· 综述 ·

生命早期应激对成年后认知功能的影响及其机制的研究进展

李丹丹　王少朋　赵弘轶　黄勇华
100700 北京，陆军总医院神经内科(李丹丹、赵弘轶、黄勇华)；030001 山西医科大学第二临床医学院(李丹丹)；712046 咸阳，陕西中医药大学第二临床医学院(王少朋)
通信作者：黄勇华，Email：huangyh@163.com
DOI：10.3969/j.issn.1009-6574.2018.03.011

【摘要】 生命早期是人类和啮齿类动物发育中大脑高度敏感的时期。生命早期应激(early life stress，ELS)能持久地影响大脑神经元的发育，进而对成年后认知功能起作用。文章对ELS对成年后相关认知功能的影响及其机制的研究进展进行了综述。大量文献表明，ELS可能是通过调节DNA甲基化、激活下丘脑－垂体－肾上腺皮质(HPA)轴、影响神经营养因子表达、改变脑区结构与功能等机制对成年后个体的认知功能产生影响。与此同时，ELS也能引起成年后焦虑抑郁样精神障碍，这也可导致认知功能的受损。

【关键词】 认知功能；　应激；　生命早期；　综述

[37] Gimenez F, Krauze MT, Valles F, et al. Image-guided convection-enhanced delivery of GDNF protein into monkey putamen[J]. Neuroimage, 2011, 54 Suppl 1: S189-S195. DOI: 10.1016/j.neuroimage.2010.01.023.

[38] Luz M, Mohr E, Fibiger HC. GDNF-induced cerebellar toxicity: A brief review[J]. Neurotoxicology, 2016, 52: 46-56. DOI: 10.1016/j.neuro.2015.10.011.

[39] Herzog CD, Dass B, Holden JE, et al. Striatal delivery of CERE-120, an AAV2 vector encoding human neurturin, enhances activity of the dopaminergic nigrostriatal system in aged monkeys[J]. Mov Disord, 2007, 22(8): 1124-1132. DOI: 10.1002/mds.21503.

[40] Marks WJ, Ostrem JL, Verhagen L, et al. Safety and tolerability of intraputaminal delivery of CERE-120 (adeno-associated virus serotype 2-neurturin) to patients with idiopathic Parkinson's disease: an open-label, phase I trial[J]. Lancet Neurol, 2008, 7(5): 400-408. DOI: 10.1016/S1474-4422(08)70065-6.

[41] Marks WJ, Bartus RT, Siffert J, et al. Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial[J]. Lancet Neurol, 2010, 9(12): 1164-1172. DOI: 10.1016/S1474-4422(10)70254-4.

[42] Hellman M, Arumae U, Yu LY, et al. Mesencephalic astrocyte-derived neurotrophic factor (MANF) has a unique mechanism to rescue apoptotic neurons[J]. J Biol Chem, 2011, 286(4): 2675-2680. DOI: 10.1074/jbc.M110.146738.

[43] Yu YQ, Liu LC, Wang FC, et al. Induction profile of MANF/ARMET by cerebral ischemia and its implication for neuron protection[J]. J Cereb Blood Flow Metab, 2010, 30(1): 79-91. DOI: 10.1038/jcbfm.2009.181.

[44] Chen YC, Sundvik M, Rozov S, et al. MANF regulates dopaminergic neuron development in larval zebrafish[J]. Dev Biol, 2012, 370(2): 237-249. DOI: 10.1016/j.ydbio.2012.07.030.

[45] Barua NU, Bienemann AS, Woolley M, et al. Convection-enhanced delivery of MANF-volume of distribution analysis in porcine putamen and substantia nigra[J]. J Neurol Sci, 2015, 357(1/2): 264-269. DOI: 10.1016/j.jns.2015.08.003.

[46] Luo J, Kaplitt MG, Fitzsimons HL, et al. Subthalamic GAD gene therapy in a Parkinson's disease rat model[J]. Science, 2002, 298(5592): 425-429. DOI: 10.1126/science.1074549.

[47] Kaplitt MG, Feigin A, Tang C, et al. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial[J]. Lancet, 2007, 369(9579): 2097-2105. DOI: 10.1016/S0140-6736(07)60982-9.

