M.F., Hellemann, G., *et al*. (2017) Modeling Deficits from Early Auditory Information Processing to Psychosocial Functioning in Schizophrenia. *JAMA Psychiatry*, **74**, 37-46. https://doi.org/10.1001/jamapsychiatry.2016.2980

[5] Joshi, Y.B., Thomas, M.L., Braff, D.L., *et al*. (2021) Anticholinergic Medication Burden-Associated Cognitive Impairment in Schizophrenia. *American Journal of Psychiatry*, **178**, 838-847. https://doi.org/10.1176/appi.ajp.2020.20081212

[6] Rasetti, R., Mattay, V.S., White, M.G., *et al*. (2014) Altered Hippocampal-Parahippocampal Function during Stimulus Encoding: A Potential Indicator of Genetic Liability for Schizophrenia. *JAMA Psychiatry*, **71**, 236-247. https://doi.org/10.1001/jamapsychiatry.2013.3911

[7] Li, Y., Mu, Y. and Gage, F.H. (2009) Development of Neural Circuits in the Adult Hippocampus. *Current Topics in Developmental Biology*, **87**, 149-174. https://doi.org/10.1016/S0070-2153(09)01205-8

[8] Jin, X. (2016) The Role of Neurogenesis during Development and in the Adult Brain. *European Journal of Neuroscience*, **44**, 2291-2299. https://doi.org/10.1111/ejn.13251

[9] Larijani, B., Parhizkar Roudsari, P., Hadavandkhani, M., *et al*. (2021) Stem Cell-Based Models and Therapies: A Key Approach into Schizophrenia Treatment. *Cell and Tissue Banking*, **22**, 207-223. https://doi.org/10.1007/s10561-020-09888-3

[10] Altman, J. and Das, G.D. (1965) Autoradiographic and Histological Evidence of Postnatal Hippocampal Neurogenesis in Rats. *Journal of Comparative Neurology*, **124**, 319-335. https://doi.org/10.1002/cne.901240303

[11] Bonaguidi, M.A., Wheeler, M.A., Shapiro, J.S., *et al*. (2011) *In Vivo* Clonal Analysis Reveals Self-Renewing and Multipotent Adult Neural Stem Cell Characteristics. *Cell*, **145**, 1142-1155. https://doi.org/10.1016/j.cell.2011.05.024

[12] Cameron, H.A. and Mckay, R.D. (2001) Adult Neurogenesis Produces a Large Pool of New Granule Cells in the Dentate Gyrus. *Journal of Comparative Neurology*, **435**, 406-417. https://doi.org/10.1002/cne.1040

[13] Van Praag, H., Schinder, A.F., Christie, B.R., *et al*. (2002) Functional Neurogenesis in the Adult Hippocampus. *Nature*, **415**, 1030-1034. https://doi.org/10.1038/4151030a

[14] Leal, G., Bramham, C.R. and Duarte, C.B. (2017) BDNF and Hippocampal Synaptic Plasticity. *Vitamins and Hormones*, **104**, 153-195. https://doi.org/10.1016/bs.vh.2016.10.004

[15] Zhu, W., Cheng, S., Xu, G., *et al*. (2011) Intranasal Nerve Growth Factor Enhances Striatal Neurogenesis in Adult Rats with Focal Cerebral Ischemia. *Drug Delivery*, **18**, 338-343. https://doi.org/10.3109/10717544.2011.557785

[16] Bobbo, V.C., Engel, D.F., Jara, C.P., *et al*. (2021) Interleukin-6 Actions in the Hypothalamus Protects against Obesity and Is Involved in the Regulation of Neurogenesis. *Journal of Neuroinflammation*, **18**, 192. https://doi.org/10.1186/s12974-021-02242-8

[17] Kapri, D., Fanibunda, S.E. and Vaidya, V.A. (2022) Thyroid Hormone Regulation of Adult Hippocampal Neurogenesis: Putative Molecular and Cellular Mechanisms. *Vitamins and Hormones*, **118**, 1-33. https://doi.org/10.1016/bs.vh.2021.10.001

