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Review

Focus: Molecular Memory

Epigenetic memory: the Lamarckian brain

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Abstract

Recent data support the view that epigenetic processes play a role in memory consolidation and help to transmit acquired memories even across generations in a Lamarckian manner. Drugs that target the epigenetic machinery were found to enhance memory function in rodents and ameliorate disease phenotypes in models for brain diseases such as Alzheimer's disease, Chorea Huntington, Depression or Schizophrenia. In this review, I will give an overview on the current knowledge of epigenetic processes in memory function and brain disease with a focus on Morbus Alzheimer as the most common neurodegenerative disease. I will address the question whether an epigenetic therapy could indeed be a suitable therapeutic avenue to treat brain diseases and discuss the necessary steps that should help to take neuroepigenetic research to the next level.

Keywords Alzheimer's disease; epigenetics; histone-acetylation; memory; neurodegeneration; non-coding RNA

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Memory formation via gene expression control

The human brain has about 100 billion neurons that are interconnected via synapses, and this is believed to provide the basis for the encoding, consolidation and retrieval of memories. How the brain achieves such miraculous tasks is one of the greatest remaining mysteries of our time. While various cellular mechanisms have been linked to memory function, an often cited view suggests that *de novo* protein synthesis is an absolute requirement for the consolidation of long-term memories; hence, tightly regulated gene expression must be a key component of memory formation. The idea that *de novo* protein synthesis is a requirement for memory formation is based on studies in which inhibitors of mRNA translation were found to impair memory formation in a time-dependent manner, indicating that at least two different phases of memory consolidation exist: an early phase that is *de novo* protein synthesis independent and a later phase that critically depends on protein synthesis (Flexner *et al*, 1962; Flexner *et al*, 1963; Davis & Squire, 1984; Igaz *et al*, 2002). The same principle has then been demonstrated for synaptic plasticity. For example, long-term potentiation (LTP), which is often referred to as the molecular correlate of learning and memory, can also be distinguished into an early phase (E-LTP) and late phase (L-LTP). Notably, L-LTP but not E-LTP can be blocked by *de novo* protein synthesis inhibitors (Frey & Morris, 1998). It was also shown that the induction of L-LTP induced molecular events that appear to trigger *de novo* protein synthesis and gene expression programs that can transform E-LTP into L-LTP (Frey & Morris, 1998). Those data led to the hypothesis of synaptic tagging and capturing (Box 1), which was also confirmed on the behavioral level (Moncada *et al*, 2011). However, pharmacological inhibition of protein synthesis was also found to cause an accumulation of mRNA transcripts which eventually leads to a super-induction of gene expression (Tronson *et al*, 2009), suggesting that the amnestic effect of *de novo* protein synthesis inhibitors is—at least in part—due to the induction of transcriptional noise. Despite such different views on the interplay and importance of synaptic events and learning-induced differential gene expression followed by *de novo* protein synthesis, it is obvious that a tightly controlled gene expression program provides the basis for memory encoding. This view is further supported by the fact that de-regulated gene expression is seen in brain diseases linked to memory impairment (Lu *et al*, 2004; Liang *et al*, 2010; Ginsberg *et al*, 2010; Twine *et al*, 2011; Blalock *et al*, 2011; Kim *et al*, 2012a; Arefin *et al*, 2012; Caldeira *et al*, 2013; Mills *et al*, 2013). To understand the mechanisms that orchestrate gene expression programs in brain cells is thus of utmost importance.

In addition to the activity of transcription factors, epigenetic (Box 1) mechanisms are key processes that control gene expression at a systems level (Allis *et al*, 2007) via DNA or nucleosome modifications.

Nucleosomes consist of the four core histones (H) around which 147 bp of DNA is wrapped. The histone tails are subjected to post-translational modifications including acetylation, methylation, phosphorylated, ubiquitination, sumoylation or ADP-ribosylation (Vaquero *et al*, 2003). This is mediated by the counteracting activities of enzymes, so-called writers and erasers (Box 1). For example, histone-acetylation and histone-methylation are mediated by histone acetyltransferases (HAT) and histone-deacetylases (HDAC) or histone-methyltransferases (HMTs) and histone-demethylases (HDM). Such modifications affect the direct interaction of the DNA with histones and thereby alter the chromatin state (Bannister & Kouzarides, 2011).

The activity of such enzymes is also believed to gives rise to a combinatorial pattern of chromatin-modifications, the so-called the histone-code, that is recognized by protein complexes that either activate or repress gene expression (Strahl & Allis, 2000). Methylation of DNA at the C-5 atom of cytosine is probably the

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Box 1.

Braak & Braak staging
Is a histological method that used staining for neurofibrillary tangels to define the degree of AD pathology in a post-mortem brain. It ranges from stage I (early stage) to stage VI (Severe stage).

Chip-Seq
DNA samples obtained after chromatin immunoprecipitation (ChIP) are not used to study selected genes via qPCR but are subjected to massive parallel sequencing. Albeit this method yields genome-wide maps of a given chromatin mark, data analysis requires intensive bioinformatic analysis. ChIP-Seq is routinely used in other research areas (Wang *et al*, 2008b), but has not been applied extensively to the learning and memory field.

