**Name of Journal: *World Journal of Psychiatry***

**ESPS Manuscript NO: 27320**

**Manuscript Type: Review**

**Gene environment interaction in periphery and brain converge to modulate behavioral outcomes: Insights from the SP1 transient early in life interference rat model**

Asor E *et al.* Sp1 model

**Eyal Asor, Dorit Ben-Shachar**

**Eyal Asor, Dorit Ben-Shachar,** Laboratory of Psychobiology, Department of Psychiatry, Rambam Medical Center and B. Rappaport Faculty of Medicine, Rappaport Family Institute for Research in the Medical Sciences, Haifa 31096, Israel

**Author contributions:** Both authors contributed equally to the writing of this review paper.

**Conflict-of-interest statement**: Authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to:** **Dorit Ben-Shachar, Professor,** Laboratory of Psychobiology, Department of Psychiatry, Rambam Medical Center and B. Rappaport Faculty of Medicine, Rappaport Family Institute for Research in the Medical Sciences, Technion, PO Box 9649, Haifa 31096, Israel. shachar@tx.technion.ac.il

**Telephone:** +972-4-8295224

**Fax:** +972-4-8295220

**Received:** May 23, 2016

**Peer-review started:** May 25, 2016

**First decision:** July 6, 2016

**Revised:** July 27, 2016

**Accepted:** August 6, 2016

**Article in press:**

**Published online:**

**Abstract**

It is generally assumed that behavior results from an interaction between susceptible genes and environmental stimuli during critical life stages. The present article reviews the main theoretical and practical concepts in the research of gene environment interaction, emphasizing the need for models simulating real life complexity. We review a novel approach to study gene environment interaction in which a brief post-natal interference with the expression of multiple genes, by hindering the activity of the ubiquitous transcription factor specificity protein 1 (Sp1) is followed by later-in-life exposure of rats to stress. Finally, this review discusses the role of peripheral processes in behavioral responses, with the Sp1 model as one example demonstrating how specific behavioral patterns are linked to modulations in both peripheral and central physiological processes. We suggest that models, which take into account the tripartite reciprocal interaction between the central nervous system, peripheral systems and environmental stimuli will advance our understanding of the complexity of behavior.

**Key words**: Gene-environmental interaction; Specificity protein 1; Mithramycin; Stress; Animal-model; Essential amino acids; Tryptophan; Insulin

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** We review the main theoretical and practical concepts in the research of gene environment interaction. We present a novel approach to study gene environment interaction in which a brief post-natal interference with the expression of multiple genes by inhibiting the activity of the ubiquitous transcription factor specificity protein 1 is followed by later-in-life exposure of rats to stress. Finally, we discuss the role of peripheral processes in behavioral responses, demonstrating how specific behavioral patterns are linked to modulations in interwoven brain and body physiological processes due to gene and environmental changes.

Asor E, Ben-Shachar D. Gene environment interaction in periphery and brain converge to modulate behavioral outcomes: Insights from the SP1 transient early in life interference rat model. *World J Psychiatr* 2016; In press

**INTRODUCTION**

The role of nature versus nurture in shaping complex behavior and in mental disorders is a matter of long running dispute and creates a split between psychobiology, which emphasizes the dominancy of the being's innate predispositions and psychotherapy supporters, which point out the surrounding influence. Evidence from decades of heredity research has suggested that complex behaviors and psychiatric disorders have a solid genetic basis[1,2]. It has been reported by many studies that consistent differences in behavioral traits between subjects, such as stress responsivity and temperament, show a familial pattern[3]. On the other hand, the impact of environmental factors on physical illness is well established[4,5] and well recognized in behavioral disturbance[6,7]. Numerous studies reported a correlation between candidate genes, and behavioral phenotype[8,9], yet with significantly lower rate of replication and a clear tendency toward positive results[10]. Environmental aspects are formulated in the vast psychoanalytical literature and in models that use a scientific platform, such as the impact of different nursing abilities of female rats, on stress responsivity of their pups[11]. Environmental physical factors such as intrauterine inflammatory reaction induced by Lipopolysaccharide, which simulates the impact of prenatal infection on behavior[12,13] were studied as well.

The stress diathesis theory, which suggests that disorders induced by the combination of varying degrees of predisposition with invers degrees of stressful stimuli, has become an accepted conceptual research framework for studying complex behaviors. Following this hypothesis numerous studies over the last decade assessed the relationship between candidate genes and behavior in the form of genome-wide association studies (GWAS)[14], most of them focusing on the pathologic consequences of genetic alteration. Despite the remarkable advances in genetic tools and techniques, very few direct genetic effects on mental health have been identified and replicated[10].

An alternative paradigm to the stress diathesis theory is the differential susceptibility theory, which assumes that individuals react differently to environmental stimulus depending on the plasticity of gene rather than their susceptibility. Thus showing higher responsiveness to both positive and negative external cues, frequently with opposing outcomes[15,16]. For example, high frequency of antisocial behavior was correlated with childhood maltreatment the in low activity MAO-A allele carriers[17]. Interestingly, low activity MAO-A allele carriers, who were not exposed to childhood maltreatment showed the lowest anti-social behavior scores compared with normal activity MAO-A carriers[16]. An additional extensively studied genetic variant in psychiatry is the short allelic form of the serotonin transporter-linked polymorphic region (5-HTTLPR), which is associated with a reduction in the transporter activity[18] and with high risk for major depression in individuals exposed to stressful life events[19]. Yet, 5HTT s-allele carriers were shown to be more responsive to the Attention Bias Modification training than long-allele carriers, supporting Belsky’s hypothesis that the s-allele may be considered as a plasticity gene rather than a susceptible gene[20]. Taken together, these examples support the differential responsiveness theory of sensitive genes in the etiology of complex behaviors[16].

Unfortunately, the current gene environment interaction models have substantial limitations, ranging from weak validation to poor predictive power and although genome studies have expanded our understanding of complex phenotypes and many human diseases, they hardly explain a small proportion of their heritability in the population[21]. Genetic variants are usually considered as having additive, suppressive or neutral effects on the phenotype, but the effect size for a single genetic variant is minor[22]. A more comprehensive model of real life interaction between multiple genes that influence the expression of each other and thereby the manifestation of a particular phenotype, is needed.

