Review Article

Epigenetics in the nervous system: An overview of its essential role

Bhavya Ravi, Manoj Kannan

Department of Biological Sciences, Birla Institute of Technology and Science, Pilani, Rajasthan, India

The role that epigenetic mechanisms play in phenomena such as cellular differentiation during embryonic development, X chromosome inactivation, and cancers is well-characterized. Epigenetic mechanisms have been implicated to be the mediators of several functions in the nervous system such as in neuronal-glial differentiation, adult neurogenesis, the modulation of neural behavior and neural plasticity, and also in higher brain functions like cognition and memory. Its particular role in explaining the importance of early life/social experiences on adult behavioral patterns has caught the attention of scientists and has spawned the exciting new field of behavioral epigenetics which may hold the key to explaining many complex behavioral paradigms. Epigenetic deregulation is known to be central in the etiology of several neuropsychiatric disorders which underscore the importance of understanding these mechanisms more thoroughly to elucidate novel and effective therapeutic approaches. In this review we present an overview of the findings which point to the essential role played by epigenetics in the vertebrate nervous system.

Key words: Behavior, cognition, development, environmental effect, epigenetics, maternal effect, neuropsychiatric disorders, plasticity, synaptic plasticity

Introduction

'Epigenetics' refers to the study of mechanisms that cause specific and heritable changes in gene expression or cellular phenotype without alteration of the underlying deoxyribonucleic acid (DNA) sequence. They encompass functionally relevant modifications to the genome that do not involve a change in the nucleotide sequence. Epigenetic mechanisms impose specific and heritable patterns of gene expression. The three key epigenetic mechanisms include: DNA methylation, histone modifications leading to nucleosome and chromatin remodeling and noncoding ribonucleic acid (RNA) mediated posttranslational regulation. The mechanisms of DNA methylation and histone modifications are well understood. Noncoding RNA molecules are a new class of molecules exhibiting epigenetic effects on gene regulation. Among the several types of noncoding RNAs, microRNAs have been reported to play roles in translational repression through either degradation of target messenger RNAs (mRNAs) or inhibition of mRNA translation.[1]

For a long time, scientists have sought to explain some fundamental questions regarding animal behavior and to verify if putative factors such as early life experiences, adversity, abuse, social interaction, etc., could explain adult behavioral patterns or if these patterns are essentially ingrained, immutable, and determined solely by our genetic makeup-the long standing "Nature versus Nurture" debate. The field of 'Behavioral Epigenetics' explores the relation between behavior and epigenetic alterations in specific brain areas and tries to interpret behavior in a broader context.[2] It is increasingly becoming apparent that epigenetic modifications play a vital role in nervous system development, function, and gene expression. Added to this we know that several functions in the nervous system such as neural development, adult neurogenesis, and modulation of synaptic plasticity

Access this article online	
Quick Response Code:	Website: www.ijhg.com
	DOI: 10.4103/0971-6866.124357

Address for correspondence: Mr. Manoj Kannan, Department of Biological Sciences, Faculty Division Three, Birla Institute of Technology and Science, Pilani, Rajasthan - 333 031, India. E-mail: manojkannan@pilani.bits-pilani.ac.in

requires stage specific gene expression for their proper progress.[3-5] Studies into the possible role of epigenetics in the nervous system have revealed that they play a pivotal role not only in the above mentioned process, but also in higher brain functions like learning and memory formation. These different roles will be the focus of this review.

Neural Stem Cell Fate and Neurodevelopment

The initial cells that give rise to the central nervous system (CNS) arise from the neuroepithilial cells and neural stem cells (NSCs) which undergo a process called neurogenesis by which they form all the cell types found in the nervous system. An intricate network formed by extrinsic factors/molecules and the resulting cascade of transcription factors that are evoked as a result of signal transduction pathway together cause changes to the epigenetic state of the neural progenitors and influence their decision to differentiate along neural or glial lineages.

During early gestation, NSCs lack multipotency and undergo mainly asymmetric divisions to form neurons. During late gestation, they acquire multipotency and undergo asymmetric divisions to form astrocytes and oligodendrocytes.[6-8] Cytokine signaling by the interleukin-6 (IL-6) family cytokines are the chief extrinsic signals for turning on astrocytic differentiation.[9,10] Leukemia inhibiting factor (LIF) and ciliary neurotrophic factor (CNTF) are able to induce astrocyte cell fate via the Janus kinase (JAK) signal transduction activation of signal transducers and activators of transcription (STAT3) factor. The methylation status of the STAT3 binding site of the astrocyte marker called glial fibrillary acidic protein (GFAP) determines if an astocyte fate is induced or not. The hypomethylated state of the STAT3 binding site in the GFAP promoter at late gestation allows the activation of astrocytic genes.[11] Bone morphogenic protein (BMP-2), a member of the IL-6 family works by increasing histone acetylation at the promoter of S100β, another astrocyte marker during late gestation.[12]