Epigenetics
The term epigenetics has been introduced by Conrad Waddington to describe heritable changes of a phenotype that do not depend on altered DNA-sequence (Holliday, 1994). Especially in the neurosciences, it is now more generally used to describe processes that are mediated via the epigenetic machinery (Stilling & Fischer, 2011). Thus, when neuroscientists nowadays refer to epigenetics, they discuss processes that involve histone-modifications, DNA-methylation as well as the more recently discovered DNA-hydroxymethylation and often also the action of non-coding RNAs (Fig 1).

Environmental enrichment
Environmental enrichment is a behavioral method consisting of cognitive and physical exercise (Nithianantharajah & Hannan, 2006) that can ameliorate cognitive disease phenotypes in mice and humans (Pajonk *et al*, 2010) but is mechanistically poorly understood.

Synaptic tagging and capturing hypothesis
This theory suggests how activity initiates transient synaptic changes that mark a given synapse for subsequent protein synthesis-dependent long-lasting plasticity changes.

TAU pathology
The TAU protein is encoded by the *mapt* gene (*microtubule-associated protein tau*). It is natively unfolded and best studied for its role in the regulation of microtubule stability. During AD pathogenesis, TAU is hyper-phosphorylated at multiple sites, which leads to the deregulation of cellular homeostasis. Hyper-phosphorylated TAU protein eventually aggregates into intracellular neurofibrillary tangles (NFTs) that are—next to amyloid plaques—a key hallmark of AD. The distribution of NFTs in the brain is an important diagnostic tool for the Braak & Braak staging.

Writers, erasers, readers
Writers and erasers add and remove epigenetic marks. Readers, as the name suggest, read the epigenetic code for example by binding to specific epigenetic modifications which initiates subsequent events that control gene expression. A well-studied example are methylated-DNA-binding enzymes (MDB) such as MeCP2 (Na *et al*, 2013).

best-studied epigenetic modification and is mediated by DNA-methyltransferases. DNA-methylation occurs often in cytosine-guanine-rich regions of the genome (CpG islands) and is generally associated with gene silencing. It is mediated by the action of DNA-methyltransferases (DNMTs). Although there is by now clear evidence that DNA-methylation can be dynamic, the precise mechanisms how DNA is de-methylated are still not well understood. Recently, it has been discovered that cytosine can also be hydroxymethylated which occurs predominantly in brain tissue (Kriaucionis & Heintz, 2009) and is a critical step in the demethylation of DNA (Guibert & Weber, 2013). In addition to coding RNAs, the majority of the transcriptome consists of non-coding RNA species of various sizes. Best studied are a group of small non-coding RNAs, the micro RNAs (miRs) that are 19–22 nt long non-coding RNAs that catalyze gene silencing by binding to a target messenger RNA that induces either its degradation or inhibition of protein translation thereby regulating protein homeostasis (Im & Kenny, 2012). Although such non-coding RNAs are not considered to be part of classical epigenetic mechanisms, there is evidence that they mediate epigenetic gene expression (Rassoulzadegan *et al*, 2006; Fatica & Bozzoni, 2013). Thus, this review will also discuss the role of non-coding RNAs in brain plasticity (Fig 1).

The emerging field of neuroepigenetics investigates the above-mentioned epigenetic processes in the context of neuronal plasticity, memory function and brain diseases. In the following, I will discuss the current knowledge on neuroepigenetics with a focus on brain plasticity that will be contrasted by the current knowledge on epigenetics in brain disease such as Alzheimer disease (AD).

Histone-modifications in memory formation

Histone-acetylation
Already in 1979, it was found that acetylation of histones is altered when rats undergo memory consolidation (Schmitt & Matthies, 1979). Such studies were later confirmed showing that specific forms of learning correlate with increased HAT activity (Swank & Sweatt, 2001) and histone-acetylation (Levenson *et al*, 2004). While Schmitt and Matthies used C14-labeled acetate to study histone-acetylation (Schmitt & Matthies, 1979), these later studies used immunoblotting to detect bulk levels of histone-modifications. The mechanistic insight from such early observations is limited since they do allow to identify the genomic regions in which altered histone-acetylation takes place. The functional relevance of histone-acetylation for memory formation was first demonstrated via genetic mouse models in which the activity of the HAT CREB-binding protein (CBP/KAT3A) was reduced (Alarcon *et al*, 2004; Korzus *et al*, 2004). These mutant mice displayed impaired memory consolidation (Fig 2), a finding that has been reproduced in various mouse models in which CBP activity was altered (Wood *et al*, 2005; Wood *et al*, 2006; Chen *et al*, 2010a; Barrett *et al*, 2011). In addition, it was found that pharmacological inhibition of HDACs in the hippocampus enhances the consolidation of associative memories in rodents (Levenson *et al*, 2004; Fischer *et al*, 2007; Stefanko *et al*, 2009; Federman *et al*, 2009). Subsequent studies started to explore the role of specific histone-modifications and the function of the corresponding enzymes in greater detail. Insight into the role of specific modifications is still limited which is also due to the fact that most studies investigate bulk histone-modifications. To overcome this issue, researchers have started to perform chromatin immunoprecipitation (ChIP) followed by qPCR analysis to study the chromatin architecture of selected genes. Surprisingly, data in which ChIP-qPCR for specific histone-modifications was analyzed during memory formation are sparse, and at least in the brain, there is also evidence that transient changes in gene expression do not always correlate with altered histone-modifications at differentially expressed genes (Kenney *et al*, 2012). Such data suggest that the