One possible gate for modelling real life gene environment interaction are through manipulation of key point genes, genes that are essential for the modulation of multiple genes’ activity, such as the ubiquitous transcription factor specificity protein 1 (Sp1). Sp1 is a member of the SP proteins family, which constitutes a group of highly conserved transcription factors present in a wide range of organisms. Their structure is defined by the presence of three highly conserved DNA-binding zinc finger domains which bind to similar, yet distinct, GC-rich target sequences. Members of the SP family function either as activators or repressors in cell *via* a promoter-dependent manner[23]. Sp1 is essential for the regulation of various physiological functions, maintains organ homeostasis, regulates tissue repair, and possibly serves as an anti-inflammatory mechanism that protects against organ inflammation and injury[24]. Sp1 regulates the expression of numerous genes in early developmental stages[25] and the expression of most growth factors and their receptors depend on Sp1[26–28]. Sp1 activity can be modulated by various environment-dependent factors including metabolic factors such as glucose and insulin, immunologic factors such as tumor necrosis factor-alpha (TNF-a), glucocorticoid receptors and several major kinases including CDK2 and ERK1/2[29-32]. Sp1 also modulates the expression of many genes implicated in psychiatry research, including neuregulin-1[33], reelin[34], GAD67[35], MAO A and B[36,37], NMDA receptor subunits (NR1 and NR2)[38,39], GABA A receptor[40], DA receptors[41] and genes of the oxidative phosphorylation system (OXPHOS)[42]. In this article we will describe how simulating real life by minor manipulation of multiple gene expression, based on Sp1 unique characteristics, models more accurately gene environment interaction in behavioral sciences.

**SP1 IN SCHIZOPHRENIA AND OTHER NEUROPSYCHIATRIC DISORDERS**

The alterations in different genetic trajectories in schizophrenia reported by numerous studies[43], can result from transcriptional dysregulation in the disorder[44]. Our group showed that the expression of Sp1 is disrupted in brain samples and peripheral blood lymphocytes of schizophrenia patients as compared with those of healthy subjects. Specifically, downregulation in Sp1 mRNA expression was prominent in the prefrontal cortex and the striatum, while upregulation was observed in the parieto-occipital cortex and in blood lymphocytes of schizophrenic patients. Sp1 levels were highly and significantly correlated with two subunits (NDUFV2 and NDUFV1) of the first complex of the OXPHOS in lymphocytes and brain specimens of normal subjects, while abolished in schizophrenic patients[45]. We have shown that Sp1 is a transcription factor of both subunits, which have been repeatedly implicated in schizophrenia[46,47]. A defect in Sp1 transcriptional activity, which leads to abnormal expression of complex I subunits, can be one of the causes for reduced complex I activity associated with mitochondrial dysfunction and reduced energy metabolism observed in schizophrenia brains by numerous imaging studies[48]. Such distortion in brain energy production can affect synaptic plasticity and connectivity of neuronal networks and thereby cognitive and emotional behaviors[49]. Additional studies by other groups substantiated the role of Sp1 in mental and neurological disorders by showing a reduction of Sp1 protein and mRNA in the postmortem prefrontal cortex brain of chronic schizophrenia patients[50], increased Sp1 mRNA levels in the hippocampus[51] and a reduction in Sp1 and Sp4 protein levels in lymphocytes of first-episode psychosis patient[52]. These reports are in line with other studies demonstrating arole of Sp1 in the regulation of many genes associated with neuropsychiatric psychiatric disorders. Thus, elevation in Sp1 protein levels was observed in autistic brains, which was associated with altered expression of autism candidate genes such as OXTR and PTEN[53]. Sp1 mRNA and protein was also found to be up-regulated in Alzheimer’s disease (AD) brains and in a transgenic mice model of the disease[54]. In Huntington disease, Sp1-regulated huntingtin transcription is dysregulated. In adrenal medulla-derived PC12 cell cultures it was shown that Sp1 is involve in the regulation of epinephrine biosynthesis in response to acute and chronic stress[55]. The, dual characteristic of Sp1, having specific environmental and internal signal regulated transcriptional activities, together with its role in the regulation of multiple genes, coincide with the multi-gene alteration and the heterogeneous symptomatology of mental disorders.

**SP1 MANIPULATION MODELS**

Complete inhibition of Sp1 is incompatible with life and Sp1 knockout mice die in utero with multiple phenotypic aberrations[56]. However, Sp1 transcriptional activity can be inhibited by Mithramycin (MTR)[57]. MTR is an antineoplastic antibiotic, which binds to GC-rich regions on the DNA displacing the Sp family transcription proteins from their binding sites[58]. MTR is a clinically approved antibiotic that is effective for the treatment many cancers such as testicular cancer[59] and also for cancer induced hypercalcemia[60]. Our group has reported that MTR induced a time dependent decrease in the expression levels of complex I subunits NDUFV1, NDUFV2 and NDUFS1, as well as of reelin, all regulated by Sp1 and implicated in schizophrenia[45]. The availability of a simple pharmacologic agent that modulates the transcription of different genes, turns it into an attractive tool for modelling multiple gene dysregulation. Indeed, neonatal rats treated for a few days (7-10 postnatal days) with MTR, showed 3 mo later cognitive and behavioral deficits such as spatial working memory impairment and anxious behavior, without any impact on their bodily well-being[61]. The effect of MTR treatment was also studied in AD experimental models. Thus, MTR injections to AD transgenic adult mice for several months, resulted in greater memory impairment in these mice and increased amyloid β peptide levels[62], with no additional behavioral differences. These data suggest that manipulation of Sp1 transcriptional activity at adulthood has long lasting effects on behavior depending on predisposing genetic aberration earlier in life. In contrast to these results chronic MTR administration to AD transgenic mice by another group resulted in cognitive improvement[63], emphasizing the need for better understanding the role of Sp1 transcriptional activity in the pathophysiology of AD. In a mouse model for Huntington disease chronic MTR treatment from PND 20 throughout life extended survival, enhanced motor performance, and improved brain histopathology[64]. The neuroprotective effect of MTR was also demonstrated in adult rats exposed to repeated administration of methamphetamine[65], an accepted model for schizophrenia[66].

**STRESS EXPOSURE MODEL**

Studying the additive effect of environmental variables on top of the predisposing susceptibility is complex and may have many bias pitfalls. Stress is commonly used to mimic environmental insults in models of mental disorders and complex behaviors. We have used peripubertal mild unpredictable stress protocol. One major parameter in modeling environmental effects is the timing of exposure to insult. However, timing and duration of exposure to stress differ between studies. There are early in-life stress models, mainly maternal separation, which increase stress reactivity in the offspring[67], while there are adult stress models, including the unpredictable chronic mild stress model, which differ in chronicity, protocol elements and actual age of stress exposure, adolescence or adulthood[68–70]. Both prenatal period and postnatal mid to late adolescence were shown to be particularly vulnerable to stress in rats[61]. Chronic adolescence stress was repeatedly shown to be associated with HPA dysfunction[71], hippocampal volume reduction and impairments in spatial learning[72] later in life. To elaborate our view on the impact of environment we compared two stress regimens differing only in duration, chronic and sub-chronic regimens, in adolescence. Interestingly, high serum corticosterone levels and higher anxiety index were related to the sub-chronic stress regimen, while rats exposed to chronic stress did not differ significantly from the controls, which implies adaptation to stress[61]. Although chronic mild stress is an accepted paradigm for induction of depressive-like symptoms in rats[73], several studies show resilience effects of long-term stress[74,75] which is in line with the adaptation to the chronic stress regimen.