Methyl-CpG binding domain (MBD) proteins are important in maintaining neuronal identity and differential plasticity.[13] They are abundantly expressed in neurons, but not in astrocytes and oligodendrocytes. Ectopic expression of MBD1 has been known to inhibit astrocyte differentiation while promoting neuronal differentiation in neuroepithelial cells which have become hypomethylated at the STAT3 binding site in the GFAP promoter, the reason being that they can still bind to DNA regions upstream of the STAT3 binding site and silence gene transcription by recruitment of repressor proteins.[13] Recently, long noncoding RNA (lncRNAs) has been shown to play a role in establishing and maintaining neural cell identity.[14]

What leads to the demethylation at the STAT3 binding site at late gestation?, The key epigenetic switch which turns on astrocyte development. Feng *et al*.,[15] observed the expression patterns of de novo DNA methyltransferases Dnmt-3a and -3b. They observed that they are differentially expressed in different types of CNS cells and their expression profiles indicated that they were dynamically regulated in the embryonic and adult CNS. They concluded that Dnmt-3a could possibly play a role in neuronal and astroglial differentiation based on its expression profile. Dnmt-1 (a maintenance methyltransferase) deficiency has been known to cause precocious astrogliogenesis.[16] Dnmt-3a and -3b also have maintenance functions.[17] Thus de-methylation may occur due to the downregulation of the maintenance methytransferases at late gestation. Apart from DNA methylation, histone modifications are involved in turning on astrocyte cell fate. Fibroblast growth factor-2 (FGF-2) and CNTF increase the accessibility of a complex formed by STAT3 and CREB (cAMP response element binding) binding protein (CBP) to the GFAP promoter by inducing H3K4 methylation and suppressing H3K9 methylation around the STAT3 binding site to induce astrogliogenesis.

Other transcriptional regulators nuclear receptor co-repressor (N-CoR) and orphan nuclear receptor TLX (tailless homolog) are responsible for promoting a neuronal cell fate by suppressing the GFAP gene. Knockout mutant lines for these genes showed precocious GFAP expression and increased differentiation to astrocytes respectively.[18,19] The role of basic Helix-Loop-Helix (bHLH) transcription factor Neurogenin1(Ngn1) which suppresses astrocyte cell fate even in the presence of CNTF and LIF was studied by Sun and colleagues.[20] They proposed a 'sequestration model' to explain the switch from neurogenesis to gliogenesis. Ngn1 sequesters an activator complex CBP/p300/Smad1 to the promoter of neuronal

fate inducing gene NeuroD. As gestation proceeds, Ngn1 is downregulated. STAT3 now complexes with Smad1 to initiate astrogliogenesis. The RE1 silencing transcription factor (REST/NRSF) complex also mediates neuronal gene expression.[21,22] When bound to the repressor element 1 or NRSE (RE-1/NRSE) site, transcription of neuronal genes is inhibited. Its dissociation from the site is sufficient to turn on some neuronal genes (Class I genes). An additional complex of corepressor CoREST and methyl DNA-binding protein (MeCP2) is involved in repression which binds to a site nearby the RE-1/NSRE site to repress transcription. It dissociates from this site in the event of membrane depolarization. When both inhibitory complexes are dissociated, a second class of neuronal genes (Class II) is expressed.[21] A review by Ballas[22] details the role played by the REST/NRSF complex in mediating neuronal gene expression.

Neural Behavior

Early work by Meaney and Szyfon the effects of maternal care on the epigenome could precisely and elegantly confirm how early life experiences leave indelible epigenetic marks consequently determining behavior. Since then a number of studies carried out in similar vein have assessed the role of several putative factors known to influence behavior. Epigenetic effects have been explained well in the case of mouse models, but the lack of clear-cut evidence in humans makes it difficult to ascertain the role played by them in the human context.[23-25]

Early life experiences and stressful events can have long-lasting effects on brain development and the capacity of an individual to respond to stress later on in life.[26] This happens by the alteration of neuroendocrine responses, metabolic and immune system function.[25] During sensitive stages, especially in early development, stimuli are transmitted to the brain and influence functions of neurons and key neural pathways which determine behavior in later life.[26] The quality of the prenatal and early postnatal environment are important phases where some of the basis for adult behavior could be hard wired including vulnerability to stress, susceptibility to disease, cognitive deficits, etc.[27,28]

The following table lists some of the known effects of early-life experiences and environmental factors which have been shown to have an epigenetic cause [Table 1].

