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Long-Lasting and Transgenerational Effects of an Environmental Enrichment on Memory Formation

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Abstract

It has long been believed that genetically-determined, but not environmentally-acquired, phenotypes can be inherited. However, a large number of recent studies have reported that phenotypes acquired from an animal's environment can be transmitted to the next generation. Moreover, epidemiology studies have hinted that a similar phenomenon occurs in humans. This type of inheritance does not involve gene mutations that change DNA sequence. Instead, it is thought that epigenetic changes in chromatin, such as DNA methylation and histone modification, occur. In this review, we will focus on one exciting new example of this phenomenon, transfer across generations of enhanced synaptic plasticity and memory formation induced by exposure to an "enriched" environment.

Keywords

LTP; epigenetics; Ras-GRF; enriched environment; transgenerational

1) Introduction

There is strong evidence supporting the idea that at least part of the mechanism underlying memory formation involves forms of synaptic plasticity. These include long-term potentiation (LTP) and long-term depression (LTD) [1], which allow for long-term changes in the efficiency of individual synapses in response to a specific type of signal. In this way, new information can be stored in activated networks of neurons. It is clear however that the molecular mechanisms that drive synaptic plasticity vary among different types of synapses and change during different stages of postnatal development. Moreover, there exists a higher level of synaptic plasticity regulation, referred to as metaplasticity [2], which sets the current synaptic state based on previous external influences. This "plasticity" of synaptic plasticity is able to regulate neuron processes for minutes, months or as discussed in detail in this review across generations. The simplest forms of metaplasticity are generated within individual neurons such that previous neurotransmitter stimulation can influence the threshold of subsequent induction of LTP or LTD[3]. More complex metaplasticity is induced by specific behavioral events. One well-studied example involves developmental metaplasticity in the visual cortex. In this system, dark rearing of animals reduces the threshold for subsequent LTP and LTD, via inhibition of the switch in the composition of NMDA receptor subtypes that normally occurs during a critical time window during

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development [4]. Another example pertinent to this review is the effect of exposure of young animals to an enriched environment, which leads to quantitative as well as qualitative changes in the way LTP is induced[5,6] for long periods of time and even across generations [7,8]. This latest finding raises the remarkable possibility that the quality of one's memory is influenced by the environment in which one's parents lived during their youth.

2. Enriched Environment (EE)

The proper execution of complex animal functions and their breakdown in disease involves an interaction between the genetics of an animal and its environment. Although much information is available on the roles that individual genes play in such processes, how environmental factors contribute is only beginning to be understood. For example, studies in humans of neurological and psychiatric disorders involving monozygotic twins have highlighted the importance of environmental factors in brain function [9]. Yet, the vast majority of experiments on LTP and LTD relied on samples from animals housed in a conventional laboratory environment, which usually involves mice in small cages with only plain bedding, food and water.

The concept of EE was first proposed by Donald Hebb, when he allowed rats to explore freely in his home, and he found that they performed better in problem solving than laboratory-housed littermates [8]. Subsequently, many studies have been performed to better understand the effects of EE on animal behavior and the mechanisms underlying them[10]. This approach has attracted attention for its potential ability to reveal novel ways to improve brain performance particularly in the elderly. The consequences of an enriched environment during early adolescence has gained much attention recently with the revelation, discussed in detail below, that enhanced memory associated with exposure to EE can be transmitted across generations [7].

A variety of EE protocols have been developed. For the most part, an enriched environment typically includes larger than normal cages, larger groups of animals with opportunity for more complex social behaviors, various stimulatory objects such as toys of different compositions, shapes and sizes, and opportunities for voluntary physical activity [11]. In this way, EE usually involves enhanced sensory, cognitive, motor and visual stimuli. Importantly, an enriched environment may be a more natural environment than a conventional lab setting for animals like mice and rats. With this, experiments delineating how EE alters brain function may be necessary to effectively understand brain function and how to modulate it to treat neurological disorders.

