



# Shaping the learning curve: epigenetic dynamics in neural plasticity

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A key characteristic of learning and neural plasticity is state-dependent acquisition dynamics reflected by the non-linear learning curve that links increase in learning with practice. Here we propose that the manner by which epigenetic states of individual cells change during learning contributes to the shape of the neural and behavioral learning curve. We base our suggestion on recent studies showing that epigenetic mechanisms such as DNA methylation, histone acetylation, and RNA-mediated gene regulation are intimately involved in the establishment and maintenance of long-term neural plasticity, reflecting specific learning-histories and influencing future learning. Our model, which is the first to suggest a dynamic molecular account of the shape of the learning curve, leads to several testable predictions regarding the link between epigenetic dynamics at the promoter, gene-network, and neural-network levels. This perspective opens up new avenues for therapeutic interventions in neurological pathologies.

**Keywords:** epigenetics, DNA methylation, non-coding small RNAs, neural plasticity, learning curve

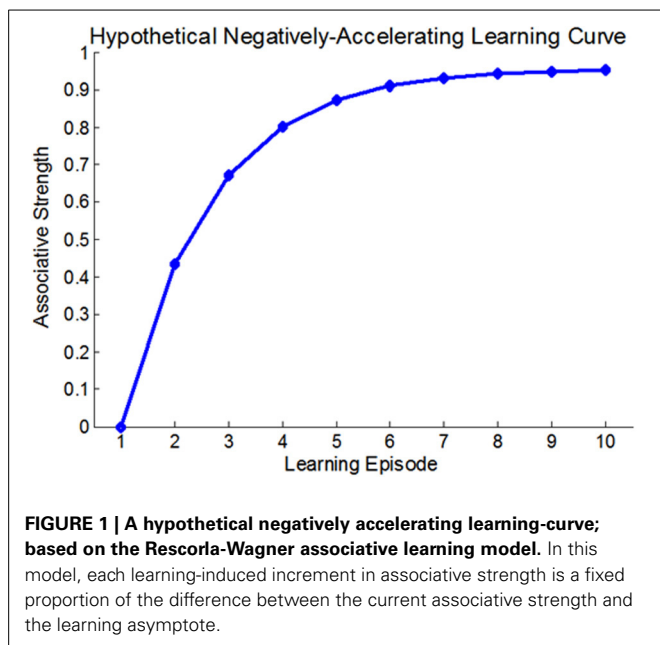
## INTRODUCTION

At the very outset of modern learning and memory research it was established that changes in behavior are usually acquired through a dynamic, gradual process of iterative experience, and that the relation between learning-strength and practice—i.e., the learning curve—is usually non-linear (Thorndike, 1898). A non-linear learning curve implies that the contribution of each learning-instance to the overall learning-strength is *state-dependent* rather than fixed (see Anderson, 2000 for many types of learning curves). For Example, the traditional Rescorla-Wagner associative learning model (Rescorla and Wagner, 1972), suggests that the associative strength increases as a fixed proportion of the difference between the current associative strength and its asymptote. Thus, this model predicts a negatively accelerating learning curve (see Figure 1). Although the vast majority of learning curves were described at the behavioral level it was realized that any behavioral manifestation of learning and memory entails some form of persistent neural plasticity. This suggested that there must be *neural learning curves* that reflect changes in neural plasticity as a function of practice. Several studies described such neural learning curves (Barnes, 1979; Cooke and Bear, 2010). For example, Cooke and Bear (2010) observed a diminishing neural learning curve in the visual cortex following a 5-day visual-exposure, showing that the stronger the current synaptic state, the smaller the increment upon future learning. These results are also consistent with most behavioral learning-curves (Anderson, 2000). However, although much has been learnt about the biochemical cascades underlying learning and memory, the molecular and cellular processes that render neural learning-dynamics state-dependent and determine the shape of the neural learning curves, are, as yet, poorly understood.

There are many different forms of long-term neural plasticity (persisting for more than 24 h). These include synaptic plasticity, which entails either changes in the efficacy of pre-existing synapses [for example, long-term potentiation (LTP; Bliss and Collingridge, 1993)] or the formation or elimination of synapses (Holtmaat and Svoboda, 2009); changes in somal depolarization (Kemenes et al., 2006) and even interactive and synergistic activity of both synaptic- and non-synaptic plasticity (Gao et al., 2012). In spite of the vast heterogeneity of mechanisms underlying long-term neural plasticity, *de-novo* transcription and translation are necessary processes common to all (reviewed in Leslie and Nedivi, 2011). The transcribed and/or translated gene products operate via diverse cellular mechanisms to modify neuronal properties that enable long-term neural plasticity such as the morphological changes taking place in the pre-synaptic axonal structures (Giuditta et al., 2002) and in the post-synaptic dendritic spines during long-term potentiation (LTP; a form of synaptic plasticity; Caroni et al., 2012). However, since there is constant turnover of proteins at synapses, it has been suggested that *epigenetic mechanisms*, which regulate experience-dependent gene expression and underlie its persistence are involved in maintaining functional neural states by supporting the persistent expression of the necessary RNAs and proteins (Miller and Sweatt, 2007; Zovkic et al., 2013).