**MANIPULATION OF GENE EXPRESSION AND THE ENVIRONMENT**

Studies modeling genetic predisposition for behavioral alterations, induce predisposition in one or more of the four following paradigms: Manipulation of a candidate gene, interference with a candidate system/pathway, intrauterine insults or exposure to early post-natal stressors that induce epigenetic changes.

Numerous studies using candidate gene knockout mice and chronic stress were published. Candidate system interference studies mostly involve HPA axis manipulation either pharmacologically by glucocorticoids administration[76] or induced by early life stress[77]. Examples for intrauterine insult models include the prenatal protein malnutrition, which affects development of the brain in utero and induces cognitive impairment and severe widespread morphological abnormalities similar to schizophrenia[78,79]. Other models are based on the intrauterine infection theory for schizophrenia[80]. These models include prenatal exposure of mice to viruses, such as the influenza virus[81] which cause brain developmental damages similar to those observed in schizophrenia brain, or maternal immune activation by lipopolysaccharide or polyinosinic:polycytidylic acid (Poly I:C) during pregnancy, which model schizophrenia and autism in the offspring[82,83]. The best studied model for epigenetic changes induced by early life stressors is the maternal separation model, which enhances behavioral changes[84,85], and causes epigenetic modifications that can be transmitted through generations[11]. We hypothesize that a transient interference with the expression of many various genes, by MTR for example, at a critical developmental stage of the brain together with an exposure of the animal to stressful environment later in life, will provide an animal model to study the role of gene environment interaction in long lasting complex behavior relevant to mental disorders. Although it may be argued that modification of the expression of numerus genes is inaccurate and difficult to monitor, we believe that it is a closer model to real life complexity. Indeed, we found that MTR treated rats exposed to sub-chronic stress demonstrated higher anxiety index, anhedonia and indifference to novel objects. However, MTR treated rats exposed to the chronic stress paradigm demonstrated normal sucrose preference, low anxiety index and high novelty seeking behavior. These findings support the differential sensitivity theory, claiming increased reactivity to environmental stimuli in genetically sensitive individuals, with differential responses to various stimuli[16].

**INTERTWINED PERIPHERAL AND BRAIN INTERACTION**

The molecular and biochemical pathways that contribute to behavioral phenotypes are still a mystery and it is almost impossible to differentiate between genetic and environmental impacts. The currently common dominate hypothesis is that changes in brain cellular pathways are responsible for alterations in behavioral responses. We and others suggest that peripheral factors are essential for formulating behavioral responses. In our rat model for example, we showed that exposing MTR treated rats to chronic stress (MTR + stress) caused a significant reduction in tryptophan brain levels, which in part stems from peripheral changes. Alteration in peripheral tryptophan levels was found to be associated with behavioral and cognitive phenotypes. For example, aggression tendencies associated with a low serum tryptophan levels[86] and impulsivity[87] was observed in the course of manic episodes[88], while increased serum tryptophan levels were observed during the recovery periods in bipolar manic patients[89]. Tryptophan depletion studies have reported association with worsening of depressive symptoms in human, yet the data are inconclusive[90,91]. In addition, it was reported that a reduction in tryptophan levels interrupts memory consolidation yet improves attention[92]. Dietary tryptophan depletion is also used in modeling major depression in rats[93] and dietary prenatal protein deprivation is used to model cognitive impairment observed in schizophrenia[78]. In our model, the reduction in brain tryptophan in the MTR + stress rats was probably not due to its extensive metabolism in brain, as no change was observed in its two major metabolic pathways the serotonin and kynurenine pathways[94]. However, being an essential amino acid tryptophan level in brain depends also on its availability, which can be modulated by several variables including its serum level and its BBB transporter (LAT1) activity[95]. Serum level of amino acids, which compete with tryptophan on its transporter, the branched chain amino acids (BCAA) for example[96,97], can affect tryptophan availability to the brain. Indeed, serum tryptophan/BCAA ratio is an established measure to estimate brain tryptophan levels[98]. In the MTR+Stress rats, reduced tryptophan brain levels were associated with reduced LAT1 protein levels and its light chain SLC3A2 transcript levels. In addition, we observed a reduction in serum tryptophan/BCCA ratio, implying a peripheral contribution to reduced brain tryptophan levels. We further suggest that tryptophan/BCCA reduction is due to a failure of these MTR treated rats to respond to stress by increasing serum glucose and insulin, a known regulator of serum BCAA[99], as did rats exposed to chronic stress only. Taken together, these data suggest that interference with brain tryptophan homeostasis is due to joint brain and peripheral physiological processes. In line with the latter is the finding that brain tryptophan levels were only affected in rats receiving the combined treatment of MTR + stress, while serum tryptophan/BCAA ratio or brain LAT1 were affected by either Stress or MTR, respectively[94]. Our data suggest that a mild modulation of both peripheral and central processes, which converge and mutually interact, can influence behavioral phenotype. A similar interaction can be seen in circuits of energy balance regulation in the body. Thus, adipose tissues secrete leptin as an afferent signal, which influences the activity of the hypothalamus. The hypothalamus signals decrease food intake by inhibiting anabolic circuits, and enhance energy expenditure through the activation of catabolic circuits[100]. It is quite intuitive, but sometimes neglected, that the brain collects both central and peripheral internal inputs, as well as external inputs and executes reaction based on the sum of predisposition and experience. The recent increasing interest in the link between microbiome and brain function and its role in mental disorders[101] further substantiates a role for peripheral inputs in behavior.

**CONCLUSION**

The ubiquitous transcription factor Sp1 plays a role in the regulation of many genes in response to internal and environmental signals and is suggested to have implication in neuropsychiatric disorders and complex behaviors. Using simple manipulation of Sp1 we showed that a wide and transient interference with gene expression in inbred rats at a critical developmental stage, can induce a long lasting impact on metabolic and behavioral response to environmental stimuli, with different and even opposite outcomes, depending on the characteristics of the environmental stimuli/insult. Already at 1963, Manfred Bleuler[102] wrote that “unfavourable nature and environment develop together and influence each other. They are interwoven from babyhood. The environment influencing the manifestation of the hereditary disposition is already a reflected image of this disposition”[102]. Peripheral and central physiological processes, which are both subjected to genetic and environmental changes, interact reciprocally to induce specific behavioral patterns (Figure 1). Further studies could shed light on the importance of these brain-periphery reciprocal interactions for whole body homeostasis and its influence on behavior. In addition, new targets may emerge from such a perspective of behavioral modulators for future clinical intervention.