3. Effects of EE on brain function

EE has been shown to improve learning and memory, induce a reversal of learning defects caused by genetic alterations in mice, as well as delay in the onset of symptoms in animal models of a variety of neurological disorders such as Huntington's, Alzheimer's disease, epilepsy, Fragile X syndrome, and Parkinson's disease [10]. EE can even restore lost memories associated with neuronal damage [12]. EE is also known to cause milder responses to stress [13] and in some settings prevent depression-like behaviors [14]. EE has also been shown to reverse the negative effects on stress response induced by poor maternal parenting [15].

Many effects of EE can be detected in assays of memory in animal models. For example, memory for contextual fear conditioning was improved in mice exposed to 8-weeks of EE [5]. In another study, enriched mice showed a significantly reduced latency in the novelty-suppressed feeding test and used a more direct route to the platform[16]. Also in Morris

water maze assays, mice enriched for 8-weeks used a more direct route to the platform [16] and displayed shorter latency [17].

EE enhancement of learning and/or memory was also reported in mice genetically impaired in these processes. In knockout mice lacking the NR1 subunit of NMDA receptors in the CA1 region of hippocampus, restored deficient memory detected in a novel object recognition test, contextual fear conditioning, and social transmission of food preference [18]. Similarly, defective memory for contextual fear conditioning was improved by a 2-week exposure of Ras-GRF knockout mice to EE [7]. It has also been reported that a 5 to 7week exposure to EE rescues learning deficits in Kv β 1.1 null mice in the social transmission of food preferences (STFP) task [19]. However, in CaMKII autophosphorylation site mutants, EE failed to rescue the impairment in Morris Water Maze [20](Need and Giese, 2003). This result suggests that EE does not randomly rescue any kinds of learning impairment, but instead it is capable to rescue learning impairment caused by deficits in a certain subset of molecules.

Many physical changes in the brain have been observed in response to EE that might account for its physiological effects, such as enhanced dendritic branching and synaptic density, neurogenesis, and expression levels and activities of key neuronal proteins like BDNF [11,21–23]. Gene array studies have detected a change in a large number of genes in response to enrichment, many of which can be linked to neuronal structure, synaptic plasticity and transmission [24]. In addition, as described below signaling networks that regulate synaptic plasticity can be modulated by an enriched environment.

4. Mechanisms of EE action on memory formation

4.1 EE enhances LTP

LTP is a phenomenon that leads to the enhancement of synaptic transmission efficiency and is tightly linked to learning and memory. The biochemical mechanism underlying this phenomenon can depend upon the specific synapse investigated, the developmental stage of the animal studied and history of activity of that region of the brain (ie metaplasticity). For example, in the well-studied CA3/CA1 synapses of the hippocampus, the primary mechanism of LTP is post-synaptic, where high-frequency/short-duration stimulation of the innervating Schaffer collaterals promotes the insertion of AMPA-type glutamate receptors into the synaptic plasma membrane of the pyramidal CA1 neuron dendrites [25]. At other synapses, however, a presynaptic mechanism, such as an increase in the efficiency of neurotransmitter release from the axons, predominates [26].

Exposure of two-week old mice to an enriched environment for a relatively brief duration (ie weeks) can lead to an enhancement of LTP and fear conditioning memories [5–7]. It can also rescue defective LTP and fear conditioning memories associated with the loss of expression of Ras-GRF2 [6], a calcium regulated exchange factor that mediates NR2A-containing NMDA receptor activation of Erk MAP kinase, CREB and LTP [27,28]. Interestingly, EE does not rescue defective LTD associated with the loss of Ras-GRF1 [6], a related exchange factor that couples NR2B-containing NMDA receptors to p38 MAP kinase and LTD [27].

In the CA3/CA1 synapse of the hippocampus EE enhancement of LTP involves the appearance of a presynaptic component [29]. Thus, EE leads to both a qualitative and quantitative change in LTP. The former is thought to be important because the site of LTP expression affects how information is transmitted across the synapse. For example, post-synaptic expression of LTP decreases the signal to noise ratio of signaling (101), while pre-synaptically derived LTP leads to increased dynamic gain control (2) and makes the

stimulated synapse more sensitive to the “temporal coherence” of a signal (i.e. how waves of signals are coordinated when they arrive at the synapse) rather than its absolute rate [133].