## THE INVOLVEMENT OF EPIGENETIC MECHANISMS IN LEARNING AND MEMORY

Persistent epigenetic changes are mediated through the operation of four types of interacting epigenetic mechanisms (Jablonka and Lamb, 2005/2014): (i) *Chromatin-marking*—whereby chromatin (the complex of DNA, proteins, and other components that



constitute the chromosome) assumes different local and global conformations as it changes in response to signals. Examples of chromatin marks are methyl (CH<sub>3</sub>) groups added to cytosines in DNA (catalyzed by DNA methyltransferases, DNMTs) which, when present in regulatory regions, can repress transcription (Yu et al., 2001) and when oxidized into 5-hydroxymethylcytosine (5-hmC) correlates with transcriptional activation (Branco et al., 2012); histone post-translational modifications (PTMs) that render histones more or less accessible to transcription factors (Gräff and Tsai, 2013); histone variants (specific histone proteins that can displace the usual histones) that alter the conformation of chromatin and its accessibility to modifying enzymes; and non-histone proteins that are bound to DNA and are involved in chromatin marking, the regulation of chromatin condensation and topology, and the control or stabilization of other chromosomal functions (Talbert and Henikoff, 2010). (ii) *RNA-mediated gene silencing*—whereby silent states are initiated and actively maintained through repressive interactions between non-coding small RNA molecules and complementary regions in mRNA and DNA. Examples include microRNAs (miRNAs) and their complementary mRNA (Spadaro and Bredy, 2012) and piRNAs that are involved in the regulation of transcription in neurons, and long non-coding RNAs (Lasalle et al., 2013); in addition, small double-stranded RNAs can also activate genes (saRNAs), adding another layer of complexity to RNA-mediated regulation (Li et al., 2006). (iii) *Structural templating*—whereby pre-existing three dimensional cellular structures act as templates for the production of similar structures within the same cell or in daughter cells, such as the cellular inheritance of prions (Shorter and Lindquist, 2005). (iv) *Self-sustaining loops*—whereby a specific pattern of intracellular activity can be maintained when genes and their products form autocatalytic loops (Lisman et al., 2002).

During the last decade many studies showed that there are causal links between epigenetic mechanisms and long-term

learning and memory. It was shown that learning induces both gene-specific and genome-wide (global) changes in neurons' epigenome (the cells' developmentally-established epigenetic state) and that manipulations of neural epigenetic activity, for example by catalyzing or inhibiting the activity of histone-modifying or DNA-methylating enzymes, affect learning and memory (for recent reviews see Blaze and Roth, 2013; Zovkic et al., 2013).

Gene-specific epigenetic changes were found in studies using rodent models of long-term neural plasticity. The majority of studies showed, as expected, that genes that support neural plasticity (i.e., genes whose expression levels increase following learning) are associated with positive regulatory epigenetic changes such as reduced DNA methylation and enhanced histone acetylation. Similarly, genes that inhibit the formation of memory are epigenetically suppressed following learning. For example, it was found that several hours after training in the contextual fear conditioning paradigm (whereby a certain chamber is associated with an electric shock) rats' hippocampal neurons are demethylated at plasticity-facilitating genes such as the immediate early-gene *Zif268* (Miller et al., 2010), *reelin* (Miller and Sweatt, 2007) and *bdnf* (Lubin et al., 2008), while *PP1*, a learning-suppressing gene, becomes methylated (Miller and Sweatt, 2007). Thirty days after contextual fear conditioning, robust methylation of *calcineurin*, a suppressor of memory, was observed in cortical neurons (Miller et al., 2010), and several days after the extinction of this memory, hippocampal neurons are deacetylated (at H3) at the *c-Fos* promoter (Bahari-Javan et al., 2012). A similar pattern was observed in other forms of learning: 2 h after the extinction of cued-fear conditioning, there is an increase in histone H4 acetylation around the *BDNF* P4 gene promoter in the pre-frontal cortex (Bredy et al., 2007) and several hours after the induction of LTP, the *bdnf* and *reelin* genes in the medial pre-frontal cortex neurons are demethylated (Sui et al., 2012).

In addition to gene-specific changes, neuroepigenetic studies also show that there are genome-wide effects, which may represent an overall "aggregate" effect of learning. A survey of these studies (Bronfman et al., 2014) points to a positive correlation between increased global levels of histone acetylation, DNA methylation, and learning. Furthermore, manipulations of the enzymes that enhance global histone acetylation or global DNA methylation enhance the strength and persistence of learning, while a decrease in these enzyme activities decreases learning. These results appear to be consistent across taxa, time, brain-region, and learning task. **Table 1** presents representative examples.

The effects of the manipulations of enzymes that regulate DNA methylation described in the Table are in line with studies showing that knocking out Piwi genes, which contribute to DNA methylation, results in reduced long-term facilitation (LTF), whereas Piwi overexpression enhances it (Rajasethupathy et al., 2012). A study showing that a gain-of-function mutation in the *Mecp2* gene (a gene that produces a protein that binds to methylated DNA and contributes to the inhibition of transcription) increases its binding to methylated DNA and enhances learning (Li et al., 2011) also points in the same direction.