**REFERENCES**

1 **Bertelsen A**, Harvald B, Hauge M. A Danish twin study of manic-depressive disorders. *Br J Psychiatry* 1977; **130**: 330-351 [PMID: 558030 DOI: 10.1192/bjp.130.4.330]

2 **Cardno AG**, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, Venturi P, Jones LA, Lewis SW, Sham PC, Gottesman II, Farmer AE, McGuffin P, Reveley AM, Murray RM. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. *Arch Gen Psychiatry* 1999; **56**: 162-168 [PMID: 10025441 DOI: 10.1001/archpsyc.56.2.162]

3 **Lupien SJ**, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci* 2009; **10**: 434-445 [PMID: 19401723 DOI: 10.1038/nrn2639]

4 **Lichtenstein P**, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000; **343**: 78-85 [PMID: 10891514 DOI: 10.1056/NEJM200007133430201]

5 **Cosselman KE**, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol* 2015; **12**: 627-642 [PMID: 26461967 DOI: 10.1038/nrcardio.2015.152]

6 **Tost H**, Champagne FA, Meyer-Lindenberg A. Environmental influence in the brain, human welfare and mental health. *Nat Neurosci* 2015; **18**: 1421-1431 [PMID: 26404717 DOI: 10.1038/nn.4108]

7 **Constantino JN**. Child Maltreatment Prevention and the Scope of Child and Adolescent Psychiatry. *Child Adolesc Psychiatr Clin N Am* 2016; **25**: 157-165 [PMID: 26980121 DOI: 10.1016/j.chc.2015.11.003]

8 **Greenwood TA**, Lazzeroni LC, Murray SS, Cadenhead KS, Calkins ME, Dobie DJ, Green MF, Gur RE, Gur RC, Hardiman G, Kelsoe JR, Leonard S, Light GA, Nuechterlein KH, Olincy A, Radant AD, Schork NJ, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Freedman R, Braff DL. Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *Am J Psychiatry* 2011; **168**: 930-946 [PMID: 21498463 DOI: 10.1176/appi.ajp.2011.10050723]

9 **Luciano M**, Houlihan LM, Harris SE, Gow AJ, Hayward C, Starr JM, Deary IJ. Association of existing and new candidate genes for anxiety, depression and personality traits in older people. *Behav Genet* 2010; **40**: 518-532 [PMID: 20052609 DOI: 10.1007/s10519-009-9326-4]

10 **Duncan LE**, Keller MC. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry* 2011; **168**: 1041-1049 [PMID: 21890791 DOI: 10.1176/appi.ajp.2011.11020191]

11 **Weaver IC**, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. Epigenetic programming by maternal behavior. *Nat Neurosci* 2004; **7**: 847-854 [PMID: 15220929 DOI: 10.1038/nn1276]

12 **Basta-Kaim A**, Budziszewska B, Leśkiewicz M, Fijał K, Regulska M, Kubera M, Wędzony K, Lasoń W. Hyperactivity of the hypothalamus-pituitary-adrenal axis in lipopolysaccharide-induced neurodevelopmental model of schizophrenia in rats: effects of antipsychotic drugs. *Eur J Pharmacol* 2011; **650**: 586-595 [PMID: 21034739 DOI: 10.1016/j.ejphar.2010.09.083]

13 **Soumiya H**, Fukumitsu H, Furukawa S. Prenatal immune challenge compromises the normal course of neurogenesis during development of the mouse cerebral cortex. *J Neurosci Res* 2011; **89**: 1575-1585 [PMID: 21732402 DOI: 10.1002/jnr.22704]

14 **Flint J**, Munafò MR. Candidate and non-candidate genes in behavior genetics. *Curr Opin Neurobiol* 2013; **23**: 57-61 [PMID: 22878161 DOI: 10.1016/j.conb.2012.07.005]

15 **Belsky J**, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. *Psychol Bull* 2009; **135**: 885-908 [PMID: 19883141 DOI: 10.1037/a0017376]

16 **Belsky J**, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? *Mol Psychiatry* 2009; **14**: 746-754 [PMID: 19455150 DOI: 10.1038/mp.2009.44]

17 **Caspi A**, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. Role of genotype in the cycle of violence in maltreated children. *Science* 2002; **297**: 851-854 [PMID: 12161658 DOI: 10.1126/science.1072290]

18 **Collier DA**, Stöber G, Li T, Heils A, Catalano M, Di Bella D, Arranz MJ, Murray RM, Vallada HP, Bengel D, Müller CR, Roberts GW, Smeraldi E, Kirov G, Sham P, Lesch KP. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. *Mol Psychiatry* 1996; **1**: 453-460 [PMID: 9154246]

19 **Caspi A**, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003; **301**: 386-389 [PMID: 12869766 DOI: 10.1126/science.1083968]

20 **Fox E**, Zougkou K, Ridgewell A, Garner K. The serotonin transporter gene alters sensitivity to attention bias modification: evidence for a plasticity gene. *Biol Psychiatry* 2011; **70**: 1049-1054 [PMID: 21840502 DOI: 10.1016/j.biopsych.2011.07.004]

21 **Manolio TA**, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH, Guttmacher AE, Kong A, Kruglyak L, Mardis E, Rotimi CN, Slatkin M, Valle D, Whittemore AS, Boehnke M, Clark AG, Eichler EE, Gibson G, Haines JL, Mackay TF, McCarroll SA, Visscher PM. Finding the missing heritability of complex diseases. *Nature* 2009; **461**: 747-753 [PMID: 19812666 DOI: 10.1038/nature08494]

22 **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]

23 **Fernandez-Zapico ME**, Lomberk GA, Tsuji S, DeMars CJ, Bardsley MR, Lin YH, Almada LL, Han JJ, Mukhopadhyay D, Ordog T, Buttar NS, Urrutia R. A functional family-wide screening of SP/KLF proteins identifies a subset of suppressors of KRAS-mediated cell growth. *Biochem J* 2011; **435**: 529-537 [PMID: 21171965 DOI: 10.1042/BJ20100773]

24 **Ye X**, Liu H, Gong YS, Liu SF. LPS Down-Regulates Specificity Protein 1 Activity by Activating NF-κB Pathway in Endotoxemic Mice. *PLoS One* 2015; **10**: e0130317 [PMID: 26103469 DOI: 10.1371/journal.pone.0130317]

25 **Zhao C**, Meng A. Sp1-like transcription factors are regulators of embryonic development in vertebrates. *Dev Growth Differ* 2005; **47**: 201-211 [PMID: 15921495 DOI: 10.1111/j.1440-169X.2005.00797.x]

26 **Abdelrahim M**, Baker CH, Abbruzzese JL, Sheikh-Hamad D, Liu S, Cho SD, Yoon K, Safe S. Regulation of vascular endothelial growth factor receptor-1 expression by specificity proteins 1, 3, and 4 in pancreatic cancer cells. *Cancer Res* 2007; **67**: 3286-3294 [PMID: 17409437 DOI: 10.1158/0008-5472.CAN-06-3831]

27 **Ammanamanchi S**, Kim SJ, Sun LZ, Brattain MG. Induction of transforming growth factor-beta receptor type II expression in estrogen receptor-positive breast cancer cells through SP1 activation by 5-aza-2'-deoxycytidine. *J Biol Chem* 1998; **273**: 16527-16534 [PMID: 9632722 DOI: [10.1074/jbc.273.26.16527](http://dx.doi.org/10.1074/jbc.273.26.16527" \t "_blank)]