4.2 EE changes the signaling pathways that promote LTP in an age-dependent manner

Biochemical studies designed to reveal the signaling pathways that mediate EE enhanced LTP confirmed the idea that EE changes how LTP is induced. One study on CA3/CA1 hippocampal synapses from newly weaned mice, showed that an 8-week exposure to EE induced the appearance of a cAMP regulated component to LTP [5]. A later study in similarly aged mice added to the previous finding by showing that only 2 weeks of exposure to EE induced the appearance of an otherwise latent NMDA receptor/p38 MAP kinase pathway that is modulated by cAMP [6], as illustrated in Fig. 1. Interestingly, previous studies on mice housed conventionally implicated Erk MAP kinase in LTP and p38 MAP kinase in LTD [30–32]. Moreover, when the Erk MAP kinase-dependent pathway to LTP was blocked in mice lacking the Ras exchange factor Ras-GRF2, EE could overcome the LTP defect by inducing this newly discovered p38 Map kinase pathway [6]. A reasonable explanation for this apparent paradox is that signaling proteins like p38 MAP kinase can play different roles depending upon the multi-component protein complex with which they associate.

Interestingly, this effect of EE on LTP was age-dependent, such that a similar exposure of 6-month old mice to EE did not rescue defective LTP. At this age, EE failed to induce the new p38-dependent pathway, indicating that the age dependency of EE rescue of LTP was due to the age dependency of EE effect on this p38-dependent signaling pathway. Expression levels of upstream or downstream components of the p38-dependent LTP pathway may change over time, so that EE can no longer gate this p38-dependent LTP pathway in adult mice. Indeed, It has been reported that EE changes expression levels of many genes, some of which are widely involved in intracellular signaling pathways [24]. Examining whether expression levels of those genes are regulated in an age-dependent manner would help to unveil the mechanism of the age-dependency of EE effects on LTP[6]. While the induction of this novel LTP - inducing signaling pathway by EE was found to be associated with enhanced memory for contextual fear conditioning, its age dependency suggests it is also involved in behaviors that, unlike fear conditioning, are specific to young mice. Understanding this role will require a strategy to specifically inhibit this NMDA/cAMP/p38 signaling pathway without interfering with other signaling pathways that influence brain function in animals.

4.3 Epigenetic mechanisms underlying EE action

The effects of EE are long-lasting. For example, a 2-week exposure of pre-adolescent mice to EE induces enhanced LTP that lasts for 3–4 months [7]. In addition, exposure of adolescent mice to EE reverses the negative effects that inadequate contact of newborns with their mothers usually has on their future nurturing behavior [15]. These findings implicate long-term EE-induced changes in the expression of key genes that regulate LTP and maternal behaviors, respectively. As such, epigenetic mechanisms, such as histone modifications are certainly involved. Histone modifications that regulate gene transcription include mainly acetylation, methylation, and phosphorylation. Among these, histone acetylation promotes transcription and histone deacetylation suppresses it. Remarkably, some histone deacetylase (HDAC) inhibitors positively affect LTP and memory function (for review see [33]).

A four-week exposure to EE rescued impaired memories in both fear conditioning and Morris Water Maze assays [12] normally found in mice with overexpressing p25 and in turn overactivating the protein kinase CDK5. This phenomenon was associated with enhanced

acetylation of multiple histone sites including H3K14, H3K9, H4K5, H4K8, and H4K12 in the hippocampus of these transgenic mice. Furthermore, daily intraperitoneal injection of an HDAC inhibitor for four weeks mimicked EE effects on memory in these transgenic mice. In a separate study implicating HDACs in LTP, HDAC2 knockout mice showed enhanced memory in contextual and cued fear conditioning, with facilitated LTP, while mice over-expressing HDAC2 in neurons showed impaired memory formation in contextual and cued fear conditioning, the Morris Water Maze, and showed suppressed LTP [34].

Consistent with this idea, the HDAC inhibitor Trichostatin A (TSA) enhanced LTP [35]. We also found that, like exposure to EE, exposure to TSA can overcome defective LTP found in mice lacking Ras-GRF2 (Li and Feig unpublished observations). In addition, like LTP enhanced by EE, LTP enhanced by TSA was also dependent upon p38-MAP kinase, which makes it plausible to speculate that EE enhancement of LTP is mediated by increased histone acetylation of key genes that regulate p38 MAP kinase activation to enhance synaptic plasticity and memory.