[18] Suh, H., Deng, W. and Gage, F.H. (2009) Signaling in Adult Neurogenesis. *Annual Review of Cell and Developmental*

Biology, **25**, 253-275. https://doi.org/10.1146/annurev.cellbio.042308.113256

[19] Roeske, M.J., Konradi, C., Heckers, S., *et al*. (2021) Hippocampal Volume and Hippocampal Neuron Density, Number and Size in Schizophrenia: A Systematic Review and Meta-Analysis of Postmortem Studies. *Molecular Psychiatry*, **26**, 3524-3535. https://doi.org/10.1038/s41380-020-0853-y

[20] Allen, K., Fung, S. and Weickert, C. (2016) Cell Proliferation Is Reduced in the Hippocampus in Schizophrenia. *Australian & New Zealand Journal of Psychiatry*, **50**, 473-480. https://doi.org/10.1177/0004867415589793

[21] Murueta-Goyena, A., Ortuzar, N., Lafuente, J., *et al*. (2020) Enriched Environment Reverts Somatostatin Interneuron loss in MK-801 Model of Schizophrenia. *Molecular Neurobiology*, **57**, 125-134. https://doi.org/10.1007/s12035-019-01762-y

[22] Tanimura, A., Liu, J., Namba, T., *et al*. (2009) Prenatal Phencyclidine Exposure Alters Hippocampal Cell Proliferation in Offspring Rats. *Synapse*, **63**, 729-736. https://doi.org/10.1002/syn.20660

[23] Yanai, J., Avraham, Y., Levy, S., *et al*. (1992) Alterations in Septohippocampal Cholinergic Innervations and Related Behaviors after Early Exposure to Heroin and Phencyclidine. *Brain Research*. *Developmental Brain Research*, **69**, 207-214. https://doi.org/10.1016/0165-3806(92)90161-O

[24] Kaneko, N., Okano, H. and Sawamoto, K. (2006) Role of the Cholinergic System in Regulating Survival of Newborn Neurons in the Adult Mouse Dentate Gyrus and Olfactory Bulb. *Genes Cells*, **11**, 1145-1159. https://doi.org/10.1111/j.1365-2443.2006.01010.x

[25] Toriumi, K., Mouri, A., Narusawa, S., *et al*. (2012) Prenatal NMDA Receptor Antagonism Impaired Proliferation of Neuronal Progenitor, Leading to Fewer Glutamatergic Neurons in the Prefrontal Cortex. *Neuropsychopharmacology*, **37**, 1387-1396. https://doi.org/10.1038/npp.2011.324

[26] Bick-Sander, A., Steiner, B., Wolf, S.A., *et al*. (2006) Running in Pregnancy Transiently Increases Postnatal Hippocampal Neurogenesis in the Offspring. *Proceedings of the National Academy of Sciences of the United States of America*, **103**, 3852-3857. https://doi.org/10.1073/pnas.0502644103

[27] Sturgeon, R.D., Fessler, R.G., London, S.F., *et al*. (1982) Behavioral Effects of Chronic Phencyclidine Administration in Rats. *Psychopharmacology* (*Berlin*), **76**, 52-56. https://doi.org/10.1007/BF00430755

[28] Keilhoff, G., Bernstein, H.G., Becker, A., *et al*. (2004) Increased Neurogenesis in a Rat Ketamine Model of Schizophrenia. *Biological Psychiatry*, **56**, 317-322. https://doi.org/10.1016/j.biopsych.2004.06.010

[29] Birnbaum, R. and Weinberger, D. (2017) Genetic Insights into the Neurodevelopmental Origins of Schizophrenia. *Nature Reviews Neuroscience*, **18**, 727-740. https://doi.org/10.1038/nrn.2017.125

[30] Takahashi, K., Nakagawasai, O., Sakuma, W., *et al*. (2019) Prenatal Treatment with Methylazoxymethanol Acetate as a Neurodevelopmental Disruption Model of Schizophrenia in Mice. *Neuropharmacology*, **150**, 1-14. https://doi.org/10.1016/j.neuropharm.2019.02.034