Epigenetics in neural plasticity, memory, and learning

Long-term changes in synaptic plasticity in the fundamental basis for learning and memory. In Aplysia, histone acetylation and deacetylation dynamics modulates the turning on or off of the memory-related genes. CBP which has histone acetyltransferase (HAT) activity is important for long-term memory particularly in the context of contextual fear conditioning and novel object recognition.[40-42] An excitatory neurotransmitter induced the expression of CREB binding protein (CBP1/CBP) leading to the activation of CCAAT-enhancer binding proteins (C/EBP) required for long-term facilitation (LTF). Inhibition of C/EBP can occur leading to long-term depression by the histone deacetylase (HDAC) repressor complex containing activating transcription factor 4 and HDAC (ATF4/HDAC5) on the target gene promoter.[43] In mammalian models of synaptic plasticity N-methyl-D-aspartate (NMDA) receptors and mitogen activated protein kinase/ extracellular signal-regulated kinase (MEK-ERK/MAPK) signalling have been implicated to increase histone acetylation (H3) especially in contextual fear conditioning.[44-46] SWItch/ sucrose non-fermentable family of chromatin remodeling proteins associate with HATs or HDACs and other transcription factors to activate and repress target memory related genes.[47] Poly ADP-ribosylation carried out by polyADP-ribose polymerase-1 is need for long-term memory.[48] Brain-derived neurotrophic factor (BDNF) is a key regulator of synaptic plasticity and memory formation.[49] Bredy *et al.*,[50] observed histone modifications around specific bdnf promoters which correlated with memory formation. During the consolidation of fear memories differential methylation is observed in the bdnf promoter which is dynamically regulated.[51] Detailed reviews have dealt with the important role played by epigenetics and the bdnf gene in synaptic plasticity, learning, and memory formation.[49,52,53]

Recently, Moutri and colleagues at the Salk Institute at La Jolla, California observed a surge of long interspersed nuclear elements (LINE) which are normally inhibited in NSCs (through chromatin condensation and Sox 2/HDAC1 repression).[54-56] They proposed that these elements which

Table 1: Early-life experiences/environmental factors and their associated epigenetic modification

Early life event/specific experience	Adult behavior that was affected	Region/gene where the epigenetic modification was observed	Possible connection	Additional remarks	Reference
Maternal effect: Pup licking and grooming (LG) and arched-back nursing (ABN)	Stress response (moderate to high hypothalamic-pituitary-adrenal (HPA) response) and fearfulness	Exon 17 (non-coding) region of GR gene. Modifications: Deoxyribonucleic acid (DNA) methylation, histone acetylation	De-methylation at NGFI-A binding site allows to increased GR expression and moderate HPA stress response	DNA methylation patterns Emerged in the first week of life Reversed by cross-fostering Reversal by histone deacetylase (HDAC) inhibitor trichostatin A (TSA)	23,24,25
Maternal effect: LG	Maternal care behavior of female rats mediated by oxytocin responsiveness	Estrogen receptor (ER)-α gene expression in medial preoptic area (MPOA) of hippocampus Modification: DNA methylation	Female offspring of low LG mothers have high levels of ERα promoter methylation hence low oxytocin responsiveness	Clearly shows epigenetic perpetuation of behavior across generations	29,30
Maternal deprivation (MD)	Hippocampus-dependent memory tasks such as reflex development	Reelin gene Modification: DNA methylation	Increased DNA methylation decreased reelin expression in the hippocampus	Neurobehavioral changes were linked to reelin expression in hippocampus	31
Early-life abuse	Neural mechanisms of cognition and emotion	BDNF gene expression in prefrontal cortex (PFC). Modification: DNA hypermethylation in the regulatory region of BDNF gene	Decreased BDNF expression in PFC leads to cognitive deficits and aberrant emotional behavior	Altered methylation pattern was found to be transmitted to offspring of females exposed to abuse Rescue through HDAC inhibitor Zebularin	32
Early-life abuse	Predisposition to suicidal behavior	Glucocorticoid receptor (GR) promoter Modification: DNA hypermethylation	Decreased GR expression linked to suicidal tendencies	Observed in post mortem brains	33
Social defeat/ bullying by bigger mouse	Depression-like behavior	BDNF gene Modification: Histone modification	Histone methylation at BDNF promoters led to suppressed BDNF gene activity in the hippocampus	Anti-depressant Ipimarine administration reversed depressive traits by downregulation of HDAC 5	34
Social conflict model	Social stress	Inflalimbic medial prefrontal cortex (mPFC) Modification: H3 acetylation and H3 phosphoacetylation	Plausible link between stress induced chromatin remodeling and increased ΔFosB expression	ΔFosB immunoreactive cells were increased in mPFC	35
Mouse strains of differential stress response	Susceptibility to stress and depression	GDNF promoter in NAc Modification: DNA methylation, histone modifications	Epigenetic regulation of GDNF promoter in the NAc		36