DNA methylation, has also been associated with learning. Methylation of CpG islands in gene promoters recruits methyl DNA binding domain (MBD)-containing proteins. MBD-containing proteins in turn recruit HDACs through adaptor proteins, leading to histone deacetylation and transcription suppression. DNA methylation is catalyzed by enzymes called DNA methyltransferases (DNMTs). A memory suppressor gene, PP1, gets methylated in its CpG island in the CA1 region of the hippocampus after fear conditioning training, decreasing its mRNA expression. On the other hand, fear conditioning training leads to demethylation of a CpG island in a memory promoting gene, reelin, with subsequent increase in reelin mRNA [36]. Additionally, BDNF gene expression is induced during learning. Demethylation of BDNF gene promoter is also associated with fear memory consolidation [37]. A study using mice genetically impaired in DNA methylation in excitatory neurons in the forebrain has also implicated DNA methylation in learning. DNMT1 and DNMT3a double-knockout mice show impaired LTP and learning in Morris Water Maze and contextual fear conditioning [38]. These findings, together with studies implicating histone modification in both learning and EE effects, imply that EE may enhance memory through either or both of these epigenetic mechanisms.

5. Transgenerational transmission of environmental effects on brain function

The concept that qualities acquired from experience can be transmitted to future offspring, a “Lamarckian-like” phenomenon, has been bolstered by a variety of recent studies. This type of phenomenon is likely achieved by transgenerational inheritance of epigenetic changes in genes induced in animals directly exposed to specific environments. Epigenetic transgenerational inheritance has been demonstrated to occur through both germ-line and somatic cells.

5.1 Germline mediated epigenetic transgenerational inheritance

Epigenetic marks on chromatin can be inherited through germ cells. In most cases studied to date, DNA methylation sites are erased during gonadal sex determination in embryogenesis. However, some survive this period and persist until the embryos become adult and sexually mature. The methylated DNA is integrated in the gametes and thus in the embryos of the next generation.

One example of this phenomenon leads to variation in the coat color of mice. This occurs in “viable yellow” mice (A^{VY}) and “Axin-fused” ($Axin^{Fu}$) mice where variably penetrant phenotypes are linked to DNA methylation of a retrotransposon driving expression of the

A^{VY} and Axin^{Fu} genes [39,40]. Interestingly, maternal diet influences the epigenetic status of F1 offspring through the alteration of methylation of the A^{VY} locus *in utero* [41,42].

Transgenerational, germline transmission of the effects of environmental toxins such as endocrine disruptors have also been observed over the past decade. For example, endocrine disruptors such as bisphenol-A (BPA), dichlorodiphenyltrichloroethane, and vinclozolin have reproductive hormone actions and influence reproduction and fertility of males in the next generation (for review see [43]). In fact, impairment in reproduction induced by endocrine disruptors can be inherited for as many as four generations through male germ line [44]. It was suggested that impairment in reproduction induced by endocrine disruptors is mediated by defective remethylation during gonadal sex determination, resulting in germ line reprogramming. Although most genes get reset in early embryonic development, a subset of genes called imprinted genes maintains their DNA methylation pattern that appears to be permanently programmed. In contrast to all somatic cells, the primordial germ cells undergo a demethylation during migration and early colonization of the embryonic gonad, followed by a remethylation starting at the time of sex determination in a sex-specific manner. The exposure of the pregnant mother at the time of sex determination to certain agents appears to have altered the remethylation in the germ line and permanently reprogrammed the imprinted pattern of DNA methylation.

5.2 Somatic cell mediated epigenetic transgenerational inheritance

Heritable epigenetic changes also occur through somatic rather than germ cells. Nevertheless, the phenotype can be passed on through multiple generations through behavioral induced epigenetic changes in chromatin. For example, it is known that there is natural variability among female rats in levels of maternal nurturing behavior, especially licking and grooming toward her pups (LG). This LG property is inherited such that the offspring of high LG mothers become high LG mothers, and the offspring of low LG mothers become low LG mothers when they mature (for review see [45]). High LG mothering results in elevated serotonin levels in the hippocampus of the pups, leading to increased expression of the transcription factor NGFI-A. This stimulates DNA hypomethylation, histone acetylation, and increased expression of glucocorticoid receptor (GR) that reduces stress levels. The opposite occurs in offspring of low LG mothers. The epigenetic marks maintain the GR expression state into adulthood and in females will determine the level of LG mothering, thus perpetuating the phenotype across generation.