[48] Tosi U, Marnell CS, Chang R, et al. Advances in Molecular Imaging of Locally Delivered Targeted Therapeutics for Central Nervous System Tumors[J]. Int J Mol Sci, 2017, 18(2). DOI: 10.3390/ijms18020351.

[49] Fuxe K, Dahlstrom AB, Jonsson G, et al. The discovery of central monoamine neurons gave volume transmission to the wired brain[J]. Prog Neurobiol, 2010, 90(2): 82-100. DOI: 10.1016/j.pneurobio.2009.10.012.

(收稿日期：2018-01-03)
(本文编辑：赵静姝)

Research progress on the effect of early-life stress on cognitive function of adults and its mechanism

Li Dandan, Wang Shaopeng, Zhao Hongyi, Huang Yonghua

Neurology Department, the PLA General Hospital, Beijing 100700, China(Li DD, Zhao HY, Huang YH); The Second Clinical Medical College of Shanxi Medical University, Taiyuan 030001, China(Li DD); The Second Clinical Medical College of Shaanxi University of Chinese Medicine, Xianyang 712046, China(Wang SP)

Corresponding author: Huang Yonghua, Email: huangyh@163.com

【Abstract】 Early life is a highly sensitive period in the development of human and rodent brains. Early life stress (ELS) can take part in the development of neurons in the brain, and affect the cognitive level of adult. This review discusses the effects of ELS on the cognitive function of adults and its possible mechanism. A large number of studies indicate that the effects of ELS on the cognitive function of individual adults is probably through regulating DNA methylation, activating the hypothalamic pituitary adrenal (HPA) axis, changing the expression of neurotrophic factors, altering the structure and function of brain regions, etc. At the same time, ELS can also cause anxiety- and depression-like mental performance in adulthood, which also leads to impaired cognitive function.

【Key words】 Cognitive function; Stress; Early-life; Review

一、生命早期应激的概述

生命早期应激(early life stress, ELS)是指个体在生命早期(包括胚胎期、围出生期、婴幼儿及儿童期、青少年期等)遭遇心理或生理创伤等负性事件时所作出的反应,如儿童期的虐待、遭受家族性创伤事件、重复的母爱剥夺等,能够影响神经系统的发育和早期情感的完善,导致神经行为和后期的神经化学改变,造成成年后多种神经精神疾病的发生[1-2]。近年来,ELS导致的成年后个体的认知功能障碍被广泛关注。临床研究表明,ELS能持续损害儿童的认知和情感功能直到成年[2-3],导致成年后出现认知功能障碍[4]。动物模型也证实,ELS可能会对成年后认知能力永久性影响[5]。

二、ELS对成年后认知功能的影响

1.对学习记忆相关认知功能:大量动物实验证实,出生后重复的母子分离能够使得大鼠成年后在学习记忆相关的动物实验中,相对于健康成年大鼠表现较差[6-7]。Tata等[8]将每窝新生Wistar大鼠在出生后随机分配到3个饲养条件:没有母子分离(NMS, n=25), 15 min的母子分离(MS 15 min, n=16), 和180 min的母子分离(MS 180 min, n=19)。在3月龄的时候,对3组大鼠进行Morris水迷宫试验测试。结果发现,在空间学习和空间参考记忆方面,相比MS 15 min和NMS组,MS 180 min动物显示延迟情况更明显($P<0.01$),而NMS和MS 15 min两组间差异无统计学意义($P>0.05$);3组在空间工作记忆方面差异无统计学意义($P>0.05$)。其数据没有显示出短暂的母子分离(MS 15 min)对学习和记忆的影响。由此可知,早期重复母子分离能够影响大鼠在成年后学习记忆相关的认知功能,并且分离时间越长,这种影响可能会越严重。