28 **Luster TA**, Johnson LR, Nowling TK, Lamb KA, Philipsen S, Rizzino A. Effects of three Sp1 motifs on the transcription of the FGF-4 gene. *Mol Reprod Dev* 2000; **57**: 4-15 [PMID: 10954851 DOI: 10.1002/1098-2795(200009)57: 1<4: : AID-MRD3>3.0.CO; 2-I]

29 **Banchio C**, Schang LM, Vance DE. Phosphorylation of Sp1 by cyclin-dependent kinase 2 modulates the role of Sp1 in CTP: phosphocholine cytidylyltransferase alpha regulation during the S phase of the cell cycle. *J Biol Chem* 2004; **279**: 40220-40226 [PMID: 15247247 DOI: 10.1074/jbc.M406468200]

30 **Denson LA**, Menon RK, Shaufl A, Bajwa HS, Williams CR, Karpen SJ. TNF-alpha downregulates murine hepatic growth hormone receptor expression by inhibiting Sp1 and Sp3 binding. *J Clin Invest* 2001; **107**: 1451-1458 [PMID: 11390427 DOI: 10.1172/JCI10994]

31 **Trisciuoglio D**, Iervolino A, Candiloro A, Fibbi G, Fanciulli M, Zangemeister-Wittke U, Zupi G, Del Bufalo D. bcl-2 induction of urokinase plasminogen activator receptor expression in human cancer cells through Sp1 activation: involvement of ERK1/ERK2 activity. *J Biol Chem* 2004; **279**: 6737-6745 [PMID: 14660675 DOI: 10.1074/jbc.M308938200]

32 **Vaulont S**, Vasseur-Cognet M, Kahn A. Glucose regulation of gene transcription. *J Biol Chem* 2000; **275**: 31555-31558 [PMID: 10934218 DOI: 10.1074/jbc.R000016200]

33 **Frensing T**, Kaltschmidt C, Schmitt-John T. Characterization of a neuregulin-1 gene promoter: positive regulation of type I isoforms by NF-kappaB. *Biochim Biophys Acta* 2008; **1779**: 139-144 [PMID: 18082154 DOI: 10.1016/j.bbagrm.2007.11.007]

34 **Chen Y**, Sharma RP, Costa RH, Costa E, Grayson DR. On the epigenetic regulation of the human reelin promoter. *Nucleic Acids Res* 2002; **30**: 2930-2939 [PMID: 12087179 DOI: [10.1093/nar/gkf401](http://dx.doi.org/10.1093/nar/gkf401" \t "_blank)]

35 **Szabó G**, Katarova Z, Körtvély E, Greenspan RJ, Urbán Z. Structure and the promoter region of the mouse gene encoding the 67-kD form of glutamic acid decarboxylase. *DNA Cell Biol* 1996; **15**: 1081-1091 [PMID: 8985122 DOI: [10.1089/dna.1996.15.1081](http://dx.doi.org/10.1089/dna.1996.15.1081" \t "_blank)]

36 **Zhu QS**, Chen K, Shih JC. Bidirectional promoter of human monoamine oxidase A (MAO A) controlled by transcription factor Sp1. *J Neurosci* 1994; **14**: 7393-7403 [PMID: 7996184]

37 **Wong WK**, Chen K, Shih JC. Regulation of human monoamine oxidase B gene by Sp1 and Sp3. *Mol Pharmacol* 2001; **59**: 852-859 [PMID: 11259630]

38 **Liu A**, Zhuang Z, Hoffman PW, Bai G. Functional analysis of the rat N-methyl-D-aspartate receptor 2A promoter: multiple transcription starts points, positive regulation by Sp factors, and translational regulation. *J Biol Chem* 2003; **278**: 26423-26434 [PMID: 12746457 DOI: 10.1074/jbc.M211165200]

39 **Okamoto S**, Sherman K, Bai G, Lipton SA. Effect of the ubiquitous transcription factors, SP1 and MAZ, on NMDA receptor subunit type 1 (NR1) expression during neuronal differentiation. *Brain Res Mol Brain Res* 2002; **107**: 89-96 [PMID: 12425938 DOI: [10.1016/S0169-328X(02)00440-0](http://dx.doi.org/10.1016/S0169-328X(02)00440-0" \t "_blank)]

40 **Ma L**, Song L, Radoi GE, Harrison NL. Transcriptional regulation of the mouse gene encoding the alpha-4 subunit of the GABAA receptor. *J Biol Chem* 2004; **279**: 40451-40461 [PMID: 15265862 DOI: 10.1074/jbc.M406827200]

41 **Yajima S**, Lee SH, Minowa T, Mouradian MM. Sp family transcription factors regulate expression of rat D2 dopamine receptor gene. *DNA Cell Biol* 1998; **17**: 471-479 [PMID: 9628590 DOI: 10.1089/dna.1998.17.471]

42 **Goffart S**, Wiesner RJ. Regulation and co-ordination of nuclear gene expression during mitochondrial biogenesis. *Exp Physiol* 2003; **88**: 33-40 [PMID: 12525853 DOI: [10.1113/eph8802500](http://dx.doi.org/10.1113/eph8802500" \t "_blank)]

43 **Harrison PJ**, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry* 2005; **10**: 40-68; image 5 [PMID: 15263907 DOI: 10.1038/sj.mp.4001558]

44 **Quednow BB**, Brzózka MM, Rossner MJ. Transcription factor 4 (TCF4) and schizophrenia: integrating the animal and the human perspective. *Cell Mol Life Sci* 2014; **71**: 2815-2835 [PMID: 24413739 DOI: 10.1007/s00018-013-1553-4]

45 **Ben-Shachar D**, Karry R. Sp1 expression is disrupted in schizophrenia; a possible mechanism for the abnormal expression of mitochondrial complex I genes, NDUFV1 and NDUFV2. *PLoS One* 2007; **2**: e817 [PMID: 17786189 DOI: 10.1371/journal.pone.0000817]

46 **Ben-Shachar D**. The interplay between mitochondrial complex I, dopamine and Sp1 in schizophrenia. *J Neural Transm* (Vienna) 2009; **116**: 1383-1396 [PMID: 19784753 DOI: 10.1007/s00702-009-0319-5]

47 **Washizuka S**, Kametani M, Sasaki T, Tochigi M, Umekage T, Kohda K, Kato T. Association of mitochondrial complex I subunit gene NDUFV2 at 18p11 with schizophrenia in the Japanese population. *Am J Med Genet B Neuropsychiatr Genet* 2006; **141B**: 301-304 [PMID: 16508936 DOI: 10.1002/ajmg.b.30285]

48 **Nakajima S**, Takeuchi H, Plitman E, Fervaha G, Gerretsen P, Caravaggio F, Chung JK, Iwata Y, Remington G, Graff-Guerrero A. Neuroimaging findings in treatment-resistant schizophrenia: A systematic review: Lack of neuroimaging correlates of treatment-resistant schizophrenia. *Schizophr Res* 2015; **164**: 164-175 [PMID: 25684554 DOI: 10.1016/j.schres.2015.01.043]