Particularly pertinent to this review is the observation that the effect of early exposure of pups to low LG maternal behavior can be reversed by exposure to an enriched environment in early adolescence. This effect is associated with increased oxytocin receptor (OTR) binding activity, a property associated high LG behavior. [46].

Another example of somatic inheritance of epigenetic marks on DNA acquired from the environment is BDNF gene methylation regulated by early-life adversity [47]. Rats raised by poor maternal care mothers during the first postnatal week display long-lasting low BDNF mRNA, and a hypermethylated BDNF gene promoter in the prefrontal cortex. These offspring then maltreat their own offspring, who also display increased methylation and decreased BDNF gene expression. Cross-fostering these pups with mothers with a history of normal treatment during early development failed to completely block the increase in BDNF gene methylation. Thus, at least part of the transmission of this epigenetic regulation from poorly raised mothers to her offspring occurs before birth, presumably *in utero*.

5.3. Transgenerational effects of environmental factors on synaptic plasticity, learning and memory

A brief report some 25 years ago was the first to suggest that the enhanced learning and memory acquired from interactions with the environment can be passed on to offspring. In particular, exposure of pregnant rats to an enriched environment enhanced not only their ability to function in a maze but also the ability of their future offspring to do the same [48]. Another early study showed that enhanced learning ability was transmitted to offspring even when the dam had been exposed to EE before pregnancy [49]. Similar results were obtained when offspring of enriched mothers were raised from birth by a non-enriched foster mother. This implied that like the effect of poor early maternal care described in the previous section, the effect of EE was transmitted to the offspring before the birth, presumably *in utero*.

Follow-up studies on the effects of early mothering on the licking and grooming (LG) phenotype in rats described previously showed that high LG mothers display higher cognitive function as tested in the Morris Water Maze [50]. As mentioned above, the offspring of high LG mothers become high LG mother themselves, which means that the property of high cognitive function of high LG mothers can be transmitted to offspring. Notably, the level of cognitive function of high LG offspring is dependent on the degree of stress, with high LG offspring showing better cognitive function under basal conditions and low LG offspring showing better learning under stressful conditions [51]. Low LG pups showed lower LTP in basal conditions but enhanced LTP when treated with glucocorticoids or beta-adrenergic antagonist, which mimics the stressed condition *in vivo* [51,52]. This suggests that maternal effects early in life may modulate optimal cognitive functioning in environments varying in demand later in life.

Finally, as mentioned previously, exposure of 2-week old (newly weaned) mice to an enriched environment for two weeks enhances synaptic plasticity by enabling an otherwise latent NMDA receptor/cAMP/p38 MAP kinase signaling cascade. This pathway increases the magnitude of LTP and fear conditioning memories in wild-type mice and rescues defective LTP and learning ability associated in Ras-GRF knockout mice [5–7]. This effect of EE lasts for at least 3 months, long enough for the mice to become fertile.

Remarkably, the 4-week old offspring of these mice also display enhanced synaptic plasticity even if they never experience EE. This is due to the appearance of the same NMDA receptor/cAMP/p38 MAP kinase signaling cascade that becomes functional in their parents when they are exposed to EE in their youth. Moreover, defective LTP and fear conditioning are reversed in offspring of enriched Ras-GRF knockout mice [7]. Fostering of the offspring of EE-trained parents by mothers that never experienced EE does not reverse this effect. Thus, unlike inheritance of LG behavior, early mother interactions with offspring are not important in transmitting effects of EE on synaptic plasticity to the next generation. Instead, transmission occurs sometime before birth. Recent studies on the how intrauterine milieu of pregnant mothers can affect the epigenome of offspring. For example, high folate in the maternal diet increases methyl donors in the circulation that cross the placenta and have a long-lasting increase in DNA methylation of many genes of offspring [53,54]. In an analogous manner, environmental enrichment may have a long-lasting effect on circulating neuroendocrine hormones that influence the epigenetic status of LTP inducing genes in the brains of both the pregnant mother and developing embryos.