2.对执行能力相关认知功能:临床研究也表明,那些经历过ELS的人群,例如那些儿童期经历过虐待或家族性创伤的人相比于健康人群,表现出过度的冒险行为、对不同结果的不敏感以及较慢的决策力等[9],并在相关的测试任务中表现更差,如工作记忆、自控力、注意力、制定规划和处理速度等方面[10]。DePrince等[11]曾招募114名学龄儿童(平均10.39岁)参加为期两个学期的压力和注意力的研究,并通过对这些儿童潜在的创伤性事件的家长报告将他们分为3个组:家族性创伤组、非家族性创伤组和无创伤组,并让他们完成儿童韦氏儿童智力量表第四版(WISC-IV)、戈登诊断系统(GDS)及斯特鲁普(Stroop)任务来评估他们的工作记忆、行为抑制、加工速度、听觉注意和干扰控制等能力。结果显示,相对于非家族性创伤组和无创伤组,家族性创伤组在执行功能相关的(包括工作记忆、抑制、听觉注意和处理速度)任务中表现更差($P<0.01$)。Hanson等[12]从某一社区随机招募61名儿童[男32名,女29名,平均年龄(142.35 ± 21.12)个月]进行了青年生活压力面试(YLSI)评定和MRI扫描,运用剑桥自动化成套神经心理测试(CANTAB)中的空间工作记忆测试来检查孩子们的执行功能,结果显示:被试者的生活压力与执行功能之间显著相关(P=0.002)。

此外,越是严重的ELS,如儿童期虐待,成年后在工作记忆方面缺陷越明显[13]。Fuge等[14]曾对451名年龄为18~90岁的受试者进行工作记忆方面的任务测试,结果显示:ELS的经历对任务的准确性有显著的影响(P=0.001), ELS严重程度为中度者较轻度者任务评分更差(P=0.03),提示所经历ELS的严重程度可能与个体成年后的认知损害严重程度相关。

ELS对记忆力造成的损害,可能在年轻时表现

较轻，易被忽视，但随年龄增长可能会加重[15]。而有文献证实，相对丰富的早期生活经历已被证明可以改善学习和记忆[16]，并且丰富多样的成长环境也可以部分逆转ELS对学习记忆的损害[17-19]。不过，ELS对成年后认知功能的影响仍应该被重视。

三、ELS通过改变个体的情感、情绪等影响认知功能

大量研究表明，早期生活压力事件可能诱导人和动物在成年期的出现一些病理状态，包括焦虑症、抑郁症和精神分裂症[20-22]，进而影响成年后的相关认知功能。

Monroy等[23]将新生雄性SD大鼠在出生后1～12 d每天母子分离4 h，在成年后进行大鼠自发性行为测试及脑组织切片微观观察，结果发现母子分离的大鼠自发活动明显低于对照组大鼠（$P<0.05$），并且其前额叶皮层（PFC）、腹侧海马CA1区、伏隔核（NACC）的神经元树突长度、树突棘密度和数量较对照组也明显减少（$P<0.01$），而这些都是影响情感、情绪的重要脑区。Li等[24]也利用母子分离这一模型，对成年大鼠进行了高架十字迷宫行为学测试、前脉冲抑制（PPI）测试及多巴胺和血清素的活动检测，证实了重复的母子分离破坏多巴胺和血清素的活动，使个体产生持续增加的焦虑样行为，兴趣低落，降低其探索新鲜事物的运动反应，进而导致成年后空间学习和记忆能力受损。

赵弘轶等[20]曾招募40例患有抑郁症的年轻成人并做了CT扫描，根据中文版的童年创伤问卷（CTQ）、HAMD-17和神经精神量表（NPI）测试结果，将受试者分为两组：抑郁症患者有ELS经历组（E+D组）与抑郁症患者没有ELS经历组（E–D组），通过比较两组HAMD评分、NPI评分、CTQ子分数及第三脑室的宽度和体积，发现ELS可能导致第三脑室增大，并认为这可能会是ELS导致成年后抑郁症的病因。

由此可见，ELS能诱导个体出现成年后焦虑或抑郁样等的精神表现，并进一步影响其成年后的学习、记忆等的相关认知功能。

四、ELS影响认知功能的机制

ELS对认知功能的损害，可能与激活下丘脑–垂体–肾上腺皮质（hypothalamic pituitary adrenal，HPA）轴、造成海马等脑区结构的永久性损伤、影响神经营养因子的表达、干预大脑神经元[25-26]和突触可塑性的发育[27]，或者改变应激相关基因的表观遗传编程有关，并通过以上机制，导致了成年后个体的相关认知功能的损害。