[31] Paylor, J., Lins, B., Greba, Q., *et al*. (2016) Developmental Disruption of Perineuronal Nets in the Medial Prefrontal Cortex after Maternal Immune Activation. *Scientific Reports*, **6**, 37580. https://doi.org/10.1038/srep37580

[32] Steullet, P., Cabungcal, J., Coyle, J., *et al*. (2017) Oxidative Stress-Driven Parvalbumin Interneuron Impairment as a Common Mechanism in Models of Schizophrenia. *Molecular Psychiatry*, **22**, 936-943. https://doi.org/10.1038/mp.2017.47

[33] Giovanoli, S., Weber, L. and Meyer, U. (2014) Single and Combined Effects of Prenatal Immune Activation and Peripubertal Stress on Parvalbumin and Reelin Expression in the Hippocampal Formation. *Brain*, *Behavior*, *and Immunity*, **40**, 48-54. https://doi.org/10.1016/j.bbi.2014.04.005

[34] Couch, A.C.M., Berger, T., Hanger, B., *et al*. (2021) Maternal Immune Activation Primes Deficiencies in Adult Hippocampal Neurogenesis. *Brain*, *Behavior*, *and Immunity*, **97**, 410-422. https://doi.org/10.1016/j.bbi.2021.07.021

[35] Uzuneser, T.C., Speidel, J., Kogias, G., *et al*. (2019) Disrupted-in-Schizophrenia 1 (DISC1) Overexpression and Juvenile Immune Activation Cause Sex-Specific Schizophrenia-Related Psychopathology in Rats. *Frontiers in Psychiatry*, **10**, 222. https://doi.org/10.3389/fpsyt.2019.00222

[36] Deng, D., Jian, C., Lei, L., *et al*. (2017) A Prenatal Interruption of DISC1 Function in the Brain Exhibits a Lasting Impact on Adult Behaviors, Brain Metabolism, and Interneuron Development. *Oncotarget*, **8**, 84798-84817. https://doi.org/10.18632/oncotarget.21381

[37] Ouchi, Y., Banno, Y., Shimizu, Y., *et al*. (2013) Reduced Adult Hippocampal Neurogenesis and Working Memory Deficits in the Dgcr8-Deficient Mouse Model of 22q11.2 Deletion-Associated Schizophrenia Can Be Rescued by IGF2. *Journal of Neuroscience*, **33**, 9408-9419. https://doi.org/10.1523/JNEUROSCI.2700-12.2013

[38] Casamassa, A., Ferrari, D., Gelati, M., *et al*. (2020) A Link between Genetic Disorders and Cellular Impairment, Using Human Induced Pluripotent Stem Cells to Reveal the Functional Consequences of Copy Number Variations in the Central Nervous System—A Close Look at Chromosome 15. *International Journal of Molecular Sciences*, **21**, 1860. https://doi.org/10.3390/ijms21051860

[39] Kim, J.Y., Duan, X., Liu, C.Y., *et al*. (2009) DISC1 Regulates New Neuron Development in the Adult Brain via Modulation of AKT-mTOR Signaling through KIAA1212. *Neuron*, **63**, 761-773. https://doi.org/10.1016/j.neuron.2009.08.008

[40] Terrillion, C.E., Abazyan, B., Yang, Z., *et al*. (2017) DISC1 in Astrocytes Influences Adult Neurogenesis and Hippocampus-Dependent Behaviors in Mice. *Neuropsychopharmacology*, **42**, 2242-2251. https://doi.org/10.1038/npp.2017.129

[41] Talbot, K., Eidem, W., Tinsley, C., *et al*. (2004) Dysbindin-1 Is Reduced in Intrinsic, Glutamatergic Terminals of the Hippocampal Formation in Schizophrenia. *Journal of Clinical Investigation*, **113**, 1353-1363. https://doi.org/10.1172/JCI200420425

[42] Weickert, C., Rothmond, D., Hyde, T., *et al*. (2008) Reduced DTNBP1 (Dysbindin-1) mRNA in the Hippocampal Formation of Schizophrenia Patients. *Schizophrenia Research*, **98**, 105-110. https://doi.org/10.1016/j.schres.2007.05.041