effect of HATs and HDACs in memory formation may involve also other mechanisms than the regulation of gene expression. The current state of the art method to study chromatin marks across the entire genome is ChIP followed by next-generation sequencing (ChIP-Seq, Box 1). A recent study performed a genome-wide analysis of H4K5ac via ChIP-sequencing and found that H4K5ac correlates with learning-induced gene expression (Park *et al*, 2013). This study used however a fear conditioning protocol for associative learning (Fig 2) in which mice received re-conditioning on consecutive days. It thus appears that gene expression and histone-acetylation at the corresponding genes correlate best in response to rather severe stimuli, as observed in disease situations or in the case of mutant mice that lack specific enzymes of the epigenetic machinery (Peleg *et al*, 2010; Kerimoglu *et al*, 2013). Due to decreased costs and better bioinformatic tools, the genome-wide analysis of histone-acetylation using ChIP-Seq is likely to become a standard procedure also in the neurosciences, which will allow for more mechanistic insight in the future.

At the same time, there is already substantial data showing that the enzymes regulating histone-modifications are essential for memory function. Especially the role of HDCAs in the adult brain has gained much attention since they have emerged as promising drug targets for brain diseases (Fischer *et al*, 2010).

The 11 mammalian HDACs belong to an ancient protein family and require a Zn^{2+} ion as cofactor (de Ruijter *et al*, 2003; Gregoretti *et al*, 2004; Table 1). Under naïve conditions, all HDAC genes are expressed within the adult rodent brain (Broide *et al*, 2007). Mice that lack HDAC1 or overexpress it in all neurons from early developmental stages on show no impairments in contextual fear learning or spatial memory formation (Guan *et al*, 2009; Fig 2), suggesting that HDAC1 has no obvious role at least in the above-mentioned types of memory function. HDAC1 was however found to be essential for fear extinction learning, a process that is important for the treatment of neuropsychiatric diseases associated with aversive behaviors as they occur in post-traumatic stress disorder (Bahari-Javan *et al*, 2012). Here, the induction of immediate early genes was suppressed via HDAC1-mediated de-acetylation of H3K9 and subsequent H3K9 tri-methylation (Bahari-Javan *et al*, 2012). Although HDAC1 and HDAC2 are close homologues that derived from gene duplications, their roles in memory function differ. Overexpression of HDAC2 in neurons impaired contextual fear learning and spatial memory formation in mice, while deletion of HDAC2 in neurons from early developmental stages on improved memory function and synaptic plasticity (Guan *et al*, 2009). Notably, enhanced learning behavior in HDAC2 knockout mice correlated with increased hippocampal H4K12 acetylation, while H3K14 acetylation was not affected. Although the authors measured bulk changes, these data are interesting taking into account that genome-wide analysis of chromatin in the aging hippocampus suggested a key role for H4K12 acetylation in age-associated memory impairment (Peleg *et al*, 2010). On the structural level, loss of HDAC2 increased the number of synapses (Guan *et al*, 2009) which is in line with a role of HDAC2—but also HDAC1—in synapse formation during development (Akhtar *et al*, 2009). Loss of HDAC2 was also found to improve fear extinction learning (Morris *et al*, 2013) which is opposite to the function of HDAC1 (Bahari-Javan *et al*, 2012). HDAC2 was found to bind promoter regions of genes linked to memory formation, but the precise mechanisms by which HDAC2 acts as a memory repressor are not well understood (Guan *et al*, 2009). One study showed that HDAC2 is essential for the survival of adult born neurons in the dentate gyrus (Jawerka *et al*, 2010). Since adult neurogenesis has been linked to memory function, it is clear that the role of HDAC2 in the adult brain awaits a more detailed analysis. An important next step would be to understand the role of HDAC1 and 2 in a cell-type-specific manner. A recent study suggests that HDAC2 is produced in many neuronal cell types and in oligodendrocytes, but not in astro- or microglia (Yao *et al*, 2013). Similar to the data available for HDAC2, mice that lack HDAC3 in the adult hippocampus show improved object recognition memory (McQuown *et al*, 2011; Fig 2), but the underlying mechanisms are not understood. The function of HDAC8 in adult brain has not been addressed in detail, but a recent study found that an HDAC inhibitor with some selectivity toward HDAC8 improves memory function in rats (Yang *et al*, 2013). In conclusion, it appears that the class I HDACs act as molecular inhibitors of memory formation.