Other neurobehavioral phenomenon with known epigenetic links

Observed phenomenon	Epigenetic link	Additional remarks	Reference
Cognitive deficits and hyper-anxiety like behaviors	KAP1 mediated epigenetic repression; Genes Mkrn3 and Cdkn1c Modification: H3K9 trimethylation, H3 and H4 acetylation	KAP1 knockouts show overexpression of genes that induce anxiety	37
Age associated memory impairment in rats	Hippocampus Modification: H4K12 acetylation	Deregulation of H4K12 acetylation leads to failure to initiate hippocampal gene expression program	38
Posttraumatic stress disorder	Altered DNA methylation profiles	Occurs possibly through low levels of DNA methylation in immune related genes	39

can insert new copies of themselves into other areas of the genome could have deeper functional consequences than was previously understood. Epigenetics and retrotransposition may confer properties such as somatic variability, plasticity, and the required complexity to the cells of the CNS to carry out their complex tasks.

Structural Plasticity: The Adult Neurogenesis Paradigm

Adult neurogenesis occurs in two principal areas in the brain namely the subgranular zone of the hippocampus dentate gyrus and the subventricular zone. In a review

by Hsieh and Eisch,[4] a detailed view of hippocampal neurogenesis and its implications in neuropsychiatric disorders has been discussed. The impediments in understanding the neurogenesis puzzle are associated with the difficulty in tracking adult-generated neurons *in vivo*, isolating NSCs and the association of several signals arising from niche cells such as astrocytes, nearby neurons, and endothelial cells.[57] However much has been learnt about the intrinsic epigenetic mechanisms involved in the process.

Ma *et al*., investigated activity-dependent neurogenesis in the adult hippocampus; one of the main types of neural plasticity exhibited by the mammalian brain.[58] They discovered the interesting role played by growth arrest and DNA-damage-inducible protein beta (Gadd45) in active DNA demethylation of specific promoters of genes required for adult neurogenesis. Mature dentate gyrus neurons were activated by electroconvulsive therapy (ECT) which saw a concomitant increase in hippocampal neurogenesis. Gadd45b which belongs to a family of proteins implicated in DNA repair[59,60] was strongly induced by ECT. Gadd45b knockouts showed less effective ECT induced neurogenesis and also attenuated dendritic growth of newborn neurons compared to their wildtype counterparts. Significant demethylation was found at regulatory regions of the bdnf and FGF-1 genes which promote dendritic growth and neural progenitor proliferation, respectively.[58] Chromatin immunoprecipitation (ChIP) assays confirmed the binding of Gadd45b to the regulatory regions of these genes confirming its role in effecting locus specific DNA demethylation in the mammalian system. The same author followed-up this discovery with a review titled 'Epigenetic choreographers of neurogenesis in the adult mammalian brain',[61] which dealt with intrinsic epigenetic mechanisms and extrinsic niche signaling involved in adult neurogenisis.

Epigenetic Dysregulation is Associated with Many Neuropsychiatric Disorders

As a consequence of the important role played by epigenetics in a number of processes in the nervous system, it is hardly surprising that the deregulation of epigenetic mechanisms has been implicated in a number of neuronal diseases.

Table 2 lists epigenetic links to certain neuropsychiatric disorders, drug addiction, and effect of substance use during pregnancy.

Conclusions and future perspectives

The studies presented above indicate that intrinsic epigenetic mechanisms play a crucial role in several processes occurring in the nervous system from NCS differentiation to complex tasks like learning and memory formation. The dynamic nature of epigenetic modifications have made them ideal for carrying out many of these functions which rely on precise spatial and timely orchestration of gene expression patterns. The large repertoire of modifications that can be performed on the histone tails and the addition and removal of methylation marks on cytosines make it possible to carry out many of these functions. With new types of modifications being discovered like the recent discovery of hydroxymethylcytosine and the implication of DNA repair enzymes in de novo demethylation, we are beginning to understand the scale of the molecules that are involved in these processes. Epigenetic mechanisms have in essence been co-opted by the nervous system to perform several of the complex tasks that it performs and as such it explains elegantly how many of these functions are carried out at the molecular level. Its particular success in explaining the effect of early life experiences, maltreatment, and social stress in animal models of behavior has garnered much attention and very soon we may have answers of how exactly they operate in the human context. So it seems that some of society's complex problems could be explained by simple molecular mechanisms occurring at the cellular level and also opens the doors for possible therapeutic interventions at the proper times to counteract the effects of abuse or neglect. Diseases with an epigenetic basis for their pathology are being investigated to device more directed approaches towards treating these ailments. Overall, the understanding of the role of epigenetics in the nervous system has opened doors for investigation in a plethora of subfields and promises to provide answers some of the deepest questions concerning the human brain and also cures for many neuropsychiatric diseases.