[43] Konopaske, G.T., Balu, D.T., Presti, K.T., *et al*. (2018) Dysbindin-1 Contributes to Prefrontal Cortical Dendritic Arbor Pathology in Schizophrenia. *Schizophrenia Research*, **201**, 270-277. https://doi.org/10.1016/j.schres.2018.04.042

[44] Wang, H., Yuan, Y., Zhang, Z., *et al*. (2014) Dysbindin-1C Is Required for the Survival of Hilar Mossy Cells and the Maturation of Adult Newborn Neurons in Dentate Gyrus. *Journal of Biological Chemistry*, **289**, 29060-29072. https://doi.org/10.1074/jbc.M114.590927

[45] Mei, L. and Nave, K.A. (2014) Neuregulin-ERBB Signaling in the Nervous System and Neuropsychiatric Diseases. *Neuron*, **83**, 27-49. https://doi.org/10.1016/j.neuron.2014.06.007

[46] Dabbah-Assadi, F., Khatib, N., Ginsberg, Y., *et al*. (2021) Short-Term Effect of $MgSO_4$ on the Expression of NRG-ErbB, Dopamine, GABA, and Glutamate Systems in the Fetal Rat Brain. *Journal of Molecular Neuroscience*, **71**, 446-454. https://doi.org/10.1007/s12031-020-01665-x

[47] Unda, B.K., Kwan, V. and Singh, K.K. (2016) Neuregulin-1 Regulates Cortical Inhibitory Neuron Dendrite and Synapse Growth through DISC1. *Neural Plasticity*, **2016**, Article ID: 7694385. https://doi.org/10.1155/2016/7694385

[48] Götze, T., Soto-Bernardini, M.C., Zhang, M., *et al*. (2021) Hyperactivity Is a Core Endophenotype of Elevated Neuregulin-1 Signaling in Embryonic Glutamatergic Networks. *Schizophrenia Bulletin*, **47**, 1409-1420. https://doi.org/10.1093/schbul/sbab027

[49] Pan, B., Huang, X.F. and Deng, C. (2011) Antipsychotic Treatment and Neuregulin 1-ErbB4 Signalling in Schizophrenia. Prog Neuropsychopharmacol *Biological Psychiatry*, **35**, 924-930. https://doi.org/10.1016/j.pnpbp.2011.04.002

[50] Asrican, B., Paez-Gonzalez, P., Erb, J., *et al*. (2016) Cholinergic Circuit Control of Postnatal Neurogenesis. *Neurogenesis* (*Austin*), **3**, e1127310. https://doi.org/10.1080/23262133.2015.1127310

[51] Ihrie, R.A. and Alvarez-Buylla, A. (2011) Lake-Front Property: A Unique Germinal Niche by the Lateral Ventricles of the Adult Brain. *Neuron*, **70**, 674-686. https://doi.org/10.1016/j.neuron.2011.05.004

[52] Kim, J.Y., Liu, C.Y., Zhang, F., *et al*. (2012) Interplay between DISC1 and GABA Signaling Regulates Neurogenesis in Mice and Risk for Schizophrenia. *Cell*, **148**, 1051-1064. https://doi.org/10.1016/j.cell.2011.12.037

[53] Toro, C.T. and Deakin, J.F. (2007) Adult Neurogenesis and Schizophrenia: A Window on Abnormal Early Brain Development? *Schizophrenia Research*, **90**, 1-14. https://doi.org/10.1016/j.schres.2006.09.030

[54] Moslem, M., Olive, J. and Falk, A. (2019) Stem Cell Models of Schizophrenia, What Have We Learned and What Is the Potential? *Schizophrenia Research*, **210**, 3-12. https://doi.org/10.1016/j.schres.2018.12.023

[55] Hong, S., Yi, J.H., Lee, S., *et al*. (2019) Defective Neurogenesis and Schizophrenia-Like Behavior in PARP-1-Deficient Mice. *Cell Death & Disease*, **10**, 943. https://doi.org/10.1038/s41419-019-2174-0