**Table 1 | Genome-wide Epigenetic changes induced by learning.**

	<b>Genome-wide epigenetic changes</b>	<b>Time/Region/Task</b>	<b>Animal</b>	<b>References</b>
<b>PTMs (HISTONE-TAIL ACETYLATION AND DI- AND TRI-METHYLATION)</b>				
1	Contextual fear conditioning increases acetylation of histone H3. Artificially elevating levels of histone acetylation <i>in vitro</i> enhances the induction of LTP	20 min–1 h Hippocampus Contextual fear conditioning	Rodents	Levenson et al., 2004
2	Increase in acetylation of Histones H3 and H4; HDAC inhibitors facilitate learning	3 h–Weeks Hippocampus and Cortex Environmental enrichment; Associative learning; Spatial learning	Rodents	Fischer et al., 2007
3	Increase in H3 acetylation across all regions of the hippocampus, while acetylation of lysine 9 on H3 is downregulated selectively in CA1. H4 acetylation is influenced in opposite directions in CA1 and DG, and is insensitive in CA3	1 h Hippocampus Spatial memory	Rodents	Castellano et al., 2012
4	Increase in H3 acetylation	15 min Right parietal ganglion Food aversion	Snails	Danilova et al., 2010
5	HAT (CBP/p300) activation (by CSP-TTK21) enhances memory (extending the time during which memory can be retrieved)	24 h Hippocampus Spatial memory	Rodents	Chatterjee et al., 2013
6	Overexpression of HDAC2 decreases dendritic spine density, synapse number, synaptic plasticity, and memory formation; HDAC2 deficiency results in increased synapse number and memory facilitation.	24 h Hippocampus Contextual fear conditioning; Spatial memory	Rodents	Guan et al., 2009
7	HDAC1 overexpression enhances extinction	Days Hippocampus Contextual fear extinction	Rodents	Bahari-Javan et al., 2012
8	Deletion of the <i>hda4</i> , a homolog of the mammalian <i>HDAC4</i> leads to enhanced memory, while the overexpression of this gene diminishes it	18–48 h The nervous system Thermotactic task	<i>C. elegans</i>	Wang et al., 2011
9	HDAC inhibition enhances memory	2 h Pre-frontal cortex Contextual fear extinction	Rodents	Bredy et al., 2007
10	HDAC inhibition enhances memory	24 h Dorsal hippocampus Object-location memory	Rodents	Hawk et al., 2011
11	HDAC inhibition enhances memory	24 h Hippocampus Contextual fear conditioning	Rodents	Mahan et al., 2012
12	Increased H3 acetylation during reconsolidation; p300 HAT inhibitor impaired reconsolidation of strong memory; HDAC inhibitor enhances reconsolidation of a weak memory and an increase in histone H3 acetylation	1 h after consolidation Central brain Context-signal memory reconsolidation	Crab	Federman et al., 2012
13	Increase in trimethylation of H3K4 and dimethylation of H3K9	1–24 h Hippocampus Contextual fear conditioning	Rodents	Gupta et al., 2010

(Continued)

Table 1 | Continued

	Genome-wide epigenetic changes	Time/Region/Task	Animal	References
14	Increase in H3 di- and tri-methylation of histones	1–24 h Entorhinal cortex Contextual fear conditioning	Rodents	Gupta-Agarwal et al., 2012
15	H3S10 phosphorylation, H3K14 and H4K5 acetylation, and H3K36 trimethylation are increased rapidly (1 h–1 day) in the hippocampus, and remotely (1 day–7 days) in the PFC; Enhanced histone PTMs (by inhibition of <i>PP1</i> ) facilitate memory, while inhibition of histone PTMs impairs memory	1 h–7 days Hippocampus and PFC; Object memory	Rodents	Graff et al., 2012
16	Increase in H3 acetylation and DNMT3A expression; HDAC inhibitor enhances memory; DNMT inhibitor impairs memory	90 min Lateral amygdala Cued fear conditioning	Rodents	Monsey et al., 2011
<b>DNA METHYLATION</b>				
17	Total DNMTs, total HATs and global acetylation of H3 and H4 are elevated; infusion of DNMT inhibitor suppresses the induction of LTP (several hours) and interferes with trace fear memory (24 h); infusion of HDAC inhibitors enhances LTP (several hours) and trace fear memory (24 h)	2–24 h Medial pre-frontal cortex LTP; trace fear conditioning	Rodents	Sui et al., 2012
18	Enhanced DNMT expression after conditioning; blocking DNMT's activity abolishes memory	1 h Hippocampus Contextual fear conditioning	Rodents	Miller and Sweatt, 2007
19	Learning involves DNMT3 upregulation and, depending on treatment time, DNMT inhibition reduces the acquisition and retention of memory and alters its extinction	5 h Mushroom bodies Pavlovian olfactory discrimination and extinction	Honey bee	Lockett et al., 2010
20	Exposure of slices to DNMT inhibitor results in an immediate diminution of LTP	3 h Hippocampus LTP ( <i>in vitro</i> )	Rodents	Levenson et al., 2006
21	Blocking DNMT activity impairs memory	2 h Hippocampus Contextual fear conditioning	Rodents	Lubin et al., 2008
22	Blocking DNMT activity impairs memory	1–30 days Hippocampus; Dorsomedial pre-frontal cortex Contextual fear conditioning	Rodents	Miller et al., 2010
23	Blocking DNMT activity impairs memory acquisition	24 h Hippocampus Conditioned place preference	Rodents	Han et al., 2010