In addition, the mother's but not the father's juvenile environment contributes to the transgenerational transmission of these effects of EE. Another important feature of this particular phenomenon that distinguishes it from others that have been found is that the positive effects of EE are transmitted to the next generation, but not to subsequent ones [7].

This appears to be due to the fact that the effects on the offspring wear off before they become fertile. It has been speculated that this phenomenon evolved as a protection mechanism to give the offspring of enriched parents the advantages of enrichment, even if their early environment lacks it. Precisely what this advantage is at the behavioral level will have to await the discovery of a strategy to specifically block this effect of EE in animals and decipher its consequences. For example, it is likely that EE works by inducing a long-term change in the expression of a specific gene that is rate limiting for the novel NMDA/cAMP/p38/LTP pathway discovered in these studies. Understanding the epigenetic mechanism underlying how this gene is regulated by EE might allow specific blockade of this form of regulation of the gene, while leaving its regulation by other factors intact, in a mouse. Since EE loses its ability to enable this signaling cascade with age, such a mouse model may be used most effectively by testing for defects in behaviors that are specific to young animals.

There is little doubt that additional examples of transgenerational epigenetic inheritance, involving negative as well as positive qualities acquired from interaction of parents with the environment, will be revealed in the near future. Inherited predisposition to diseases have been studied mostly by approaches assuming the participation of only classical genetic inheritance. Studies on the newly appreciated role of transgenerational epigenetic inheritance of qualities acquired from the environment may open new avenues to aid in the detection and treatment of these diseases.

References

1. Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. *Neuron*. 2004; 44(1):5–21. [PubMed: 15450156]
2. Abraham WC. Metaplasticity: tuning synapses and networks for plasticity. *Nat Rev Neurosci*. 2008; 9(5):387. [PubMed: 18401345]
3. Huang YY, et al. The influence of prior synaptic activity on the induction of long-term potentiation. *Science*. 1992; 255(5045):730–733. [PubMed: 1346729]
4. Philpot BD, Cho KK, Bear MF. Obligatory role of NR2A for metaplasticity in visual cortex. *Neuron*. 2007; 53(4):495–502. [PubMed: 17296552]
5. Duffy SN, et al. Environmental enrichment modifies the PKA-dependence of hippocampal LTP and improves hippocampus-dependent memory. *Learn Mem*. 2001; 8(1):26–34. [PubMed: 11160761]
6. Li S, et al. The environment versus genetics in controlling the contribution of MAP kinases to synaptic plasticity. *Curr Biol*. 2006; 16(23):2303–2313. [PubMed: 17141611]
7. Arai JA, et al. Transgenerational rescue of a genetic defect in long-term potentiation and memory formation by juvenile enrichment. *J Neurosci*. 2009; 29(5):1496–1502. [PubMed: 19193896]
8. Hebb DO. The effects of early experience on problem solving at maturity. *Am. Psychol*. 1947; 2:306–307.
9. Mayeux R. Epidemiology of neurodegeneration. *Annu Rev Neurosci*. 2003; 26:81–104. [PubMed: 12574495]
10. Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nat Rev Neurosci*. 2006; 7(9):697–709. [PubMed: 16924259]
11. van Praag H, Kempermann G, Gage FH. Neural consequences of environmental enrichment. *Nat Rev Neurosci*. 2000; 1(3):191–198. [PubMed: 11257907]
12. Fischer A, et al. Recovery of learning and memory is associated with chromatin remodelling. *Nature*. 2007; 447(7141):178–182. [PubMed: 17468743]
13. Morley-Fletcher S, et al. Environmental enrichment during adolescence reverses the effects of prenatal stress on play behaviour and HPA axis reactivity in rats. *Eur J Neurosci*. 2003; 18(12):3367–3374. [PubMed: 14686910]