Table 2: Epigenetics in neuropsychiatric disorders

Neuropsychiatric disease	Epigenetic link	Reference
Rett's syndrome	MeCP2 mutation	62, 63
Rubinstein-Taybi syndrome	Heterozygous mutation in CREB (cAMP response element binding) binding protein (CBP)	62, 64
Fragile X syndrome	Hypermethylation of deoxyribonucleic acid (DNA) at the FMR1 and FMR2 promoters, caused by trinucleotide repeat expansion	62, 65
Immunodeficiency-centromeric instability-facial anomalies (ICF) syndrome	Mutations in Dnmt3B; hypomethylation at centromeric regions of chromosomes 1, 9, and 16	62, 66
Coffin-Lowry syndrome	Mutation in RSK2, which can interact with CREB and CBP and can phosphorylate H3 *in vitro* 106	66,67
Prader-Willi syndrome	Abnormal imprinting (DNA methylation) of paternal chromosomal region 15q11-13	68,69
Anglemann's syndrome	Abnormal imprinting (DNA methylation) of maternal chromosomal region 15q11-13	68,69
Depression	Epigenetic deregulation leads to reduced neurogenesis and impaired neuronal plasticity; main factors in the pathogenesis of depression, behavioral despair, and cognitive deficits	70
Pediatric and adult nervous system tumors	Epigenetic alterations implicated in tumor maintenance and progression	71
Schizophrenia	Epigenetic repression of Reelin and glutamic acid decarboxylase 1 or GAD67	72
Epilepsy	Through epigenetic deregulation of synaptic plasticity and neurogliogenesis	73,74
Epigenetics in drug addiction and compulsive drug-seeking behaviors		
Drug	**Epigenetic modification**	**Reference**
Chronic cocaine administration	Two genes silent mating type information regulation homologs 1 and 2 (SIRT1 and SIRT2) were hyperacetylated at H3 in NAc	75
	H4 hyperacetylation was seen at the cFos gene promoter and H3 hyperacetylation in BDNF and cyclin dependent kinase (CDK5) gene promoters in the striatum	76
Epigenetic changes in offspring occurring due to the quality of prenatal environment		
Environmental effect	**Epigenetic modification**	**Reference**
Consumption of alcohol during pregnancy	Unknown	77
High levels of depression and anxiety during the third trimester	Increased methylation of GR promoter (as observed in cord blood cells)	78
Exposure to cocaine during second and third trimesters of gestation	Global changes in DNA methylation in the hippocampus	79

References

1. Hsieh J, Gage FH. Epigenetic control of neural stem cell fate. Curr Opin Genet Dev 2004;14:461-9.
2. Miller G. Epigenetics. The seductive allure of behavioral epigenetics. Science 2010;329:24-7.
3. Namihira M, Kohyama J, Abematsu M, Nakashima K. Epigenetic mechanisms regulating fate specification of neural stem cells. Philos Trans R Soc Lond B Biol Sci 2008;363:2099-109.
4. Hsieh J, Eisch AJ. Epigenetics, hippocampal neurogenesis, and neuropsychiatric disorders: Unraveling the genome to understand the mind. Neurobiol Dis 2010;39:73-84.
5. Jiang Y, Langley B, Lubin FD, Renthal W, Wood MA, Yasui DH, *et al*. Epigenetics in the nervous system. J Neurosci 2008;28:11753-9.
6. Temple S. The development of neural stem cells. Nature 2001;414:112-7.
7. Fujita S. The discovery of the matrix cell, the identification of the multipotent neural stem cell and the development of the central nervous system. Cell Struct Funct 2003;28:205-28.
8. Miller RH. Oligodendrocyte origins. Trends Neurosci 1996;19:92-6.
9. Bonni A, Sun Y, Nadal-Vicens M, Bhatt A, Frank DA, Rozovsky I, *et al*. Regulation of gliogenesis in the central nervous system by the JAK–STAT signaling pathway. Science 1997;278:477-83.
10. Rajan P, McKay RD. Multiple routes to astrocytic differentiation in the CNS. J Neurosci 1998;18:3620-9.
11. Takizawa T, Nakashima K, Namihira M, Ochiai W, Uemura A, Yanagisawa M, *et al*. DNA methylation is a critical cell-intrinsic determinant of astrocyte differentiation in the fetal brain. Dev Cell 2001;1:749-58.
12. Namihira M, Nakashima K, Taga T. Developmental stage dependent regulation of DNA methylation and chromatin modification in an immature astrocyte specific gene promoter. FEBS Lett 2004;572:184-8.
13. Setoguchi H, Namihira M, Kohyama J, Asano H, Sanosaka T, Nakashima K. Methyl-CpG binding proteins are involved in restricting differentiation plasticity in neurons. J Neurosci Res 2006;84:969-79.
14. Shi-Yan Ng, Johnson R, Stanton LW. Human long non-coding RNAs promote pluripotency and neuronal differentiation by association with chromatin modifiers and transcription factors. EMBO J 2012;31:522-33.
15. Feng J, Chang H, Li E, Fan G. Dynamic Expression of de novo DNA Methyltransferases Dnmt3a and Dnmt3b in the central nervous system. J Neurosci Res 2005;79:734-46.
16. Fan G, Martinowich K, Chin MH, He F, Fouse SD, Hutnick L, *et al*. DNA methylation controls the timing of