As for the class II HDACs (Table 1), HDAC4 is known to shuttle between the cytoplasm and the nucleus of cultured hippocampal neurons in response to Calcium signaling and CamKII activity (Chawla *et al*, 2003; Backs *et al*, 2006). In an *C. elegans* model, deletion of HDAC4 gene increases long-term memory for thermosensation in an CamKII-dependent manner (Wang *et al*, 2011). Specific expression of mammalian HDAC4 in the nucleus was able to revert this phenotype, suggesting that nuclear export of HDAC4 is a critical process for memory formation. In line with these data, cytoplasmatic expression of HDAC4 increased memory formation in wild-type worms (Wang *et al*, 2011), suggesting that during learning, HDAC4 regulates counteracting molecular processes in the nucleus and the cytoplasm. In contrast to such findings, a recent study suggests that HDAC4 is essential for memory function in mammalian systems. Mice that lack HDAC4 in the adult forebrain exhibit impaired hippocampus-dependent memory formation and plasticity (Kim *et al*, 2012b). These data are in line with findings showing that haploinsufficiency of HDAC4 is linked to mental retardation in humans (Williams *et al*, 2010). Another study confirmed that lack of HDAC4 in the adult brain results in impaired memory function and synaptic plasticity in mice and could identify synaptic plasticity genes that are regulated by nuclear HDAC4 (Sando *et al*, 2012). Loss of HDAC5 in the nucleus accumbens renders mice hypersensitive to chronic cocaine (Renthal *et al*, 2007), while 2-month-old mice that lack HDAC5 from the adult forebrain show no changes in hippocampus-dependent memory formation (Kim *et al*, 2012b). A role of HDAC5 in memory formation may not only be brain region but also age-related. To this end, 10-month-old mice that lack HDAC5 show hippocampus-dependent memory disturbances (Agis-Balboa *et al*, 2013). HDAC6 has a unique position in the HDAC family in that its main targets are cytoplasmatic proteins such as tubulin or heat-shock protein 90 (Govindarajan *et al*, 2013). As will be discussed below, HDAC6 is emerging as promising drug target in neurodegenerative diseases. However, loss of HDAC6 in mice has no overt phenotype and does not impact on memory formation (Govindarajan *et al*, 2013). The role of the remaining zinc-dependent HDACs in the adult brain has not been investigated in great detail.

Compared to the increasing numbers of studies that investigate the role of HDACs in memory formation, there are comparatively little data on the role of HATs. The mammalian genome encodes for