14. Sifonios L, et al. An enriched environment restores normal behavior while providing cytoskeletal restoration and synaptic changes in the hippocampus of rats exposed to an experimental model of depression. *Neuroscience*. 2009; 164(3):929–940. [PubMed: 19729049]
15. Champagne FA, Meaney MJ. Transgenerational effects of social environment on variations in maternal care and behavioral response to novelty. *Behav Neurosci*. 2007; 121(6):1353–1363. [PubMed: 18085888]
16. Meshi D, et al. Hippocampal neurogenesis is not required for behavioral effects of environmental enrichment. *Nat Neurosci*. 2006; 9(6):729–731. [PubMed: 16648847]
17. Williams BM, et al. Environmental enrichment: effects on spatial memory and hippocampal CREB immunoreactivity. *Physiol Behav*. 2001; 73(4):649–658. [PubMed: 11495671]
18. Rampon C, et al. Enrichment induces structural changes and recovery from nonspatial memory deficits in CA1 NMDAR1-knockout mice. *Nat Neurosci*. 2000; 3(3):238–244. [PubMed: 10700255]
19. Need AC, Irvine EE, Giese KP. Learning and memory impairments in Kv beta 1.1-null mutants are rescued by environmental enrichment or ageing. *Eur J Neurosci*. 2003; 18(6):1640–1644. [PubMed: 14511342]
20. Need AC, Giese KP. Handling and environmental enrichment do not rescue learning and memory impairments in alphaCamKII(T286A) mutant mice. *Genes Brain Behav*. 2003; 2(3):132–139. [PubMed: 12931786]
21. Leggio MG, et al. Environmental enrichment promotes improved spatial abilities and enhanced dendritic growth in the rat. *Behav Brain Res*. 2005; 163(1):78–90. [PubMed: 15913801]
22. Greenough WT, Volkmar FR, Juraska JM. Effects of rearing complexity on dendritic branching in frontolateral and temporal cortex of the rat. *Exp Neurol*. 1973; 41(2):371–378. [PubMed: 4126876]
23. Ickes BR, et al. Long-term environmental enrichment leads to regional increases in neurotrophin levels in rat brain. *Exp Neurol*. 2000; 164(1):45–52. [PubMed: 10877914]
24. Rampon C, et al. Effects of environmental enrichment on gene expression in the brain. *Proc Natl Acad Sci U S A*. 2000; 97(23):12880–12884. [PubMed: 11070096]
25. Kessels HW, Malinow R. Synaptic AMPA receptor plasticity and behavior. *Neuron*. 2009; 61(3):340–350. [PubMed: 19217372]
26. Lisman J, Raghavachari S. A unified model of the presynaptic and postsynaptic changes during LTP at CA1 synapses. *Sci STKE*. 2006; 2006(356):re11. [PubMed: 17033044]
27. Li S, et al. Distinct roles for Ras-guanine nucleotide-releasing factor 1 (Ras-GRF1) and Ras-GRF2 in the induction of long-term potentiation and long-term depression. *J Neurosci*. 2006; 26(6):1721–1729. [PubMed: 16467520]
28. Jin SX, Feig LA. Long-term potentiation in the CA1 hippocampus induced by NR2A subunit-containing NMDA glutamate receptors is mediated by Ras-GRF2/Erk map kinase signaling. *PLoS One*. 2010; 5(7):e11732. [PubMed: 20661302]
29. Grilli M, et al. Exposure to an enriched environment selectively increases the functional response of the pre-synaptic NMDA receptors which modulate noradrenaline release in mouse hippocampus. *J Neurochem*. 2009; 110(5):1598–1606. [PubMed: 19723266]
30. Sweatt JD. Mitogen-activated protein kinases in synaptic plasticity and memory. *Curr Opin Neurobiol*. 2004; 14(3):311–317. [PubMed: 15194111]
31. Huang CC, et al. Rap1-induced p38 mitogen-activated protein kinase activation facilitates AMPA receptor trafficking via the GDI.Rab5 complex. Potential role in (S)-3,5-dihydroxyphenylglycine-induced long term depression. *J Biol Chem*. 2004; 279(13):12286–12292. [PubMed: 14709549]
32. Bolshakov VY, et al. Dual MAP kinase pathways mediate opposing forms of long-term plasticity at CA3-CA1 synapses. *Nat Neurosci*. 2000; 3(11):1107–1112. [PubMed: 11036267]
33. Roth TL, Sweatt JD. Regulation of chromatin structure in memory formation. *Curr Opin Neurobiol*. 2009; 19(3):336–342. [PubMed: 19539459]
34. Guan JS, et al. HDAC2 negatively regulates memory formation and synaptic plasticity. *Nature*. 2009; 459(7243):55–60. [PubMed: 19424149]
35. Levenson JM, et al. Regulation of histone acetylation during memory formation in the hippocampus. *J Biol Chem*. 2004; 279(39):40545–40559. [PubMed: 15273246]