1.通过激活HPA轴产生作用：HPA轴是神经内分泌系统的重要部分，参与调节机体对各类应激的反应。许多研究表明，ELS能够激活HPA轴，释放一连串的神经递质、激素和其他化学物质，诱导机体的行为和代谢的变化，其中最主要也是最重要的是糖皮质激素（glucocorticoid，GC）[28-29]。GC通过糖皮质激素受体（glucocorticoid receptor，GR）在几个关键的大脑区域如垂体、下丘脑、海马和PFC等通过负反馈作用调节HPA轴的活性[30]。在成人，当压力去除后，其相应的影响会消散；然而，在生命早期，这种压力的影响的持久性远远超出应激期[31]。

2.通过改变神经营养因子的表达产生作用：ELS也可能改变神经营养因子如脑源性神经营养因子（BDNF）的表达水平，进而影响脑内神经元的发育成熟，造成成年后认知功能的损害。动物实验证实，出生后早期重复母子分离可以引起大鼠3个不同时期即幼年、青少年和成年大鼠前脑的BDNF表达发生变化，同时揭示不同脑区BDNF的表达随年龄的变化而变化[32-33]。Wang等[34]将新生Wistar大鼠幼崽随机分成MS和NMS组，MS组的幼崽在出生后第1～21天每天与母鼠分离4 h，NMS作为对照不处理，分别在出生后第21、35、56天取材切片进行BDNF抗体染色观察。通过计数BDNF阳性细胞来估计内侧前额叶皮质区（mPFC）、伏隔核和海马CA1-3及DG区的BDNF表达水平。结果表明，在mPFC和海马CA1及DG区，出生后早期母子分离对BDNF蛋白的表达均有显著影响（$P<0.05$）。

3.通过改变关键脑区的结构产生作用：作为大脑边缘系统的重要组成部分，海马是学习记忆等相关认知功能的关键脑区[35]，并且很容易受到各种危险因素伤害[36]。动物实验证实，持续的母爱剥夺，将会导致海马CA1、CA3区锥体细胞的树突萎缩、苔藓纤维发芽及突触可塑性缺陷出现，进一步出现海马功能的显著下降[37]，影响学习记忆等相关的认知功能[36, 38]。相应地，执行力相关的认知功能也涉及多个特定脑区[39-40]，包括背外侧前额叶皮质（DLPFC）、mPFC和前扣带回（ACC）等，而重复母子分离导致的PFC神经元树突长度、树突棘密度和数量减少[23]也已经在动物实验中证实。同时，ELS会导致海马和杏仁核体积减小[41]，这些区域不仅对记忆至关重要，在传递环境信息中也起着很重要的作用[42]。

4.通过DNA甲基化产生作用：ELS对大脑活动和行为造成持久影响的机制，可能是通过改变基因表达[43]，如DNA去甲基化。例如，儿童期虐待可能

与FKBP5(FK506 binding protein 51)基因甲基化有关，Zannas和Binder[44]认为FKBP5是GR活性的重要调节器，它可以结合Hsp90、P23蛋白等促使受体复合物具有皮质醇低亲和力，进一步降低GR活性，促进GRβ-异构体的非核转位信号，影响GC的亲免蛋白核转位和GR的转录活性，故而认为FKBP5对GR活性起抑制作用。在非人类的动物，长期高浓度的接触GC也会影响PFC的结构和功能的发展[45]。

五、小结

综上所述，ELS能够通过调节DNA甲基化、激活HPA轴、改变神经营养因子表达、改变脑区结构和改变大脑功能等多种机制，或者通过引起焦虑、抑郁样精神障碍，影响个体成年后的认知功能。然而，ELS作为一种特殊的应激，其对成年后认知功能产生的影响及其相应的分子机制是十分复杂的，还需要进一步进行临床研究和动物实验加以完善，以揭秘ELS与成年后认知障碍的关系，指导和规范相关的预防措施和治疗方法。

利益冲突 文章所有作者共同认可文章无相关利益冲突

作者贡献声明 论文撰写为李丹丹、王少朋、赵弘轶，论文审校为黄勇华

参 考 文 献

[1] 王兴兴，王晓东.早年应激影响成年海马神经元再生的机制[J].心理科学进展，2017，25(12)：2030-2035. DOI：10.3724/SP.J.1042.2017.02030.
Wang XX, Wang XD. The mechanisms for the effects of early-life stress on adult hippocampal neurogenesis[J]. Advances in Psychological Science, 2017, 25(12): 2030-2035.