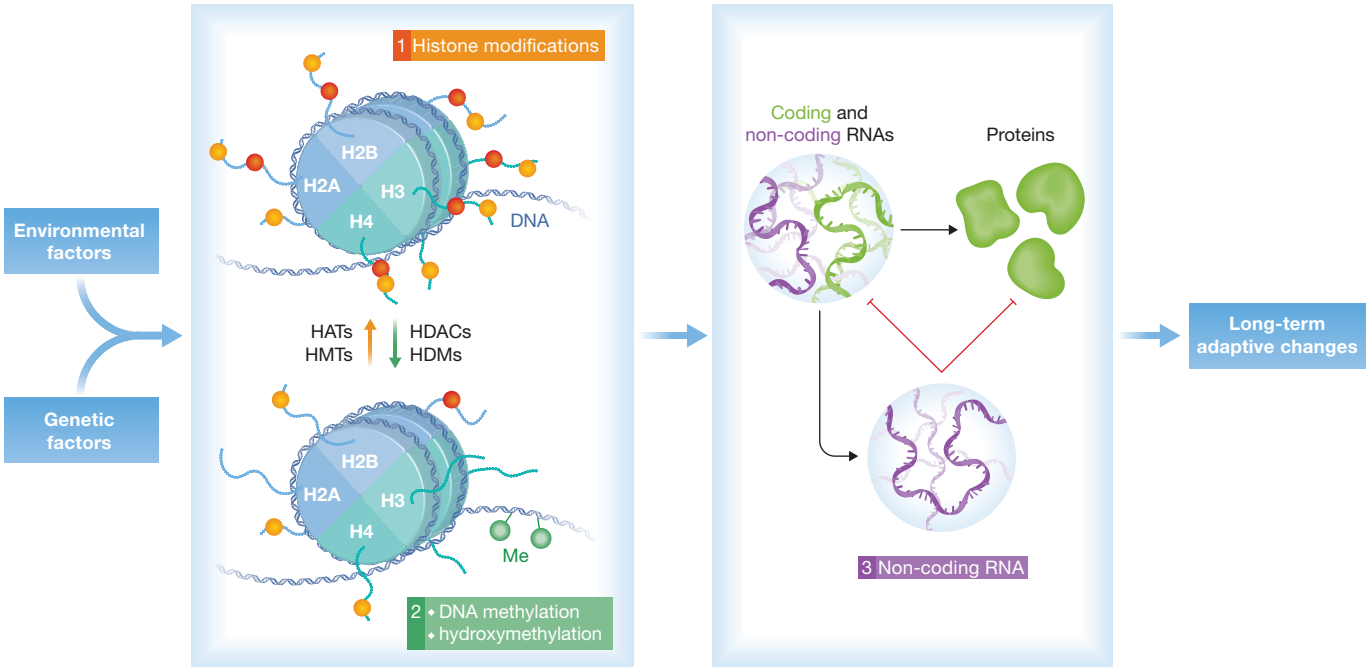

Figure 1. Epigenetic and non-coding RNA mechanisms.
(1) DNA is wrapped around the nucleosome which consists of the four core histones (H). Histone tails are subjected to post-translational modification including acetylation and methylation, which give rise to the "histone-code" that affects gene expression. Histone acetylation and methylation are regulated by the counteracting activity of histone acetyltransferases (HATs) and histone-deacetylases (HDACs) or histone-methyltransferases (HMTs) and histone-demethylases (HDMs), respectively. (2) Methylation of DNA at the C-5 atom of cytosine is mediated by DNA-methyltransferases and often occurs in cytosine-guanine-rich regions of the genome (CpG islands). DNA-methylation is generally associated with gene silencing. DNA-hydroxymethylation is mediated by ten-eleven translocation proteins and also regulates gene expression. (3) Non-coding RNAs affect gene expression and protein function. The best-studied non-coding RNAs are micro RNAs (miRs) that catalyze gene silencing or inhibition of protein translation. These processes are key regulators of genome–environment interactions and provide to a cell the molecular tools to transform the variable combinations of genetic and environmental factors into long-term adaptive changes. There is now emerging evidence that the epigenome also regulates the consolidation of processed information into long-term memories.

at least 18 HATs that are subdivided into the GNAT (Gcn5 *N*-acetyl-transferases) family, the MYST (MOZ, Ybf2/Sas3, Sas2, TIP60) family, the p300/CBP family and several other HATs that cannot be grouped into a certain family (Lee & Workman, 2007; Allis *et al*, 2007). The best-studied HATs belong to the p300/CBP family. Multiple studies demonstrated a role for CBP/KAT3A in memory consolidation (Alarcon *et al*, 2004; Korzus *et al*, 2004; Wood *et al*, 2005; Wood *et al*, 2006; Chen *et al*, 2010a; Barrett *et al*, 2011), though it does not seem to be essential for all types of memory and especially for the highly hippocampus-dependent Morris water maze test, existing data are conflicting (Josselyn, 2005).

However, overexpression of a dominant negative form of P300/KAT3B in the mouse brain impairs memory consolidation (Oliveira *et al*, 2007), and similar data were observed for mice that lack one allele of PCAF/KAT2B (Maurice *et al*, 2008), but mechanistic insight is limited at present. There is evidence that CBP mediates its role in brain plasticity via histone-acetylation-dependent gene expression (Vecsey *et al*, 2007), and one study provided evidence that the role of CBP/KAT3A during learning critically depends on its ability to induce the expression of nuclear receptor 4a1 (Nr4a1; McNulty *et al*, 2012). However, detailed genome-wide analysis of transcriptional networks associated with CBP function in the adult brain is

Figure 2. Analyzing memory function in rodents.
This image illustrates three commonly used tests to study memory formation in rodents. (A) The Morris water maze Test measures spatial reference memory that is highly hippocampus-dependent. A mouse or rat is placed in a pool that contains opaque water and an escape platform that is located underneath the water surface. During the training, the rodent learns to locate the hidden platform based on spatial orientation. Such memory is normally acquired gradually throughout multiple training sessions on subsequent days (e.g., 10 days of training). (B) The Pavlovian fear conditioning is used to assess associative memory. The rodent is allowed to explore the test box representing a novel context for about 3 min before it receives a mild electric foot shock. When placed back into the context 24 h later, the animal shows freezing, inborn behavior that rodents express in response to threatening situations. The amount of freezing is quantified and reflects learning ability. In contrast to the water maze, fear conditioning is successfully acquired after a single training session, and memory can be tested even 1 year later. (C) In the novel object recognition paradigm, the animal is habituated to the test arena and eventually presented with two objects that it explores equally. After a delay that can vary from minutes (short-term memory) to 24 h (long-term memory), the animal is re-exposed to the arena that now contains one novel object. Based on the previous training session, the animal remembers the object that has already been explored and will show a preference for the novel object. (D) To elucidate the mechanisms that underlie memory consolidation, a suitable approach is to subject animals to a training session and isolate afterward at distinct time points tissue for molecular analysis. Especially paradigms such as fear conditioning are often used since memory is acquired within a distinct time window after a single training session allowing for a "molecular snapshot" of memory consolidation. Based on such results, hypothesis can be formed and suitable gain- and loss-of-function mouse models are generated that are then again tested for memory function.