36. Miller CA, Sweatt JD. Covalent modification of DNA regulates memory formation. *Neuron*. 2007; 53(6):857–869. [PubMed: 17359920]
37. Lubin FD, Roth TL, Sweatt JD. Epigenetic regulation of BDNF gene transcription in the consolidation of fear memory. *J Neurosci*. 2008; 28(42):10576–10586. [PubMed: 18923034]
38. Feng J, et al. Dnmt1 and Dnmt3a maintain DNA methylation and regulate synaptic function in adult forebrain neurons. *Nat Neurosci*. 13(4):423–430. [PubMed: 20228804]
39. Morgan HD, et al. Epigenetic inheritance at the agouti locus in the mouse. *Nat Genet*. 1999; 23(3): 314–318. [PubMed: 10545949]
40. Rakyan VK, et al. Transgenerational inheritance of epigenetic states at the murine Axin(Fu) allele occurs after maternal and paternal transmission. *Proc Natl Acad Sci U S A*. 2003; 100(5):2538–2543. [PubMed: 12601169]
41. Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Mol Cell Biol*. 2003; 23(15):5293–5300. [PubMed: 12861015]
42. Dolinoy DC, et al. Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. *Environ Health Perspect*. 2006; 114(4):567–572. [PubMed: 16581547]
43. Skinner MK, Manikkam M, Guerrero-Bosagna C. Epigenetic transgenerational actions of environmental factors in disease etiology. *Trends Endocrinol Metab*. 2010; 21(4):214–222. [PubMed: 20074974]
44. Anway MD, et al. Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science*. 2005; 308(5727):1466–1469. [PubMed: 15933200]
45. Weaver IC, et al. Epigenetic programming by maternal behavior. *Nat Neurosci*. 2004; 7(8):847–854. [PubMed: 15220929]
46. Champagne F, et al. Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. *Proc Natl Acad Sci U S A*. 2001; 98(22):12736–12741. [PubMed: 11606726]
47. Roth TL, et al. Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biol Psychiatry*. 2009; 65(9):760–769. [PubMed: 19150054]
48. Kiyono S, et al. Facilitative effects of maternal environmental enrichment on maze learning in rat offspring. *Physiol Behav*. 1985; 34(3):431–435. [PubMed: 4011724]
49. Dell PA, Rose FD. Transfer of effects from environmentally enriched and impoverished female rats to future offspring. *Physiol Behav*. 1987; 39(2):187–190. [PubMed: 3575452]
50. Liu D, et al. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science*. 1997; 277(5332):1659–1662. [PubMed: 9287218]
51. Champagne DL, et al. Maternal care and hippocampal plasticity: evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. *J Neurosci*. 2008; 28(23):6037–6045. [PubMed: 18524909]
52. Bagot RC, et al. Maternal care determines rapid effects of stress mediators on synaptic plasticity in adult rat hippocampal dentate gyrus. *Neurobiol Learn Mem*. 2009; 92(3):292–300. [PubMed: 19292996]
53. Cooney CA. Germ cells carry the epigenetic benefits of grandmother's diet. *Proc Natl Acad Sci U S A*. 2006; 103(46):17071–17072. [PubMed: 17101997]
54. Cropley JE, et al. Germ-line epigenetic modification of the murine A vy allele by nutritional supplementation. *Proc Natl Acad Sci U S A*. 2006; 103(46):17308–17312. [PubMed: 17101998]

Fig. 1. Model describing the effect of an enriched environment on the signaling pathways that promote LTP in the CA1 region of the hippocampus

A. After exposure of young animals (3–4 weeks of age) to an enriched environment for 2 weeks a new LTP inducing signaling pathway appears that involves NMDA type glutamate receptor activation of p38 MAP kinase potentiated by cAMP. **B.** In conventionally housed animals this signaling pathway is non-functional.