[2] Gershon A, Sudheimer K, Tirouvanziam R, et al. The long-term impact of early adversity on late-life psychiatric disorders[J]. Curr Psychiatry Rep, 2013, 15(4): 352. DOI: 10.1007/s11920-013-0352-9.

[3] Pesonen AK, Eriksson JG, Heinonen K, et al. Cognitive ability and decline after early life stress exposure[J]. Neurobiol Aging, 2013, 34(6): 1674-1679. DOI: 10.1016/j.neurobiolaging.2012.12.012.

[4] Kaplan Z, Iancu I, Bodner E. A review of psychological debriefing after extreme stress[J]. Psychiatr Serv, 2001, 52(6): 824-827. DOI: 10.1176/appi.ps.52.6.824.

[5] Pardon MC, Rattray I. What do we know about the long-term consequences of stress on ageing and the progression of age-related neurodegenerative disorders?[J]. Neurosci Biobehav Rev, 2008, 32(6): 1103-1120. DOI: 10.1016/j.neubiorev.2008.03.005.

[6] Thomas AW, Caporale N, Wu C, et al. Early maternal separation impacts cognitive flexibility at the age of first independence in mice[J]. Dev Cogn Neurosci, 2016, 18: 49-56. DOI: 10.1016/j.dcn.2015.09.005.

[7] 何静，王高华.早期母婴分离对大鼠成年后再应激及海马神经可塑性的影响[J].神经疾病与精神卫生，2017，17(11)：765-768. DOI：10.3969/j.issn.1009-6574.2017.11.002.
He J, Wang GH. Long term effects of early maternal deprivation on adult rats exposed to chronic unpredictable mild[J]. Journal of Neuroscience and Mental Health, 2017, 17(11): 765-768.

[8] Tata DA, Markostamou I, Ioannidis A, et al. Effects of maternal separation on behavior and brain damage in adult rats exposed to neonatal hypoxia-ischemia[J]. Behav Brain Res, 2015, 280(280): 51-61. DOI: 10.1016/j.bbr.2014.11.033.

[9] Weller JA, Fisher PA. Decision-making deficits among maltreated children[J]. Child Maltreat, 2013, 18(3): 184-194. DOI: 10.1177/1077559512467846.

[10] Pollak SD. Multilevel developmental approaches to understanding the effects of child maltreatment: Recent advances and future challenges[J]. Dev Psychopathol, 2015, 27(4 Pt 2): 1387-1397. DOI: 10.1017/S0954579415000826.

[11] DePrince AP, Weinzierl KM, Combs MD. Executive function performance and trauma exposure in a community sample of children[J]. Child Abuse Negl, 2009, 33(6): 353-361. DOI: 10.1016/j.chiabu.2008.08.002.

[12] Hanson JL, Chung MK, Avants BB, et al. Structural variations in prefrontal cortex mediate the relationship between early childhood stress and spatial working memory[J]. J Neurosci, 2012, 32(23): 7917-7925. DOI: 10.1523/JNEUROSCI.0307-12.2012.

[13] Cowell RA, Cicchetti D, Rogosch FA, et al. Childhood maltreatment and its effect on neurocognitive functioning: Timing and chronicity matter[J]. Dev Psychopathol, 2015, 27(2): 521-533. DOI: 10.1017/S0954579415000139.

[14] Fuge P, Aust S, Fan Y, et al. Interaction of early life stress and corticotropin-releasing hormone receptor gene: effects on working memory[J]. Biol Psychiatry, 2014, 76(11): 888-894. DOI: 10.1016/j.biopsych.2014.04.016.

[15] Brunson KL, Kramár E, Lin B, et al. Mechanisms of late-onset cognitive decline after early-life stress[J]. J Neurosci, 2005, 25(41): 9328-9338. DOI: 10.1523/JNEUROSCI.2281-05.2005.