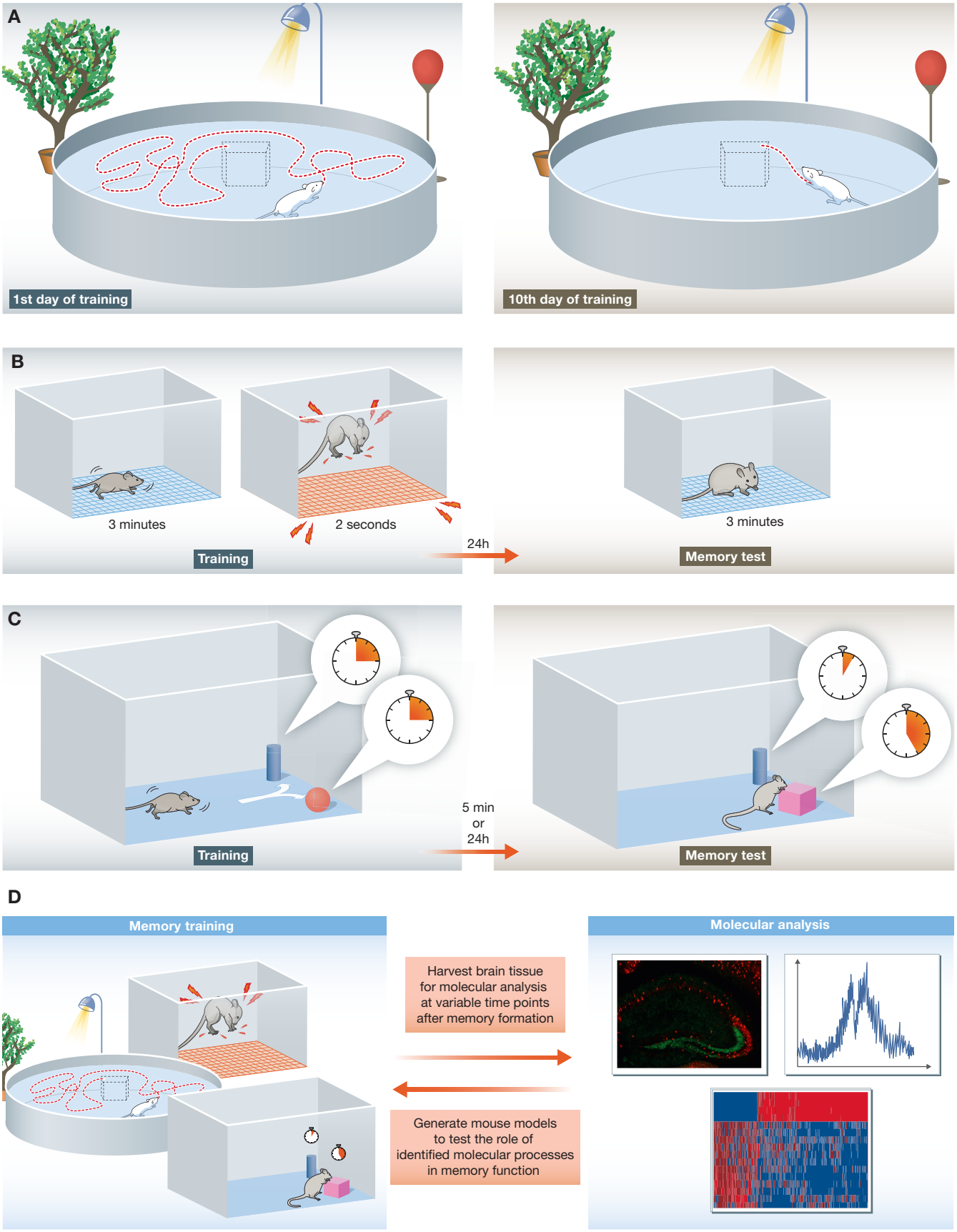

Table 1. HDACs in the adult brain

	Protein	Subcellular localization	Potential function in memory formation
CLASS I	HDAC1	Mainly nuclear, cyoplasmatic in response to axonal damage	Regulates fear extinction
	HDAC2	Mainly nuclear	Negative regulator of memory formation mice
	HDAC3	Nuclear/cytoplasmatic	Negative regulator of memory formation mice
	HDAC8	Mainly nuclear	Unclear
CLASS II	HDAC4	Cytoplasmatic/nuclear/Synaptic	Required for memory formation in mice
	HDAC5	Cytoplasmatic/nuclear	Required for memory formation in mice
	HDAC6	Cytoplasmatic/centrosomal	Not required for memory formation in mice but inhibition reinstates memory function in Alzheimer disease mouse models
	HDAC7	Cytoplasmatic/nuclear	Unclear
	HDAC9	Cytoplasmatic/nuclear	Unclear
	HDAC10	Cytoplasmatic/nuclear	Unclear
CLASS IV	HDAC11	Cytoplasmatic/nuclear	Unclear

This table illustrates the current classification of the 11 mammalian HDACs and points to their role in memory formation (for further information see text).

sparse and gene array approaches thus far linked CBP function to calcium signaling, transcription and synaptic plasticity (Chen *et al*, 2010a) and de-regulated gene expression in response to environmental enrichment training (Lopez-Atalaya *et al*, 2011).