49 **Magistretti PJ**, Allaman I. A cellular perspective on brain energy metabolism and functional imaging. *Neuron* 2015; **86**: 883-901 [PMID: 25996133 DOI: 10.1016/j.neuron.2015.03.035]

50 **Pinacho R**, Villalmanzo N, Roca M, Iniesta R, Monje A, Haro JM, Meana JJ, Ferrer I, Gill G, Ramos B. Analysis of Sp transcription factors in the postmortem brain of chronic schizophrenia: a pilot study of relationship to negative symptoms. *J Psychiatr Res* 2013; **47**: 926-934 [PMID: 23540600 DOI: 10.1016/j.jpsychires.2013.03.004]

51 **Pinacho R**, Valdizán EM, Pilar-Cuellar F, Prades R, Tarragó T, Haro JM, Ferrer I, Ramos B. Increased SP4 and SP1 transcription factor expression in the postmortem hippocampus of chronic schizophrenia. *J Psychiatr Res* 2014; **58**: 189-196 [PMID: 25175639 DOI: 10.1016/j.jpsychires.2014.08.006]

52 **Fusté M**, Pinacho R, Meléndez-Pérez I, Villalmanzo N, Villalta-Gil V, Haro JM, Ramos B. Reduced expression of SP1 and SP4 transcription factors in peripheral blood mononuclear cells in first-episode psychosis. *J Psychiatr Res* 2013; **47**: 1608-1614 [PMID: 23941741 DOI: 10.1016/j.jpsychires.2013.07.019]

53 **Thanseem I**, Anitha A, Nakamura K, Suda S, Iwata K, Matsuzaki H, Ohtsubo M, Ueki T, Katayama T, Iwata Y, Suzuki K, Minoshima S, Mori N. Elevated transcription factor specificity protein 1 in autistic brains alters the expression of autism candidate genes. *Biol Psychiatry* 2012; **71**: 410-418 [PMID: 22030357 DOI: 10.1016/j.biopsych.2011.09.020]

54 **Citron BA**, Dennis JS, Zeitlin RS, Echeverria V. Transcription factor Sp1 dysregulation in Alzheimer's disease. *J Neurosci Res* 2008; **86**: 2499-2504 [PMID: 18449948 DOI: 10.1002/jnr.21695]

55 **Wong DL**, Tai TC, Wong-Faull DC, Claycomb R, Meloni EG, Myers KM, Carlezon WA, Kvetnansky R. Epinephrine: a short- and long-term regulator of stress and development of illness : a potential new role for epinephrine in stress. *Cell Mol Neurobiol* 2012; **32**: 737-748 [PMID: 22090159 DOI: 10.1007/s10571-011-9768-0]

56 **Gilmour J**, Assi SA, Jaegle U, Kulu D, van de Werken H, Clarke D, Westhead DR, Philipsen S, Bonifer C. A crucial role for the ubiquitously expressed transcription factor Sp1 at early stages of hematopoietic specification. *Development* 2014; **141**: 2391-2401 [PMID: 24850855 DOI: 10.1242/dev.106054]

57 **Blume SW**, Snyder RC, Ray R, Thomas S, Koller CA, Miller DM. Mithramycin inhibits SP1 binding and selectively inhibits transcriptional activity of the dihydrofolate reductase gene in vitro and in vivo. *J Clin Invest* 1991; **88**: 1613-1621 [PMID: 1834700 DOI: 10.1172/JCI115474]

58 **Fernández-Guizán A**, Mansilla S, Barceló F, Vizcaíno C, Núñez LE, Morís F, González S, Portugal J. The activity of a novel mithramycin analog is related to its binding to DNA, cellular accumulation, and inhibition of Sp1-driven gene transcription. *Chem Biol Interact* 2014; **219**: 123-132 [PMID: 24907531 DOI: 10.1016/j.cbi.2014.05.019]

59 **Kennedy BJ**, Torkelson J, Fraley EE. Optimal number of chemotherapy courses in advanced nonseminomatous testicular carcinoma. *Am J Clin Oncol* 1995; **18**: 463-468 [PMID: 8526185 DOI: [10.1097/00000421-199512000-00001](http://dx.doi.org/10.1097/00000421-199512000-00001" \t "_blank)]

60 **Lumachi F**, Brunello A, Roma A, Basso U. Cancer-induced hypercalcemia. *Anticancer Res* 2009; **29**: 1551-1555 [PMID: 19443365]

61 **Asor E**, Belhanes H, Kavushansky A, Zubedat S, Klein E, Avital A, Ben-Shachar D. Early postnatal interference with the expression of multiple Sp1 regulated genes leads to disparate behavioral response to sub-chronic and chronic stress in rats. *Psychoneuroendocrinology* 2013; **38**: 2173-2183 [PMID: 23669323 DOI: 10.1016/j.psyneuen.2013.04.005]

62 **Citron BA**, Saykally JN, Cao C, Dennis JS, Runfeldt M, Arendash GW. Transcription factor Sp1 inhibition, memory, and cytokines in a mouse model of Alzheimer's disease. *Am J Neurodegener Dis* 2015; **4**: 40-48 [PMID: 26807343]

63 **Wei C**, Zhang W, Zhou Q, Zhao C, Du Y, Yan Q, Li Z, Miao J. Mithramycin A Alleviates Cognitive Deficits and Reduces Neuropathology in a Transgenic Mouse Model of Alzheimer's Disease. *Neurochem Res* 2016; **41**: 1924-1938 [PMID: 27072684 DOI: 10.1007/s11064-016-1903-3]

64 **Ferrante RJ**, Ryu H, Kubilus JK, D'Mello S, Sugars KL, Lee J, Lu P, Smith K, Browne S, Beal MF, Kristal BS, Stavrovskaya IG, Hewett S, Rubinsztein DC, Langley B, Ratan RR. Chemotherapy for the brain: the antitumor antibiotic mithramycin prolongs survival in a mouse model of Huntington's disease. *J Neurosci* 2004; **24**: 10335-10342 [PMID: 15548647 DOI: 10.1523/JNEUROSCI.2599-04.2004]

65 **Hagiwara H**, Iyo M, Hashimoto K. Mithramycin protects against dopaminergic neurotoxicity in the mouse brain after administration of methamphetamine. *Brain Res* 2009; **1301**: 189-196 [PMID: 19748494 DOI: 10.1016/j.brainres.2009.09.010]

66 **Sato M**, Numachi Y, Hamamura T. Relapse of paranoid psychotic state in methamphetamine model of schizophrenia. *Schizophr Bull* 1992; **18**: 115-122 [PMID: 1553491 DOI: [10.1093/schbul/18.1.115](http://dx.doi.org/10.1093/schbul/18.1.115" \t "_blank)]

67 **Meaney MJ**. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu Rev Neurosci* 2001; **24**: 1161-1192 [PMID: 11520931 DOI: 10.1146/annurev.neuro.24.1.1161]