[56] Sun, G., Cui, Q. and Shi, Y. (2017) Nuclear Receptor TLX in Development and Diseases. *Current Topics in Developmental Biology*, **125**, 257-273. https://doi.org/10.1016/bs.ctdb.2016.12.003

[57] Pieper, A.A., Wu, X., Han, T.W., *et al*. (2005) The Neuronal PAS Domain Protein 3 Transcription Factor Controls FGF-Mediated Adult Hippocampal Neurogenesis in Mice. *Proceedings of the National Academy of Sciences of the United States of America*, **102**, 14052-14057. https://doi.org/10.1073/pnas.0506713102

[58] Schreiber, R. and Newman-Tancredi, A. (2014) Improving Cognition in Schizophrenia with Antipsychotics That Elicit Neurogenesis through 5-HT(1A) Receptor Activation. *Neurobiology of Learning and Memory*, **110**, 72-80. https://doi.org/10.1016/j.nlm.2013.12.015

[59] Kobayashi, M., Hayashi, Y., Fujimoto, Y., *et al*. (2018) Decreased Parvalbumin and Somatostatin Neurons in Medial Prefrontal Cortex in BRINP1-KO Mice. *Neuroscience Letters*, **683**, 82-88. https://doi.org/10.1016/j.neulet.2018.06.050

[60] Hur, E.M. and Zhou, F.Q. (2010) GSK3 Signalling in Neural Development. *Nature Reviews Neuroscience*, **11**, 539-551. https://doi.org/10.1038/nrn2870

[61] Na, K.S., Jung, H.Y. and Kim, Y.K. (2014) The Role of Pro-Inflammatory Cytokines in the Neuroinflammation and

Neurogenesis of Schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, **48**, 277-286. https://doi.org/10.1016/j.pnpbp.2012.10.022

[62] Jena, M., Ranjan, R., Mishra, B.R., *et al*. (2019) Effect of Lurasidone vs Olanzapine on Neurotrophic Biomarkers in Unmedicated Schizophrenia: A Randomized Controlled Trial. *Journal of Psychiatric Research*, **112**, 1-6. https://doi.org/10.1016/j.jpsychires.2019.02.007

[63] Kalkman, H.O. (2009) Altered Growth Factor Signaling Pathways as the Basis of Aberrant Stem Cell Maturation in Schizophrenia. *Pharmacology & Therapeutics*, **121**, 115-122. https://doi.org/10.1016/j.pharmthera.2008.11.002

[64] Mesman, S., Bakker, R. and Smidt, M.P. (2020) Tcf4 Is Required for Correct Brain Development during Embryogenesis. *Molecular and Cellular Neuroscience*, **106**, Article ID: 103502. https://doi.org/10.1016/j.mcn.2020.103502

[65] De Jesús-Cortés, H., Rajadhyaksha, A.M. and Pieper, A.A. (2016) Cacna1c: Protecting Young Hippocampal Neurons in the Adult Brain. *Neurogenesis* (*Austin*), **3**, e1231160. https://doi.org/10.1080/23262133.2016.1231160

[66] Nandra, K.S. and Agius, M. (2012) The Differences between Typical and Atypical Antipsychotics: The Effects on Neurogenesis. *Psychiatria Danubina*, **24**, S95-S99.

[67] Haan, N., Westacott, L.J., Carter, J., *et al*. (2021) Haploinsufficiency of the Schizophrenia and Autism Risk Gene Cyfip1 Causes Abnormal Postnatal Hippocampal Neurogenesis through Microglial and Arp2/3 Mediated Actin Dependent Mechanisms. *Translational Psychiatry*, **11**, 313. https://doi.org/10.1038/s41398-021-01415-6

[68] Shang, Y., Wang, X., Li, F., *et al*. (2019) rTMS Ameliorates Prenatal Stress-Induced Cognitive Deficits in Male-Offspring Rats Associated with BDNF/TrkB Signaling Pathway. *Neurorehabilitation and Neural Repair*, **33**, 271-283. https://doi.org/10.1177/1545968319834898