[16] Fenoglio KA, Brunson KL, Avishai-Eliner S, et al. Enduring, handling-evoked enhancement of hippocampal memory function and glucocorticoid receptor expression involves activation of the corticotropin-releasing factor type 1 receptor[J]. Endocrinology, 2005, 146(9): 4090-4096. DOI: 10.1210/en.2004-1285.

[17] Hilal ML, Moreau MM, Racca C, et al. Activity-Dependent Neuroplasticity Induced by an Enriched Environment Reverses Cognitive Deficits in Scribble Deficient Mouse[J]. Cereb Cortex, 2017, 27(12): 5635-5651. DOI: 10.1093/cercor/bhw333.

[18] Madhavadas S, Subramanian S, Kutty BM. Environmental enrichment improved cognitive deficits more in peri-adolescent than in adult rats after postnatal monosodium glutamate treatment[J]. Physiol Int, 2017, 104(4): 271-290. DOI: 10.1556/2060.104.2017.4.7.

[19] Murueta-Goyena A, Ortuzar N, Gargiulo PÁ, et al. Short-Term Exposure to Enriched Environment in Adult Rats Restores MK-801-Induced Cognitive Deficits and GABAergic Interneuron Immunoreactivity Loss[J]. Mol Neurobiol, 2018, 55(1): 26-41. DOI: 10.1007/s12035-017-0715-z.

[20] Zhao H, Wei T, Li X, et al. Early life adversity induced third ventricular enlargement in young adult male patients suffered from major depressive disorder: A study of brain morphology[J].

Folia Morphol (Warsz), 2017. DOI: 10.5603/FM.a2017.0113.

[21] Gordon JA, Dzirasa K. Animal models of psychiatric disorders[J]. Neuroscience, 2016, 321: 1-2. DOI: 10.1016/j.neuroscience.2016.02.004.

[22] 王学义, 张本, 马文有, 等. 唐山大地震对母孕期胎儿情绪障碍的远期研究[J]. 中国健康心理学杂志, 2005, 13(1): 31-32. DOI: 10.3969/j.issn.1005-1252.2005.01.013.
Wang XY, Zhang B, Ma WY, et al. Affective Disorder in Offspring Exposed Prenatally to a Severe Earthquake[J]. Chinese Journal of Health Psychology, 2005, 13(1): 31-32.

[23] Monroy E, Hernández-Torres E, Flores G. Maternal separation disrupts dendritic morphology of neurons in prefrontal cortex, hippocampus, and nucleus accumbens in male rat offspring [J]. J Chem Neuroanat, 2010, 40(2): 93-101. DOI: 10.1016/j.jchemneu.2010.05.005.

[24] Li M, Xue X, Shao S, et al. Cognitive, emotional and neurochemical effects of repeated maternal separation in adolescent rats[J]. Brain Res, 2013, 1518(26): 82-90. DOI: 10.1016/j.brainres.2013.04.026.

[25] Korosi A, Naninck EF, Oomen CA, et al. Early-life stress mediated modulation of adult neurogenesis and behavior[J]. Behav Brain Res, 2012, 227(2): 400-409. DOI: 10.1016/j.bbr.2011.07.037.

[26] 孙菲菲, 王冉, 王学义. 早年应激所致认知障碍与促肾上腺皮质激素释放激素受体 1 型的相关性研究进展[J]. 神经疾病与精神卫生, 2017, 17(11): 788-790. DOI: 10.3969/j.issn.1009-6574.2017.11.007.
Sun FF, Wang R, Wang XY. Advances in the relationship between cognitive impairment induced by stress and corticotropin releasing hormone receptor type 1 [J]. Journal of Neuroscience and Mental Health, 2017, 17(11): 788-790.

[27] Aisa B, Elizalde N, Tordera R, et al. Effects of neonatal stress on markers of synaptic plasticity in the hippocampus: implications for spatial memory [J]. Hippocampus, 2009, 19 (12): 1222-1231. DOI: 10.1002/hipo.20586.

[28] van Bodegom M, Homberg JR, Henckens Marloes JAG. Modulation of the Hypothalamic-Pituitary-Adrenal Axis by Early Life Stress Exposure [J]. Front Cell Neurosci, 2017, 11: 87. DOI: 10.3389/fncel.2017.00087.