68 **Avital A**, Richter-Levin G. Exposure to juvenile stress exacerbates the behavioural consequences of exposure to stress in the adult rat. *Int J Neuropsychopharmacol* 2005; **8**: 163-173 [PMID: 15546500 DOI: 10.1017/S1461145704004808]

69 **Barbaccia ML**, Concas A, Serra M, Biggio G. Stress and neurosteroids in adult and aged rats. *Exp Gerontol* 1998; **33**: 697-712 [PMID: 9951617]

70 **Mathews IZ**, Wilton A, Styles A, McCormick CM. Increased depressive behaviour in females and heightened corticosterone release in males to swim stress after adolescent social stress in rats. *Behav Brain Res* 2008; **190**: 33-40 [PMID: 18342957 DOI: 10.1016/j.bbr.2008.02.004]

71 **Tsoory M**, Richter-Levin G. Learning under stress in the adult rat is differentially affected by 'juvenile' or 'adolescent' stress. *Int J Neuropsychopharmacol* 2006; **9**: 713-728 [PMID: 16321169 DOI: 10.1017/S1461145705006255]

72 **Isgor C**, Kabbaj M, Akil H, Watson SJ. Delayed effects of chronic variable stress during peripubertal-juvenile period on hippocampal morphology and on cognitive and stress axis functions in rats. *Hippocampus* 2004; **14**: 636-648 [PMID: 15301440 DOI: 10.1002/hipo.10207]

73 **Willner P**, Muscat R, Papp M. Chronic mild stress-induced anhedonia: a realistic animal model of depression. *Neurosci Biobehav Rev* 1992; **16**: 525-534 [PMID: 1480349 DOI: [10.1016/S0149-7634(05)80194-0](http://dx.doi.org/10.1016/S0149-7634(05)80194-0" \t "_blank)]

74 **Binder E**, Malki K, Paya-Cano JL, Fernandes C, Aitchison KJ, Mathé AA, Sluyter F, Schalkwyk LC. Antidepressants and the resilience to early-life stress in inbred mouse strains. *Pharmacogenet Genomics* 2011; **21**: 779-789 [PMID: 22016050 DOI: 10.1097/FPC.0b013e32834b3f35]

75 **Ricon T**, Toth E, Leshem M, Braun K, Richter-Levin G. Unpredictable chronic stress in juvenile or adult rats has opposite effects, respectively, promoting and impairing resilience. *Stress* 2012; **15**: 11-20 [PMID: 21682654 DOI: 10.3109/10253890.2011.572207]

76 **Kamphuis PJ**, Croiset G, Bakker JM, Van Bel F, Van Ree JM, Wiegant VM. Neonatal dexamethasone treatment affects social behaviour of rats in later life. *Neuropharmacology* 2004; **47**: 461-474 [PMID: 15275835 DOI: 10.1016/j.neuropharm.2004.04.008]

77 **Dettmer AM**, Wooddell LJ, Rosenberg KL, Kaburu SSK, Novak MA, Meyer JS, Suomi SJ. Associations between early life experience, chronic HPA axis activity, and adult social rank in rhesus monkeys. *Soc Neurosci* 2016: 1-10 [PMID: 27063359 DOI: 10.1080/17470919.2016.1176952]

78 **Morgane PJ**, Austin-LaFrance R, Bronzino J, Tonkiss J, Díaz-Cintra S, Cintra L, Kemper T, Galler JR. Prenatal malnutrition and development of the brain. *Neurosci Biobehav Rev* 1993; **17**: 91-128 [PMID: 8455820 DOI: [10.1016/S0149-7634(05)80234-9](http://dx.doi.org/10.1016/S0149-7634(05)80234-9" \t "_blank)]

79 **Lipska BK**, Weinberger DR. To model a psychiatric disorder in animals: schizophrenia as a reality test. *Neuropsychopharmacology* 2000; **23**: 223-239 [PMID: 10942847 DOI: 10.1016/S0893-133X(00)00137-8]

80 **Adams W**, Kendell RE, Hare EH, Munk-Jørgensen P. Epidemiological evidence that maternal influenza contributes to the aetiology of schizophrenia. An analysis of Scottish, English, and Danish data. *Br J Psychiatry* 1993; **163**: 522-534 [PMID: 8252293 DOI: [10.1192/bjp.163.4.522](http://dx.doi.org/10.1192/bjp.163.4.522" \t "_blank)]

81 **Fatemi SH**, Folsom TD, Rooney RJ, Mori S, Kornfield TE, Reutiman TJ, Kneeland RE, Liesch SB, Hua K, Hsu J, Patel DH. The viral theory of schizophrenia revisited: abnormal placental gene expression and structural changes with lack of evidence for H1N1 viral presence in placentae of infected mice or brains of exposed offspring. *Neuropharmacology* 2012; **62**: 1290-1298 [PMID: 21277874 DOI: 10.1016/j.neuropharm.2011.01.011]

82 **Nawa H**, Takei N. Recent progress in animal modeling of immune inflammatory processes in schizophrenia: implication of specific cytokines. *Neurosci Res* 2006; **56**: 2-13 [PMID: 16837094 DOI: 10.1016/j.neures.2006.06.002]

83 **Piontkewitz Y**, Arad M, Weiner I. Tracing the development of psychosis and its prevention: what can be learned from animal models. *Neuropharmacology* 2012; **62**: 1273-1289 [PMID: 21703648 DOI: 10.1016/j.neuropharm.2011.04.019]

84 **Caldji C**, Diorio J, Meaney MJ. Variations in maternal care in infancy regulate the development of stress reactivity. *Biol Psychiatry* 2000; **48**: 1164-1174 [PMID: 11137058 DOI: [10.1016/S0006-3223(00)01084-2](http://dx.doi.org/10.1016/S0006-3223(00)01084-2" \t "_blank)]

85 **Lehmann J**, Feldon J. Long-term biobehavioral effects of maternal separation in the rat: consistent or confusing? *Rev Neurosci* 2000; **11**: 383-408 [PMID: 11065281 DOI: [10.1515/REVNEURO.2000.11.4.383](http://dx.doi.org/10.1515/REVNEURO.2000.11.4.383" \t "_blank)]

86 **Moeller FG**, Dougherty DM, Swann AC, Collins D, Davis CM, Cherek DR. Tryptophan depletion and aggressive responding in healthy males. *Psychopharmacology* (Berl) 1996; **126**: 97-103 [PMID: 8856827 DOI: [10.1007/BF02246343](http://dx.doi.org/10.1007/BF02246343" \t "_blank)]

87 **Walderhaug E**, Lunde H, Nordvik JE, Landrø NI, Refsum H, Magnusson A. Lowering of serotonin by rapid tryptophan depletion increases impulsiveness in normal individuals. *Psychopharmacology* (Berl) 2002; **164**: 385-391 [PMID: 12457268 DOI: 10.1007/s00213-002-1238-4]