[69] Zhao, X.F., Kohen, R., Parent, R., *et al*. (2018) PlexinA2 Forward Signaling through Rap1 GTPases Regulates Dentate Gyrus Development and Schizophrenia-Like Behaviors. *Cell Reports*, **22**, 456-470. https://doi.org/10.1016/j.celrep.2017.12.044

[70] Stilo, S.A. and Murray, R.M. (2019) Non-Genetic Factors in Schizophrenia. *Current Psychiatry Reports*, **21**, 100. https://doi.org/10.1007/s11920-019-1091-3

[71] Coe, C., Kramer, M., Czéh, B., *et al*. (2003) Prenatal Stress Diminishes Neurogenesis in the Dentate Gyrus of Juvenile Rhesus Monkeys. *Biological Psychiatry*, **54**, 1025-1034. https://doi.org/10.1016/S0006-3223(03)00698-X

[72] Lemaire, V., Koehl, M., Le Moal, M., *et al*. (2000) Prenatal Stress Produces Learning Deficits Associated with an Inhibition of Neurogenesis in the Hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, **97**, 11032-11037. https://doi.org/10.1073/pnas.97.20.11032

[73] Patterson, P. (2009) Immune Involvement in Schizophrenia and Autism: Etiology, Pathology and Animal Models. *Behavioural Brain Research*, **204**, 313-321. https://doi.org/10.1016/j.bbr.2008.12.016

[74] Smith, P., Blumenthal, J., Hoffman, B., *et al*. (2010) Aerobic Exercise and Neurocognitive Performance: A Meta-Analytic Review of Randomized Controlled Trials. *Psychosomatic Medicine*, **72**, 239-252. https://doi.org/10.1097/PSY.0b013e3181d14633

[75] Yi, Y., Song, Y. and Lu, Y. (2020) Parvalbumin Interneuron Activation-Dependent Adult Hippocampal Neurogenesis Is Required for Treadmill Running to Reverse Schizophrenia-Like Phenotypes. *Frontiers in Cell and Developmental Biology*, **8**, 24. https://doi.org/10.3389/fcell.2020.00024

[76] Kurebayashi, Y., Mori, K. and Otaki, J. (2022) Effects of Mild-Intensity Physical Exercise on Neurocognition in Inpatients with Schizophrenia: A Pilot Randomized Controlled Trial. *Perspectives in Psychiatric Care*, **58**, 1037-1047. https://doi.org/10.1111/ppc.12896

[77] Epp, J.R., Spritzer, M.D. and Galea, L.A. (2007) Hippocampus-Dependent Learning Promotes Survival of New Neurons in the Dentate Gyrus at a Specific Time during Cell Maturation. *Neuroscience*, **149**, 273-285. https://doi.org/10.1016/j.neuroscience.2007.07.046

[78] Huo, Y., Li, S., Liu, J., *et al*. (2019) Functional Genomics Reveal Gene Regulatory Mechanisms Underlying Schizophrenia Risk. *Nature Communications*, **10**, 670. https://doi.org/10.1038/s41467-019-08666-4

[79] Richetto, J. and Meyer, U. (2021) Epigenetic Modifications in Schizophrenia and Related Disorders: Molecular Scars of Environmental Exposures and Source of Phenotypic Variability. *Biological Psychiatry*, **89**, 215-226. https://doi.org/10.1016/j.biopsych.2020.03.008

[80] Takahashi, K. and Yamanaka, S. (2006) Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell*, **126**, 663-676. https://doi.org/10.1016/j.cell.2006.07.024

[81] Noh, H., Shao, Z., Coyle, J.T., *et al*. (2017) Modeling Schizophrenia Pathogenesis Using Patient-Derived Induced Pluripotent Stem Cells (iPSCs). *Biochimica et Biophysica Acta—Molecular Basis of Disease*, **1863**, 2382-2387. https://doi.org/10.1016/j.bbadis.2017.06.019

[82] Osacka, J., Kiss, A., Bacova, Z., *et al*. (2022) Effect of Haloperidol and Olanzapine on Hippocampal Cells' Prolifera-

tion in Animal Model of Schizophrenia. *International Journal of Molecular Sciences*, **23**, 7711. https://doi.org/10.3390/ijms23147711