How can one explain these global, robust correlations in a highly context-sensitive functional system? The positive correlation between neural plasticity and global increase in histone acetylation seems natural, since this type of PTM renders the DNA, which is wound around the histones, more accessible to transcription factors, and hence more prone to activity-induced gene-expression supporting neural plasticity. However, DNA methylation is usually associated with gene silencing, especially in gene promoter regions (Yu et al., 2001)—a property that seems to be at odds with the overall positive relation of

increased DNA methylation with enhanced learning and memory. Three explanations have been suggested to account for this correlation (i) that methylation leads to the repression of the synthesis of specific memory-repressors, and hence to improved learning (e.g., Yu et al., 2011; Sui et al., 2012); (ii) that increased methylation in the body of the gene is associated with increased transcriptional activity; and (iii) that DNMTs are involved in both DNA methylation and demethylation and its demethylating role explains why its level increases with learning (Chen et al., 2012). However, although such suggestions may explain some specific

effects, they do not account very well for the correlation between *global* increase in DNA methylation and improved learning. It is not clear that the methylation of suppressor genes is more prevalent than demethylation of learning enhancing genes, that the demethylating role of DNMT I is more common than its methylating role, and that methylation in the body of the gene has a greater quantitative effect on overall methylation than the suppression of promoters by methylation.

We propose an elaboration and an extension of the first proposal, and suggest that the increased global levels of DNA methylation is related to the suppressor of learning-suppressing sequences, but that the class of suppressors are not protein coding genes but rather the genomically widespread clusters coding for precursor sequences of miRNAs (pre-miRNAs), which, when processed, interfere with the gene-expression necessary for plasticity. Our suggestion is consistent with a study showing that knock-out of *Dicer1* (a key enzyme in the biogenesis of miRNAs) in mice, led to improvement in a variety of learning tasks (Konopka et al., 2010). Further studies should investigate whether the correlation between global increase in DNA methylation levels and long-term learning and memory is indeed mediated by the suppression of pre-miRNAs, and if so by what means.

Another possible explanation for the positive correlation between DNA methylation levels and learning may be related to the central role of inhibition and pruning in learning. The increased levels of global DNA methylation may reflect lateral inhibition, whereby gene-activity in “competing” neural networks (i.e., neurons that are not involved in the specific learning) is being actively silenced so as to enable the efficient establishment of the relevant associations. Such a process may include the migration of positive regulators of DNMTs, such as piRNAs through exosomes from the focal network to the neighboring networks. Exosomes are vesicles measuring 50–90 nm contained in larger intracellular multivesicular bodies (MVBs), which are released from certain cells into the extracellular environment by MVBs fusing with the plasma membrane. Neurons are known to secrete exosomes (Lachenal et al., 2011; Lai and Breakefield, 2012). If this inactivation plays an important role in learning we predict that the global increase in methylation would be specific to formerly active (“competing”) neurons that *are not* directly participating in the learning process (i.e., not necessary for the formation of the specific memory), while the (relatively few) “relevant” neurons will exhibit more demethylation, especially in learning-related genes. This possibility is consistent with recent findings showing that global methylation levels in neurons increase throughout ontogeny (Lister et al., 2013) and may thus reflect the selection-processes during synaptic pruning (for early discussions see Changeux et al., 1973; Changeux and Danchin, 1976; Edelman, 1987).

Finally, and perhaps most intriguingly, the global effects involving methylation and acetylation may represent a mnemonic principle first suggested in the early 20th century by Semon (1921, 1923); discussed by Schacter (2001), where acquisition-encoding processes bear on changes in inter- and intra-network resonance dynamics, dynamics which are “reawakened,” expanded and modified upon retrieval. Under this conceptualization, global epigenetic effects, which are involved in the encoding and retrieval

processes that occur during the episodes that follow the first exposure to the learning conditions, involve an increase in the number of encoding cells and hence in the expansion of the size and number of neural networks involved in learning. Hence, the changes occurring during learning can be best observed at the global level rather than only the gene or cell level.

Several predictions follow from these proposals: (i) negative correlation between increased DNA methylation and miRNAs abundance will be found in single neurons that exhibit plasticity; (ii) increased methylation will be found in neighboring neurons that interfere with focused learning; (iii) neighboring neurons will exhibit increased levels of piRNAs that positively regulate DNMT activity; (iv) the number of neurons that undergo epigenetic changes such as DNA methylation and histone acetylation will increase and spread during learning.