astrogliogenesis through regulation of JAK-STAT signaling. Development 2005;132:3345-56.
17. Ooi SK, O'Donnell AH, Bestor TH. Mammalian cytosine methylation at a glance. J Cell Sci 2009;122:2787-91.
18. Hermanson O, Jepsen K, Rosenfeld MG. N-CoR controls differentiation of neural stem cells into astrocytes. Nature 2002;419:934-9.
19. Shi Y, Lie DC, Taupin P, Nakashima K, Ray J, Yu RT, *et al*. Expression and function of orphan nuclear receptor TLX in adult neural stem cells. Nature 2004;427:78-83.
20. Sun Y, Nadal-Vicens M, Misono S, Lin MZ, Zubiaga A, Hua X, *et al*. Neurogenin promotes neurogenesis and inhibits glial differentiation by independent mechanisms. Cell 2001;104:365-76.
21. Ballas N, Grunseich C, Lu DD, Speh JC, Mandel G. REST and its corepressors mediate plasticity of neuronal gene chromatin throughout neurogenesis. Cell 2005;121:645-57.
22. Ballas N, Mandel G. The many faces of REST oversee epigenetic programming of neuronal genes. Curr Opin Neurobiol 2005;15:500-6.
23. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, *et al*. Epigenetic programming by maternal behavior. Nat Neurosci 2004;7:847-54.
24. Szyf M, Weaver IC, Champagne FA, Diorio J, Meaney MJ. Maternal programming of steroid receptor expression and phenotype through DNA methylation in the rat. Front Neuroendocrinol 2005;26:139-62.
25. Weaver IC, Champagne FA, Brown SE, Dymov S, Sharma S, Meaney MJ, *et al*. Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: Altering epigenetic marking later in life. J Neurosci 2005;25:11045-54.
26. McEwen BS, Eiland L, Hunter RG, Miller MM. Stress and anxiety: Structural plasticity and epigenetic regulation as a consequence of stress. Neuropharmacol 2012;62:3-12.
27. Mustard JF. Early brain development and human development. In: Tremblay RE, Boivin M, Peters RDeV, eds. Encyclopedia on Early Childhood Development [online]. Montreal, Quebec: Centre of Excellence for Early Childhood Development and Strategic Knowledge Cluster on Early Child Development; 2010:1-5. Available at: http://www.child-encyclopedia.com/documents/MustardANGxp.pdf. Accessed on 2012-Oct-21.
28. Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. Nat Rev Genet 2007;8:253-62.
29. Champagne FA, Weaver IC, Diorio J, Sharma S, Meaney MJ. Natural variations in maternal care are associated with estrogen receptor alpha expression and estrogen sensitivity in the medial preoptic area. Endocrinology 2003;144:4720-4.
30. Champagne FA, Weaver IC, Diorio J, Dymov S, Szyf M, Meaney MJ. Maternal care associated with methylation of the estrogen receptor-alpha1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring. Endocrinology 2006;147:2909-15.
31. Qin L, Tu W, Sun X, Zhang J, Chen Y, Zhao H. Retardation of neurobehavioral development and reelin down-regulation regulated by further DNA methylation in the hippocampus of the rat pups are associated with maternal deprivation. Behav Brain Res 2011;217:142-7.
32. Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the *BDNF* gene. Biol Psychiatry 2009;65:760-9.
33. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, *et al*. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 2009;12:342-8.
34. Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nat Neurosci 2006;9:519-25.
35. Hinwood M, Tynan RJ, Day TA, Walker FR. Repeated social defeat selectively increases ΔFosB expression and histone H3 acetylation in the infralimbic medial prefrontal cortex. Cereb Cortex 2011;21:262-71.
36. Uchida S, Hara K, Kobayashi A, Otsuki K, Yamagata H, Hobara T, *et al*. Epigenetic status of Gdnf in the ventral striatum determines susceptibility and adaptation to daily stressful events. Neuron 2011;69:359-72.
37. Jakobsson J, Cordero MI, Bisaz R, Groner AC, Busskamp V, Bensadoun JC, *et al*. KAP1-mediated epigenetic repression in the forebrain modulates behavioral vulnerability to stress. Neuron 2008;60:818-31.
38. Peleg S, Sananbenesi F, Zovoilis A, Burkhardt S, Bahari-Javan S, Agis-Balboa RC, *et al*. Altered histone acetylation is associated with age-dependent memory impairment in mice. Science 2010;328:753-6.
39. Uddin M, Aiello AE, Wildman DE, Koenen KC, Pawelec G, De Los Santos R, *et al*. Epigenetic and immune function profiles associated with posttraumatic stress disorder. Proc Natl Acad Sci U S A 2010;107:9470-5.
40. Vecsey CG, Hawk JD, Lattal KM, Stein JM, Fabian SA, Attner MA, *et al*. Histone deacetylase inhibitors enhance memory and synaptic plasticity via CREB: CBP-dependent transcriptional activation. J Neurosci 2007;27:6128-40.
41. Korzus E, Rosenfeld MG, Mayford M. CBP histone acetyltransferase activity is a critical component of memory consolidation. Neuron 2004;42:961-72.
42. Alarcón JM, Malleret G, Touzani K, Vronskaya S, Ishii S, Kandel ER, *et al*. Chromatin acetylation, memory, and LTP are impaired in CBP+/-mice: A model for the cognitive deficit in Rubinstein-Taybi syndrome and its amelioration. Neuron 2004;42:947-59.
43. Guan Z, Giustetto M, Lomvardas S, Kim JH, Miniaci MC, Schwartz JH, *et al*. Integration of long-term-memory-related synaptic plasticity involves bidirectional regulation of gene expression and chromatin structure. Cell 2002;111:483-93.
44. Fanselow MS, Kim JJ, Yipp J, De Oca B. Differential effects of the N-methyl-D-aspartate antagonist DL-2-amino- 5-phosphonovalerate on acquisition of fear of auditory and contextual cues. Behav Neurosci 1994;108:235-40.
45. Atkins CM, Selcher JC, Petraitis JJ, Trzaskos JM, Sweatt JD. The MAPK cascade is required for mammalian associative learning. Nat Neurosci 1998;1:602-9.
46. Rampon C, Tang YP, Goodhouse J, Shimizu E, Kyin M, Tsien JZ. Enrichment induces structural changes and recovery from nonspatial memory deficits in CA1 NMDAR1-knockout mice. Nat Neurosci 2000;3:238-44.
47. Knoepfler PS, Eisenman RN. Sin meets NuRD and other tails of repression. Cell 1999;99:447-50.
48. Cohen-Armon M, Visochek L, Katzoff A, Levitan D,