[83] Song, J.C., Seo, M.K., Park, S.W., *et al*. (2016) Differential Effects of Olanzapine and Haloperidol on MK-801-Induced Memory Impairment in Mice. *Clinical Psychopharmacology and Neuroscience*, **14**, 279-285. https://doi.org/10.9758/cpn.2016.14.3.279

[84] Bortolasci, C.C., Spolding, B., Kidnapillai, S., *et al*. (2020) Transcriptional Effects of Psychoactive Drugs on Genes Involved in Neurogenesis. *International Journal of Molecular Sciences*, **21**, 8333. https://doi.org/10.3390/ijms21218333

[85] Chikama, K., Yamada, H., Tsukamoto, T., *et al*. (2017) Chronic Atypical Antipsychotics, but Not Haloperidol, Increase Neurogenesis in the Hippocampus of Adult Mouse. *Brain Research*, **1676**, 77-82. https://doi.org/10.1016/j.brainres.2017.09.006

[86] Xue, F., Chen, Y.C., Zhou, C.H., *et al*. (2017) Risperidone Ameliorates Cognitive Deficits, Promotes Hippocampal Proliferation, and Enhances Notch Signaling in a Murine Model of Schizophrenia. *Pharmacology Biochemistry and Behavior*, **163**, 101-109. https://doi.org/10.1016/j.pbb.2017.09.010

[87] Mishra, B.R., Agrawal, K., Biswas, T., *et al*. (2022) Comparison of Acute Followed by Maintenance ECT vs Clozapine on Psychopathology and Regional Cerebral Blood Flow in Treatment-Resistant Schizophrenia: A Randomized Controlled Trial. *Schizophrenia Bulletin*, **48**, 814-825. https://doi.org/10.1093/schbul/sbac027

[88] Sorri, A., Järventausta, K., Kampman, O., *et al*. (2021) Electroconvulsive Therapy Increases Temporarily Plasma Vascular Endothelial Growth Factor in Patients with Major Depressive Disorder. *Brain and Behavior*, **11**, e02001. https://doi.org/10.1002/brb3.2001

[89] Ito, M., Seki, T., Liu, J., *et al*. (2010) Effects of Repeated Electroconvulsive Seizure on Cell Proliferation in the Rat Hippocampus. *Synapse*, **64**, 814-821. https://doi.org/10.1002/syn.20796

[90] Guo, Q., Li, C. and Wang, J. (2017) Updated Review on the Clinical Use of Repetitive Transcranial Magnetic Stimulation in Psychiatric Disorders. *Neuroscience Bulletin*, **33**, 747-756. https://doi.org/10.1007/s12264-017-0185-3

[91] Xie, Y., Cai, Y., Guan, M., *et al*. (2022) The Alternations of Nucleus Accumbent in Schizophrenia Patients with Auditory Verbal Hallucinations during Low-Frequency rTMS Treatment. *Frontiers in Psychiatry*, **13**, Article ID: 971105. https://doi.org/10.3389/fpsyt.2022.971105

[92] Sathappan, A., Luber, B. and Lisanby, S. (2019) The Dynamic Duo: Combining Noninvasive Brain Stimulation with Cognitive Interventions. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, **89**, 347-360. https://doi.org/10.1016/j.pnpbp.2018.10.006

[93] Ueyama, E., Ukai, S., Ogawa, A., *et al*. (2011) Chronic Repetitive Transcranial Magnetic Stimulation Increases Hippocampal Neurogenesis in Rats. *Psychiatry and Clinical Neurosciences*, **65**, 77-81. https://doi.org/10.1111/j.1440-1819.2010.02170.x

[94] Girdler, S., Confino, J. and Woesner, M. (2019) Exercise as a Treatment for Schizophrenia: A Review. *Psychopharmacology Bulletin*, **49**, 56-69.