The studies summarized in this section strongly support the growing consensus that there is a complex, “bidirectional” relation between the epigenetic system and long-term neural plasticity. Learning induces multiple changes to neurons’ epigenome, and at least some of these changes persist, thus enabling the necessary ongoing gene-expression that maintains the neural state. Upon future learning, each neuron’s epigenome constrains or actively regulates the activity-induced gene-expression pattern and hence shapes future plasticity (Zovkic et al., 2013). This unique “time-bridging” involvement of the epigenetic system in neural plasticity implies that learning may be history-sensitive via epigenetic dynamics: the influence of future learning may be dependent, upon the cell-specific epigenetic state, which is in turn, a function of learning history.

The idea that present and past experience can alter the future susceptibility and responsiveness of synapses via diverse molecular mechanisms was suggested by Abraham and Bear (1996) who called this phenomenon metaplasticity, or “the plasticity of synaptic plasticity” (Abraham, 2008). For example, short exposures to environmental enrichment that do not enhance late-LTP (>24 h), facilitate it upon re-exposure 6 weeks later (Buschler and Manahan-Vaughan, 2012). Another example is weak (sub-threshold) induction of LTP that does not change synaptic efficacy, yet can alter future changes in plasticity, by mediating the processes of silent synapses unmasking (a process also referred to as “priming”; Ward et al., 2006). However, little is currently known about the factors that affect the shape and dynamics of neural learning-curves upon continuous (prolonged) learning acquisition, and many of the underlying mechanisms remain to be identified.

In spite of the appreciation of metaplasticity, the majority of studies linking epigenetic changes to enhanced learning focused on the relation between the “end-points” of a specific learning task and the corresponding end-point epigenetic states and did not address the epigenetic dynamics *during* learning acquisition. We therefore present simple models, describing how different patterns of epigenetic changes that occur throughout the learning process may determine the shape of the neural learning curve.

## MODELS OF NEURAL EPIGENETIC LEARNING-CURVES

Our proposal is based on the observation that epigenetic mechanisms possess “mnemonic” properties and can therefore lead to

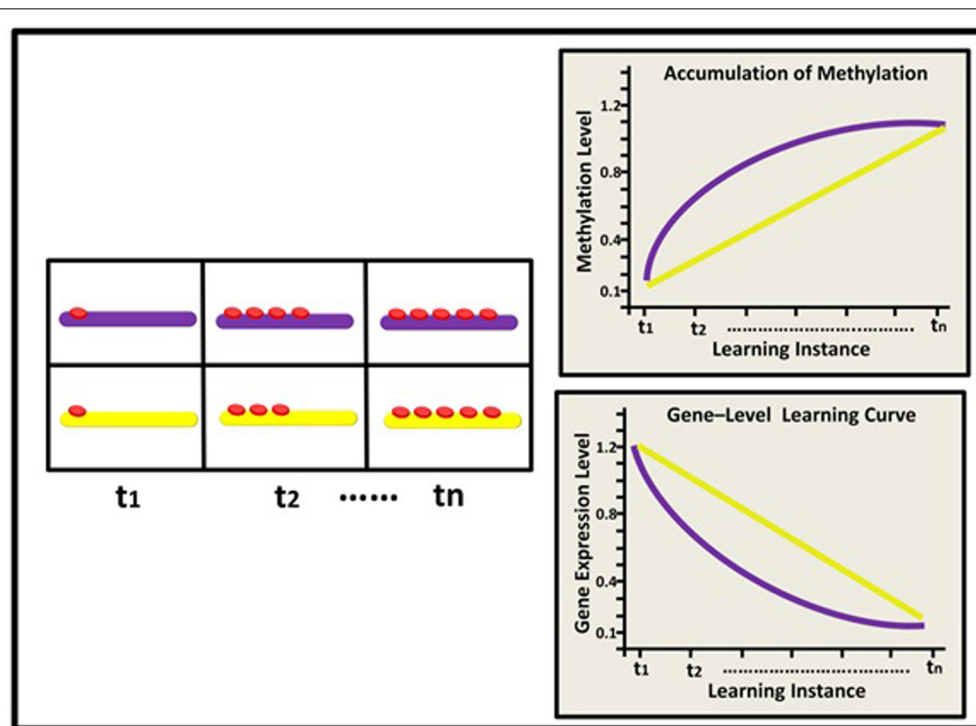
the dynamic, time-dependent, encoding, and storage of information during learning. The unique self-perpetuating biochemical activity of the interacting epigenetic mechanisms ensures that epigenetic patterns (e.g., patterns of histone modifications or of DNA methylation) persist long after the initial induction period (Fischer et al., 2007; Miller et al., 2010; Zovkic et al., 2013). Hence, unlike most of the genome, the epigenome is “history-sensitive,” in the sense that it changes as a function of learning and development over time. Moreover, the epigenome regulates future activity-induced gene-expression, thus causally determining the effect of experience on plasticity. This combination of properties suggests that epigenetic dynamics during learning may render learning state-sensitive.