In conclusion, there is substantial evidence that HATs and HDACs are critical for memory formation. Based on their general role in the regulation of cellular processes, it is tempting to speculate that they coordinate gene expression programs linked to long-term memory consolidation, but a major effort in future research will be to understand the mechanisms by which HATs and HDACs regulate plasticity in specific brain cells.

Histone-methylation in memory formation

In addition to acetylation, histone proteins can be methylated, phosphorylated, ubiquitinated, sumoylated, biotinylated or ADP-ribosylated (Vaquero *et al*, 2003). While histone-phosphorylation and histone 1 ADP-ribosylation has been linked to memory training (Chwang *et al*, 2006; Fontán-Lozano *et al*, 2010), the best studied histone-modification in the brain next to acetylation is histone-methylation. Similar to histone-acetylation, it is regulated by the counteracting activity of HMTs and HMDs. However, in contrast to acetylation, the lysine residues of histones can be either mono-, di- or tri-methylated which is catalyzed by specific enzymes. As such there are more HMTs and HDMs than there are HATs and HDACs, and their general role has been discussed in a number of recent review articles (Shi, 2007; Shi & Whetstine, 2007; Badeaux & Shi, 2013). Early studies found that histone-methylation is implicated with neuronal plasticity and memory formation. Especially H3K4-trimethylation (H3K4me3), a mark for active gene promoters, has been studied. For example, H3K4me3 correlates with the expression of glutamate receptors in the human brain (Stadler *et al*, 2005). Moreover, bulk levels of hippocampal H3K4me3 were found to increase in response to fear conditioning training (Gupta *et al*, 2010). H3K4me3 is regulated by at least 10 different enzymes that catalyze mono-, di and tri-methylation (Badeaux & Shi, 2013). Mice that lack one allele of the H3K4 HMT Mll1/KMT2A display impaired memory formation (Gupta *et al*, 2010). A recent study also demonstrated a role for the H3K4 specific HMT Mll2/KMT2B in memory function. Mice that lack KMT2B in the dorsal dentate gyrus of hippocampal region show memory impairment that is linked to deregulation of learning-relevant genes (Kerimoglu *et al*, 2013). Loss of KMT2B not only affected H3K4me3 at the promoter regions of learning-regulated genes but also reduced H3K9 acetylation, while H4K16 acetylation and H3K4me1 was unaffected at the same gene promoters (Kerimoglu *et al*, 2013). Such data further confirm the view that histone-methylation and histone-acetylation are tightly linked, and also demonstrate the need to better understand the protein complexes that regulate chromatin plasticity in the adult brain. Other H3K4 HMTs or HDMs have not been tested for a role in memory formation, but an inhibitor of the H3K4 HMD LSD1/KDM1a was found to impair memory formation when injected to mice (Neelamegam *et al*, 2012). These data would suggest that increased H3K4me3 in the brain causes cognitive impairments, which is in contrast to the data obtained from the knockout studies of H3K4 HMTs KMT2A and KMT2B. However, at present, it is unclear which gene expression programs are controlled by H3K4me3 and which HTMs and HDMs are indeed involved in the regulation of such learning-relevant genes. Moreover, LSD1/KDM1a also affects H3K9 methylation. H3K9 methylation is linked to heterochromatin formation and gene silencing. Interestingly, the H3K9 di-methylation-specific HMT G9a/KMT1C was found to play a key role in neuronal integrity. In fact, mice that lack G9a/KMT1C in the adult forebrain develop mental retardation-like phenotypes (Schaefer *et al*, 2009). However, loss of G9a/KMT1C in the nucleus accumbens increases cocaine-induced neuronal plasticity (Maze *et al*, 2010), and yet another study found that pharmacological inhibition of G9a in the entorhinal cortex facilitated memory function, while administration of the same inhibitor into the hippocampus resulted in impaired memory function in mice (Gupta-Agarwal *et al*, 2012). A critical role for G9a/KMT1C in memory formation is also supported from studies in Drosophila, where loss of G9a/KMT1C impaired memory formation (Kramer *et al*, 2011). Another H3K9 methyltransferase is SETDB1/KMT1E. Increased expression of SETDB1/KMT1E in the forebrain of mice reduced depressive-like behavior via a mechanism that involved regulation of NMDA receptor subunit 2B (Jiang *et al*, 2010). As for the HDMs, there are even less data investigating the role of such enzymes in memory formation. Recent studies could link mutations in JARID1C/KDM5C, an H3K4 demethylase, to

short-term memory deficits in female humans (Simensen *et al*, 2012) and to mental retardation (Rujirabanjerd *et al*, 2012). As for the H3K9 demethylases, JMJD2A/KDM4A was found in a complex with HDAC1 and protein phosphatase 1 (PP1) which was required for memory formation (Koshibu *et al*, 2009). In conclusion, the current data suggest that histone-methylation, as well as the activity of HMTs and HDMs, plays a role in memory formation, but a clear picture is not yet emerging.