[95] Fabel, K., Wolf, S.A., Ehninger, D., *et al*. (2009) Additive Effects of Physical Exercise and Environmental Enrichment on Adult Hippocampal Neurogenesis in Mice. *Frontiers in Neuroscience*, **3**, 50. https://doi.org/10.3389/neuro.22.002.2009

[96] Maurus, I., Roell, L., Keeser, D., *et al*. (2022) Fitness Is Positively Associated with Hippocampal Formation Subfield Volumes in Schizophrenia: A Multiparametric Magnetic Resonance Imaging Study. *Translational Psychiatry*, **12**, 388. https://doi.org/10.1038/s41398-022-02155-x

[97] Nuechterlein, K.H., Mcewen, S.C., Ventura, J., *et al*. (2022) Aerobic Exercise Enhances Cognitive Training Effects in First-Episode Schizophrenia: Randomized Clinical Trial Demonstrates Cognitive and Functional Gains. *Psychological Medicine*, 1-11. https://doi.org/10.1017/S0033291722001696

[98] Shimada, T., Ito, S., Makabe, A., *et al*. (2022) Aerobic Exercise and Cognitive Functioning in Schizophrenia: An Updated Systematic Review and Meta-Analysis. *Psychiatry Research*, **314**, Article ID: 114656. https://doi.org/10.1016/j.psychres.2022.114656

[99] Kempermann, G., Kuhn, H.G. and Gage, F.H. (1997) More Hippocampal Neurons in Adult Mice Living in an Enriched Environment. *Nature*, **386**, 493-495. https://doi.org/10.1038/386493a0

[100] Kang, M.S., Kim, W., Kim, T.H., *et al*. (2020) Changes of Fat-Mass and Obesity-Associated Protein Expression in the Hippocampus in Animal Models of High-Fat Diet-Induced Obesity and D-Galactose-Induced Aging. *Laboratory Animal Research*, **36**, 20. https://doi.org/10.1186/s42826-020-00046-0

[101] Heberden, C. (2016) Modulating Adult Neurogenesis through Dietary Interventions. *Nutrition Research Reviews*, **29**, 163-171. https://doi.org/10.1017/S0954422416000081

[102] Aucoin, M., Lachance, L., Cooley, K., *et al*. (2020) Diet and Psychosis: A Scoping Review. *Neuropsychobiology*, **79**,

20-42. https://doi.org/10.1159/000493399

[103] 马雪倩, 岳伟华. 限时饮食可能是改善精神分裂症患者代谢的新兴干预措施[J]. 国际神经精神科学杂志, 2021(10): 42-51.

[104] Osumi, N., Guo, N., Matsumata, M., *et al*. (2015) Neurogenesis and Sensorimotor Gating: Bridging a Microphenotype and an Endophenotype. *Current Molecular Medicine*, **15**, 129-137. https://doi.org/10.2174/1566524015666150303002834

[105] Mattei, D., Djodari-Irani, A., Hadar, R., *et al*. (2014) Minocycline Rescues Decrease in Neurogenesis, Increase in Microglia Cytokines and Deficits in Sensorimotor Gating in an Animal Model of Schizophrenia. *Brain*, *Behavior*, *and Immunity*, **38**, 175-184. https://doi.org/10.1016/j.bbi.2014.01.019

[106] Kardashev, A., Ratner, Y. and Ritsner, M.S. (2018) Add-On Pregnenolone with L-Theanine to Antipsychotic Therapy Relieves Negative and Anxiety Symptoms of Schizophrenia: An 8-Week, Randomized, Double-Blind, Placebo-Controlled Trial. *Clinical Schizophrenia & Related Psychoses*, **12**, 31-41. https://doi.org/10.3371/CSRP.KARA.070415

[107] Marx, C.E., Bradford, D.W., Hamer, R.M., *et al*. (2011) Pregnenolone as a Novel Therapeutic Candidate in Schizophrenia: Emerging Preclinical and Clinical Evidence. *Neuroscience*, **191**, 78-90. https://doi.org/10.1016/j.neuroscience.2011.06.076

[108] Luo, C., Xu, H. and Li, X.M. (2005) Quetiapine Reverses the Suppression of Hippocampal Neurogenesis Caused by Repeated Restraint Stress. *Brain Research*, **1063**, 32-39. https://doi.org/10.1016/j.brainres.2005.09.043