[29] Silberman DM, Acosta GB, Zorrilla Zubilete MA. Long-term effects of early life stress exposure: Role of epigenetic mechanisms[J]. Pharmacol Res, 2016, 109: 64-73. DOI: 10.1016/j.phrs.2015.12.033.

[30] de Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease[J]. Nat Rev Neurosci, 2005, 6(6): 463-475. DOI: 10.1038/nrn1683.

[31] Lajud N, Torner L. Early life stress and hippocampal neurogenesis in the neonate: sexual dimorphism, long term consequences and possible mediators[J]. Front Mol Neurosci, 2015, 8: 3. DOI: 10.3389/fnmol.2015.00003.

[32] Roceri M, Cirulli F, Pessina C, et al. Postnatal repeated maternal deprivation produces age-dependent changes of brain-derived neurotrophic factor expression in selected rat brain regions[J]. Biol Psychiatry, 2004, 55(7): 708-714. DOI: 10.1016/j.biopsych.2003.12.011.

[33] Kuma H, Miki T, Matsumoto Y, et al. Early maternal deprivation induces alterations in brain-derived neurotrophic factor expression in the developing rat hippocampus [J]. Neurosci Lett, 2004, 372(1/2): 68-73. DOI: 10.1016/j.neulet.2004.09.012.

[34] Wang Q, Shao F, Wang W. Maternal separation produces alterations of forebrain brain-derived neurotrophic factor expression in differently aged rats[J]. Front Mol Neurosci, 2015, 8: 49. DOI: 10.3389/fnmol.2015.00049.

[35] Hollup SA, Kjelstrup KG, Hoff J, et al. Impaired recognition of the goal location during spatial navigation in rats with hippocampal lesions[J]. J Neurosci, 2001, 21(12): 4505-4513.

[36] Kim JJ, Diamond DM. The stressed hippocampus, synaptic plasticity and lost memories[J]. Nat Rev Neurosci, 2002, 3(6): 453-462. DOI: 10.1038/nrn849.

[37] Huot RL, Plotsky PM, Lenox RH, et al. Neonatal maternal separation reduces hippocampal mossy fiber density in adult Long Evans rats[J]. Brain Res, 2002, 950(1/2): 52-63.

[38] Alfarez DN, Joëls M, Krugers HJ. Chronic unpredictable stress impairs long-term potentiation in rat hippocampal CA1 area and dentate gyrus in vitro[J]. Eur J Neurosci, 2003, 17(9): 1928-1934.

[39] Menon V, Adleman NE, White CD, et al. Error-related brain activation during a Go/NoGo response inhibition task[J]. Hum Brain Mapp, 2001, 12(3): 131-143.

[40] 高媛媛, 王育梅, 赵晓川, 等. 孕期经历地震应激对成年子代执行及记忆功能的影响[J]. 中国神经精神疾病杂志, 2016, 42(5): 277-281. DOI: 10.3969/j.issn.1002-0152.2016.05.005.
Gao YY, Wang YM, Zhao XC, et al. Effects of executive and memory function of fetus with earthquake stress[J]. Chin J Nerv Ment Dis, 2016, 42(5): 277-281.

[41] Hodel AS, Hunt RH, Cowell RA, et al. Duration of early adversity and structural brain development in post-institutionalized adolescents[J]. Neuroimage, 2015, 105: 112-119. DOI: 10.1016/j.neuroimage.2014.10.020.

[42] Bick J, Nelson CA. Early Adverse Experiences and the Developing Brain[J]. Neuropsychopharmacology, 2016, 41(1): 177-196. DOI: 10.1038/npp.2015.252.

[43] Zannas AS, Wiechmann T, Gassen NC, et al. Gene-Stress-Epigenetic Regulation of FKBP5: Clinical and Translational Implications[J]. Neuropsychopharmacology, 2016, 41(1): 261-274. DOI: 10.1038/npp.2015.235.

[44] Zannas AS, Binder EB. Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism [J]. Genes Brain Behav, 2014, 13(1): 25-37. DOI: 10.1111/gbb.12104.

[45] Belanoff JK, Gross K, Yager A, et al. Corticosteroids and cognition[J]. J Psychiatr Res, 2001, 35(3): 127.

(收稿日期: 2018-01-17)
(本文编辑: 赵静姝)