88 **Myint AM**, Kim YK, Verkerk R, Park SH, Scharpé S, Steinbusch HW, Leonard BE. Tryptophan breakdown pathway in bipolar mania. *J Affect Disord* 2007; **102**: 65-72 [PMID: 17270276 DOI: 10.1016/j.jad.2006.12.008]

89 **Peet M**, Moody JP, Worrall EP, Walker P, Naylor GJ. Plasma tryptophan concentration in depressive illness and mania. *Br J Psychiatry* 1976; **128**: 255-258 [PMID: 1252689 DOI: [10.1192/bjp.128.3.255](http://dx.doi.org/10.1192/bjp.128.3.255" \t "_blank)]

90 **Jans LA**, Riedel WJ, Markus CR, Blokland A. Serotonergic vulnerability and depression: assumptions, experimental evidence and implications. *Mol Psychiatry* 2007; **12**: 522-543 [PMID: 17160067 DOI: 10.1038/sj.mp.4001920]

91 **Toker L**, Amar S, Bersudsky Y, Benjamin J, Klein E. The biology of tryptophan depletion and mood disorders. *Isr J Psychiatry Relat Sci* 2010; **47**: 46-55 [PMID: 20686199]

92 **Schmitt JA**, Jorissen BL, Sobczak S, van Boxtel MP, Hogervorst E, Deutz NE, Riedel WJ. Tryptophan depletion impairs memory consolidation but improves focussed attention in healthy young volunteers. *J Psychopharmacol* 2000; **14**: 21-29 [PMID: 10757249]

93 **Franklin M**, Bermudez I, Murck H, Singewald N, Gaburro S. Sub-chronic dietary tryptophan depletion--an animal model of depression with improved face and good construct validity. *J Psychiatr Res* 2012; **46**: 239-247 [PMID: 22074993 DOI: 10.1016/j.jpsychires.2011.10.003]

94 **Asor E**, Stempler S, Avital A, Klein E, Ruppin E, Ben-Shachar D. The role of branched chain amino acid and tryptophan metabolism in rat's behavioral diversity: Intertwined peripheral and brain effects. *Eur Neuropsychopharmacol* 2015; **25**: 1695-1705 [PMID: 26271721 DOI: 10.1016/j.euroneuro.2015.07.009]

95 **Fernstrom JD**. Effects on the diet on brain neurotransmitters. *Metabolism* 1977; **26**: 207-223 [PMID: 13261]

96 **Blomstrand E**, Celsing F, Newsholme EA. Changes in plasma concentrations of aromatic and branched-chain amino acids during sustained exercise in man and their possible role in fatigue. *Acta Physiol Scand* 1988; **133**: 115-121 [PMID: 3227900 DOI: 10.1111/j.1748-1716.1988.tb08388.x]

97 **Hawkins RA**, O'Kane RL, Simpson IA, Viña JR. Structure of the blood-brain barrier and its role in the transport of amino acids. *J Nutr* 2006; **136**: 218S-226S [PMID: 16365086]

98 **Pérez-Cruet J**, Chase TN, Murphy DL. Dietary regulation of brain tryptophan metabolism by plasma ratio of free tryptophan and neutral amino acids in humans. *Nature* 1974; **248**: 693-695 [PMID: 4275348]

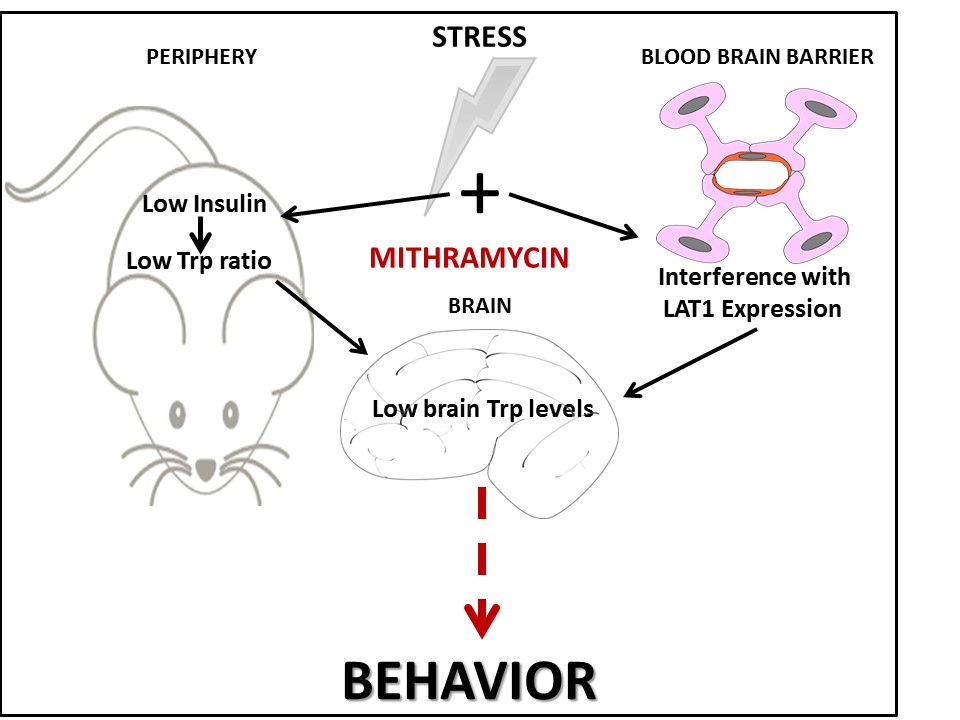
99 **Brooks DC**, Bessey PQ, Black PR, Aoki TT, Wilmore DW. Insulin stimulates branched chain amino acid uptake and diminishes nitrogen flux from skeletal muscle of injured patients. *J Surg Res* 1986; **40**: 395-405 [PMID: 3517494]

100 **Suzuki K**, Simpson KA, Minnion JS, Shillito JC, Bloom SR. The role of gut hormones and the hypothalamus in appetite regulation. *Endocr J* 2010; **57**: 359-372 [PMID: 20424341 DOI: [10.1038/518S13a](http://dx.doi.org/10.1038/518S13a" \t "_blank)]

101 **Schmidt C**. Mental health: thinking from the gut. *Nature* 2015; **518**: S12-S15 [PMID: 25715275 DOI: 10.1038/518S13a]

102 **Bleuler M**. Conception of Schizophrenia Within the Last Fifty Years and Today [Abridged]. *Proc R Soc Med* 1963; **56**: 945-952 [PMID: 19994296]

**P-Reviewer:** Malli R, Noll-Hussong M **S-Editor:** Ji FF **L-Editor: E-Editor:**



**Figure 1 Brain and periphery combined effects modulate behavior in the specificity protein 1 rat model.** Early in life transient interference with specificity protein 1 activity by mithramycin and later in life exposure to chronic stress, affect availability of tryptophan (Trp) to the brain, both by reducing serum Trp ratio and brain LAT1 expression. Deficits in brain Trp levels may affect behavior. LAT1: BBB transporter.