We present a model based on the chromatin marking system of DNA methylation. Although other epigenetic systems may be as suitable, we chose DNA methylation because of the acknowledged persistence of DNA methylation marks (e.g., Cedar and Bergman, 2012; Smith and Meissner, 2013), because methylation marks can accumulate (e.g., Ibrahim et al., 2011; Lu et al., 2013), and because global increase in DNA methylation levels is consistently correlated with enhanced learning (Table 1). However, the model can easily be adapted to any other epigenetic mechanism, for example to the accumulation of acetylation of histones and to the more complex construction of activity-specific epigenetic modifications, involving, for example, various types of histone modifications. In the model we make the simplifying assumption

that there is a linear relationship between levels of DNA methylation, gene expression, and synaptic plasticity. This assumption is made solely for illustrative purposes and relaxing it does not alter the model’s predictions. For example, the model can describe learning that is dependent on crossing a certain epigenetic marking threshold (for example, a certain number of chromatin marks must be reached for transcriptional activation or inactivation). In this case, while the accumulation of chromatin marks may be gradual, the effect on learning will be abrupt and step-like.

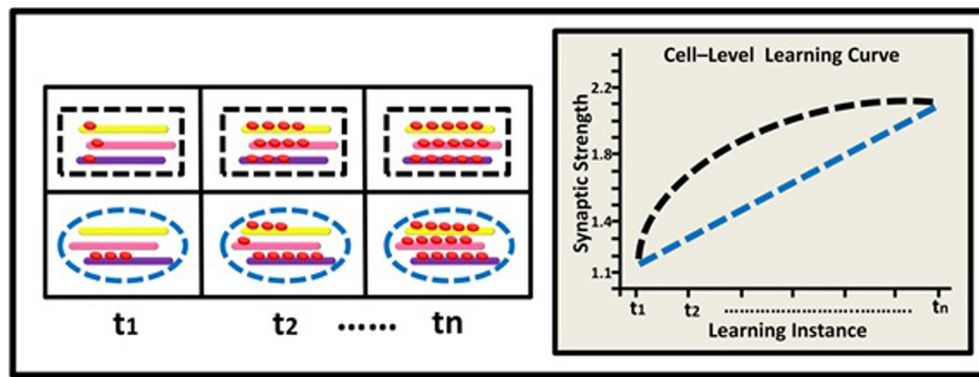
The model describes hypothetical kinetics of DNA methylation accumulation at three levels: the level of a suppressor single gene (Figure 2); the level of a gene network within a single neuron (Figure 3), and the level of a neural network involving three neurons (Figure 4). It shows how a specific pattern of accumulated epigenetic marks—a pattern we call the *epigenetic profile*—can eventually affect learning acquisition dynamics. At each level, two patterns are demonstrated, since we assume that epigenetic learning profiles are influenced by DNA sequence, cell type and ontogenetic stage, and hence may differ between genes, neurons, and brain regions (different brain regions indeed show different methylation patterns; Hata et al., 2013).

At the level of a single gene, we suggest that the manner by which methylation accumulates at the gene’s promoter region during learning would determine the gene’s expression level upon future learning (i.e., the gene’s “learning curve”). Consider for example a *plasticity-suppressing* gene. In our model, each instance



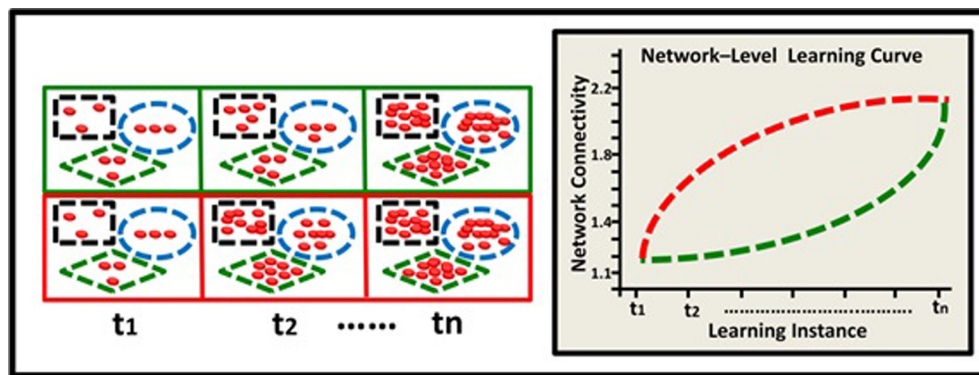
**FIGURE 2 | Epigenetic dynamics during learning can shape the neural learning-curve at the single gene level: Initially ( $t_1$ ), two learning-suppressing gene promoters (purple and yellow rods) have similar basal methylation level (red buttons). During learning, ( $t_2$ – $t_n$ ) these two genes exhibit different patterns of epigenetic change and subsequently,**

different changes in expression levels. The purple gene exhibits a diminishing pattern of methylation marks accumulation (purple line; right upper panel) and therefore an inverse, diminishing “gene-expression learning curve” (purple line; right lower panel). The yellow gene exhibits a linear pattern of methylation accumulation and a linear learning curve (yellow line).



**FIGURE 3 | Epigenetic dynamics during learning can shape the neural learning-curve at the single neuron's gene-network level.** At ( $t_1$ ), two types of neurons (black rectangle and blue ellipse) have similar overall basal methylation level (depicted by a 3-gene network: yellow, pink, and purple rods). During learning, ( $t_2$ – $t_n$ ) the two neurons exhibit different patterns of

changes in their overall methylation level, their genes' expression profiles, and eventually their synaptic strength. The black neuron exhibits a diminishing pattern of overall methylation accumulation and a diminishing learning curve (black line) while the blue neuron exhibits a linear pattern of methylation accumulation and a linear learning curve (blue line).