Susswein AJ, Klein R, *et al*. Long-term memory requires polyADP-ribosylation. Science 2004;304:1820-2.
49. Woo NH, Lu B. BDNF in synaptic plasticity and memory. Encyclopedia of neuroscience. Amsterdam: Elsevier Ltd; 2009. p. 135-43.
50. Bredy TW, Wu H, Crego C, Zellhoefer J, Sun YE, Barad M. Histone modifications around individual BDNF gene promoters in prefrontal cortex are associated with extinction of conditioned fear. Learn Mem 2007;14:268-76.
51. Lubin FD. Epigenetic gene regulation in the adult mammalian brain: Multiple roles in memory formation. Neurobiol Learn Mem 2011;96:68-78.
52. Gómez-Palacio Schjetnan A, Escobar-Rodríguez ML. Memory coding and retention: brain-derived neurotrophic factor (BDNF) in synaptic plasticity. Rev Neurol 2007;45:409-17.
53. Bekinschtein P, Cammarota M, Izquierdo I, Medina JH. Reviews: BDNF and memory formation and storage. Neuroscientist 2008;14:147-56.
54. Muotri AR, Chu VT, Marchetto MC, Deng W, Moran JV, Gage FH. Somatic mosaicism in neuronal precursor cells mediated by L1 retrotransposition. Nature 2005;435:903-10.
55. Muotri AR, Zhao C, Marchetto MC, Gage FH. Environmental influence on L1 retrotransposons in the adult hippocampus. Hippocampus 2009;19:1002-7.
56. Singer T, McConnell MJ, Marchetto MC, Coufal NG, Gage FH. LINE-1 retrotransposons: Mediators of somatic variation in neuronal genomes? Trends Neurosci 2010;33:345-54.
57. Mateus-Pinheiro A, Pinto L, Sousa N. Epigenetic (de) regulation of adult hippocampal neurogenesis: Implications for depression. Clin Epigenetics 2011;3:5.
58. Ma DK, Jang MH, Guo JU, Kitabatake Y, Chang ML, Pow-Anpongkul N, *et al*. Neuronal activity–induced Gadd45b promotes epigenetic DNA demethylation and adult neurogenesis. Science 2009;323:1074-7.
59. Jung HJ, Kim EH, Mun JY, Park S, Smith ML, Han SS, *et al*. Base excision DNA repair defect in Gadd45a-deficient cells. Oncogene 2007;26:7517-25.
60. Tran H, Brunet A, Grenier JM, Datta SR, Fornace AJ Jr, DiStefano PS, *et al*. DNA repair pathway stimulated by the forkhead transcription factor FOXO3a through the Gadd45 protein. Science 2002;296:530-4.
61. Ma DK, Marchetto MC, Guo JU, Ming GL, Gage FH, Song H. Epigenetic choreographers of neurogenesis in the adult mammalian brain. Nat Neurosci 2010;13:1338-44.
62. Ausio J, Levin DB, De Amorim GV, Bakker S, Macleod PM. Syndromes of disordered chromatin remodeling. Clin Genet 2003;64:83-95.
63. Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet 1999;23:185-8.
64. Vo N, Goodman RH. CREB-binding protein and p300 in transcriptional regulation. J Biol Chem 2001;276:13505-8.
65. Lim JH, Booker AB, Fallon JR. Regulating fragile X gene transcription in the brain and beyond. J Cell Physiol 2005;205:170-5.
66. Merienne K, Pannetier S, Harel-Bellan A, Sassone-Corsi P. Mitogen-regulated RSK2-CBP interaction controls their kinase and acetylase activities. Mol Cell Biol 2001;21:7089-96.
67. Weeber EJ, Levenson JM, Sweatt JD. Molecular genetics of human cognition. Mol Interv 2002;2:376-91, 339.
68. Tsankova N, Renthal W, Kumar A, Nestler EJ. Epigenetic regulation in psychiatric disorders. Nat Rev Neurosci 2007;8:355-67.
69. Davies W, Isles AR, Wilkinson LS. Imprinted gene expression in the brain. Neurosci Biobehav Rev 2005;29:421-30.
70. Pinheiro M, Pinto L, Sousa N. Epigenetic (de)regulation of adult hippocampal neurogenesis: Implications for depression. Clin Epigenetics 2011;3:5.
71. Qureshi IA, Mehler MF. Epigenetics, nervous system tumors, and cancer stem cells. Cancers 2011;3:3525-56.
72. Foti SB, Roskams AJ. A tale of two epiphenomena: The complex interplay of epigenetics and epilepsy, underlying mechanisms of epilepsy. In: Kaneez FS, editor. InTech, 2011. Available from: http://www.intechopen.com/books/underlying-mechanisms-of-epilepsy/a-tale-of-two-epiphenomena-the-complex-interplay-of-epigenetics-and-epilesy. [Last accessed on 2012-Oct-21].
73. Lubin FD. Epileptogenesis: Can the science of epigenetics give us answers? Epilepsy Curr 2012;1:105-10.
74. Levenson JM. DNA (Cytosine-5) methyltransferase inhibitors: A potential therapeutic agent for schizophrenia. Mol Pharmacol 2007;71:635-7.
75. Renthal W, Kumar A, Xiao G, Wilkinson M, Covington HE 3rd, Maze I, *et al*. Genome-wide analysis of chromatin regulation by cocaine reveals a role for sirtuins. Neuron 2009;62:335-48.
76. Kumar A, Choi KH, Renthal W, Tsankova NM, Theobald DE, Truong HT, *et al*. Chromatin remodeling is a key mechanism underlying cocaine-induced plasticity in striatum. Neuron 2005;48:303-14.
77. Haycock PC. Fetal alcohol spectrum disorders: The epigenetic perspective. Biol Reprod 2009;81:607-17.
78. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics 2008;3:97-106.
79. Novikova SI, He F, Bai J, Cutrufello NJ, Lidow MS, Undieh AS. Maternal cocaine administration in mice alters DNA methylation and gene expression in hippocampal neurons of neonatal and prepubertal offspring. PLoS One 2008;3:e1919.

Cite this article as: Ravi B, Kannan M. Epigenetics in the nervous system: An overview of its essential role. Indian J Hum Genet 2013;19:384-91.

Source of Support: Nil, **Conflict of Interest:** None declared.