**FIGURE 4 | Epigenetic dynamics during learning can shape the neural learning-curve at the neural-network level.** Two neural networks (green and red squares) comprised of 3 neurons each (black rectangle, blue ellipse, and green diamond), have similar overall basal methylation level at ( $t_1$ ). During learning, ( $t_2$ – $t_n$ ) these two networks exhibit different patterns of

epigenetic change and subsequently different levels of overall methylation. The green network exhibits an accelerating pattern of overall methylation accumulation and therefore an accelerating learning curve (green line). The red network exhibits a diminishing pattern of methylation accumulation and therefore a diminishing learning curve (red line).

of learning is assumed to induce additional methylation marks at the gene's promoter region, down-regulating its expression—a process necessary for the manifestation and maintenance of plasticity. Importantly, different suppressor genes (or the same suppressor gene in different cells) may have different epigenetic profiles and thus exhibit different cumulative patterns. This would result in different expression levels during different states of learning acquisition, even if at the “end-point” of learning these genes may be similarly methylated (see **Figure 2**). Similar logic applies to learning-supporting genes, where progressive decrease in DNA methylation (demethylation) is expected during learning.

At the level of a single neuron, we focus on the *global* methylation level of the neuron's genome, illustrated here by the overall level of methylation in a gene-network comprised of 3 learning-related suppressor genes or gene regulators. We assume that as a result of learning, the neuron's global methylation increases. Note that the pattern of increase could differ between neurons: some neurons may exhibit non-linear increase in global methylation,

whereas the pattern of changes in global methylation in other types of neurons could be linear (**Figure 3**).

Learning depends, of course, on complex networks involving interactions among many neurons. The observed alterations in epigenetic patterns as a result of learning may therefore reflect the *average change* at the neural network level, where different neurons may have different epigenetic learning profiles and hence contribute differentially to the observed aggregated effect. In a simplified 3-neuron-network (**Figure 4**) the learning curves show diminishing and accelerating changes in time in the averaged accumulation of DNA methylation within the entire network (across specific neurons and their underlying genes).

Behavioral learning curves and epigenetic effects are mostly described using average data. However, the shape of the learning curve may change when describing it at the individual (Gallistel et al., 2004) or at the trial-by-trial levels (Glautier, 2013) even to the extent of rendering it “threshold-like.” We suggest that the same logic applies to the presumed epigenetic kinetics: some

epigenetic changes may seem as gradual, just as behavioral acquisition does, yet at finer granularity, epigenetic processes may also reflect (or affect learning in) a threshold-like process. The relations between gradual and discrete changes both in the epigenetic and the behavioral domains remain wide-open for future studies to investigate.

The model can be expanded to heed Semon's suggestion that networks expand during acquisition (Semon, 1921, 1923). Thus, rather than the number of chromatin marks on a single gene promoter increasing as a function of acquisition (Figure 2) it may be the case that the number of genes participating in learning increases with experience, and with it the number of the learning-linked chromatin marks we observe. Similarly, not only the number of marks on a single gene network (Figure 3), but the number of gene networks responsive to learning may increase with practice. Finally, and most importantly from this point of view, the accumulation of marks may occur not just within one pre-given network (Figure 4), but lead to the increase of the number of networks participating in learning and retrieval as a function of the number of learning episodes. The observation that the effects of learning in one area of the brain are "transferred" to additional areas (Graff et al., 2012) may support this conjecture. We believe that in addition to local cumulative epigenetic changes (such as genes, gene-networks, and neural networks; Figures 2–4) described in our model, learning also induces an expansion in the size and quantity of these factors.

The model can be tested by observing the epigenetic changes that occur *at several different points in time during learning acquisition*—and not just at the completion of the training protocol (as has been done in most studies), at the point in time where consolidation is thought to peak (e.g., Bousiges et al., 2010) or at several points in time *after* learning took place (e.g., Sui et al., 2012). Any standard neuroepigenetic learning paradigm, such as those reviewed in the first section and those mentioned above can be used to acquire these data<sup>1</sup>. We predict that such kinetic studies will show various patterns of *cumulative* epigenetic changes (such as decrease in methylation and increase in hydroxyl-methylation of learning-facilitating genes, increase in methylation of learning-suppressing genes and increase in global DNA methylation levels). Critically though, variations in these patterns of epigenetic dynamics should correspond to variations in behavioral learning curves. For example, we predict that following the induction of neural plasticity (via LTP, for example) one will find that: (i) different neurons (for example hippocampal vs. cerebellar) exhibit different neural learning-curves; (ii) these neurons manifest corresponding differences in their learning-induced epigenetic marks, such as patterns of changes in DNA methylation and histone acetylation; and (iii) manipulation of these neuronal epigenetic kinetics *during acquisition*, for example by using inhibitors of epigenetic enzymes, will affect the shape of their learning-curve.

<sup>1</sup>A recent study showing that extinction of fear conditioning is associated with the accumulation of 5-hydroxycytosine (hmC, a chromatin mark associated with gene activity), provides the first example of such trial-dependent epigenetic dynamics (Li et al., 2014).

How can epigenetic changes at the level of single genes, gene networks, or even neural networks predict change at the behavioral level? The relation between the behavioral and the molecular levels is clearly very complex, and we do not expect to see a simple mapping among the behavioral, neural, and epigenetic learning curves. However, as the review of the relations between epigenetic modifications and learning reviewed above has shown, in spite of the multiplicity of relations among different epigenetic factors and processes that underlie behavior, some robust correlations have been found between changes in the methylation of single genes and learning, and even more robustly, between more global changes and learning. We therefore believe that taking into consideration the kinetics of epigenetic changes as a function of learning may add to and enrich this picture.

If supported, we believe that our model may have implications for the interpretation and study of neurological diseases that show clear learning impairments, or of anxiety disorders, like post-traumatic stress disorder (PTSD), where memory regulation is specifically impaired (Zwissler et al., 2012; Zlomuzica et al., 2014). Accumulating evidence suggests that many neurological and neuropsychiatric disorders such as autistic spectrum disorder (ASD), Alzheimer's disease (AD) and schizophrenia (SZ) are associated with altered epigenetic activity. For example, ASD is associated with a decreased capacity for DNA methylation (Wu et al., 2010; Melnyk et al., 2012). Furthermore, some of the DNA methylation deficits in humans were recently found to be specific to brain-regions such as the temporal cortex and the cerebellum (Ladd-Acosta et al., 2013) that are associated with different forms of learning and memory. Similarly, AD is associated with epigenetic alterations in DNA methylation (Mastroeni et al., 2010) and abnormal micro-RNAs expression (Barak et al., 2013). Altered patterns of DNA methylation in immune system and nervous system development genes were found in PTSD (Uddin et al., 2010; Mehta et al., 2013), and schizophrenic patients show decreased genome-wide DNA methylation (Bonsch et al., 2012) and altered DNA demethylation mechanisms (Dong et al., 2012). Independently, these (and other) disorders were also characterized by abnormal learning curves: for example, ASD patients and animal models exhibit more moderate curves, (with slower acquisition rate), even when they ultimately reach, or are close to reach, control performance (Solomon et al., 2011; Walker et al., 2011). Although the methylation changes associated with AD, PTSD, and ASD have not been related to learning impairments, we believe that it may be worthwhile testing if some of these methylation changes influence their epigenetic learning curves. The epigenetics of PTSD in humans and of acute psychological stress in animal models of PTSD suggest that the epigenetic changes may contribute to the behavioral and cognitive effects of such psychological stresses (Yehuda and Bierer, 2009; Blaze and Roth, 2013). We speculate that in people suffering from different (global and trauma-specific) learning and memory impairments, learning acquisition dynamics may be found to be abnormal, with specific brain regions and epigenetic dynamics varying according to the syndrome. We also predict that task-specific learning curves that rely on different brain regions would be correlated with distinct regional epigenetic profile abnormalities, specifically in DNA methylation, hydroxymethylation and histone acetylation.



Although learning impairments are only one facet of these syndromes, a better understanding of the dynamics of the epigenetics underlying them may uncover mechanisms and loci that escape detection with more static tests. If so, changes in the epigenetic learning curve may suggest possible novel avenues for therapeutic interventions by focusing on specific points *in time* for manipulating brain-region-specific epigenetic states.

## CONCLUSION

An overview of recent studies that investigate the involvement of the epigenetic system in long-term learning and memory reveals that the epigenome changes as a result of learning both at the level of specific genes and globally, across the entire genome (Blaze and Roth, 2013; Zovkic et al., 2013; Bronfman et al., 2014). Due to its mnemonic-like, self-sustaining activity (Miller and Sweatt, 2007; Ginsburg and Jablonka, 2009), the state of the epigenome can both represent neuronal history and affect future gene activity, thus bridging future and past learning. If this is indeed the case, we predict that epigenetic learning profiles that describe the manner by which the epigenome cumulatively changes as a function of learning will contribute to the shape of the cell's learning curve and to the overall learning curve of the neural networks that are involved in learning. We suggest that this profile could differ between tasks and brain regions and correspond to similar differences in behavioral learning curves observed for example in spatial learning (hippocampus) or eye-blink conditioning (cerebellum). Future studies should therefore investigate how differences in pattern of dynamic epigenetic change (especially DNA methylation, histone acetylation, and global microRNA profiles) correlate with differences in the shape of behavioral and neuronal learning curves, identify the factors that determine the neuronal epigenetic profiles and discover which manipulations result in changed learning curves.

Learning and the neural plasticity underlying it are cumulative and state-dependent processes. The epigenetic mechanisms that are involved in mediating, enabling and determining these dynamics are therefore of both theoretical and practical importance. The independent observations of abnormal learning curves and impairments in epigenetic processes in neurological pathologies such as ASD may reflect abnormal epigenetic profiles, and if so may open up new therapeutic possibilities. The future characterization of epigenetic dynamics during learning acquisition is therefore likely to be both fascinating and useful.

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