Histone-modifications in Alzheimer's disease

An increasing number of studies show that targeting the epigenetic machinery in neurodegenerative diseases could be a novel and promising therapeutic avenue (Fischer *et al*, 2010). Especially, inhibitors of HDAC proteins have gained much attention in brain disorders such as AD (Sananbenesi & Fischer, 2009). AD is a debilitating disease that arises on the pathological background of amyloid-beta plaques, neurofibrillary tangles and severe neuronal loss, eventually leading to dementia (Haass & Selkoe, 2007). About 5% of all AD cases are caused by mutations in genes that regulate processing of the amyloid precursor protein (Haass & Selkoe, 2007). More common is however the late onset form (loAD) of AD that comprises 95% of all cases and is driven by variable combinations of genetic and environmental risk factors (Sananbenesi & Fischer, 2009; Goate & Hardy, 2012). Despite intensive research and increasing molecular insight to the patho-mechanisms underlying loAD, no effective therapy is currently available (Mangialasche *et al*, 2010).

The therapeutic potential of HDAC inhibitors in AD was first tested in a mouse model that overexpresses the p25 protein—a pathological activator of cyclin-dependent kinase 5—in a region and time-restricted manner (Fischer *et al*, 2007). Inducible overexpression of p25 causes amyloid and tau pathology, severe neurodegeneration and memory impairment (Cruz *et al*, 2003; Fischer *et al*, 2005; Cruz *et al*, 2006). Intra-peritoneal (ip) administration of the HDAC inhibitor sodium butyrate for 4 weeks was able to reinstate learning behavior and synaptic plasticity in this mouse model even after the onset of severe synaptic and neuronal loss (Fischer *et al*, 2007). In this experimental setting, the rational to apply an HDAC inhibitor to an AD mouse model was based on the hypothesis that environmental enrichment (EE, Box 1) is mediated via changes in neuronal histone-acetylation (Fischer *et al*, 2007; Sananbenesi & Fischer, 2009).

The therapeutic effect of HDAC inhibitors in AD was also observed in mouse models for amyloid deposition. HDAC inhibitors such as trichostatin A, phenylbutyrate, valproate, sodiumbutyrate or suberoylanilide hydroxamic acid (SAHA, Vorinostat) have been administered mainly via i.p. injections to APP/PS1, Tg2576 and APPPS1-21 mice (Francis *et al*, 2009; Ricobaraza *et al*, 2009; Ricobaraza *et al*, 2010; Kilgore *et al*, 2010; Govindarajan *et al*, 2011). All these studies found that HDAC inhibitors improved memory function, and in some cases, increased bulk levels of histone-acetylation in brain regions were observed. One study also investigated hippocampal spine density and found it to be enhanced after phenylbutyrate treatment (Ricobaraza *et al*, 2010), while another studies observed a reduction in pathological phospho-Tau levels (Ricobaraza *et al*, 2009) or a reinstatement of gene expression (Govindarajan *et al*, 2011). The work of Govindarajan *et al* is of note since the HDAC inhibitor sodiumbutyrate was only applied after the onset of severe AD pathology and was still able to improve memory function. Equally important is the fact that none of the above studies could demonstrate an effect of HDAC inhibitor treatment on amyloid pathology itself. Since all of the above-described HDAC inhibitors show different pharmacological profiles and affect multiple HDAC proteins, it is still possible that other HDAC inhibitors may alter amyloid pathology, probably via regulation of genes linked to APP processing or clearance mechanisms. In line with this view, a recent study found that orally administered MS-275 (Entinostat), a class I HDAC inhibitor that shows selectivity toward HDAC1 (Hu *et al*, 2003; Khan *et al*, 2008; Bahari-Javan *et al*, 2012), improved dysregulated nesting behavior in APPPS1-21 mice and reduced neuroinflammation and also amyloid plaque deposition (Zhang & Schluesener, 2013). Another study found that a new class II HDAC inhibitor lowered Aß40, Aß42 and Thr181 phospho-TAU levels and improved memory function when administered for 4 weeks to 3xTG AD mice (Sung *et al*, 2013).

It has to be mentioned that one recent study reported that the HDAC inhibitor SAHA facilitates hippocampal long-term potentiation (LTP) in wild-type mice but failed to improve cognitive function in Tg2567 mouse model for Alzheimer's disease (Hanson *et al*, 2013). As an explanation the authors demonstrate poor brain availability of SAHA after i.p. injection. This could explain why improved memory function was observed in the same mouse model when phenylbutyrate was administered (Ricobaraza *et al*, 2009) and the fact that SAHA could rescue age-associated memory impairment in mice when injected directly into the hippocampus (Peleg *et al*, 2010). However, the same dose of SAHA that was used in the Hansson *et al* study was found effective in APP/PS1delta9 mice when administered i.p. for only 3 weeks (Kilgore *et al*, 2010) and the discrepancy for these data is not clear at present.

Importantly, most of the data on HDAC inhibitors in AD were obtained using mouse models that recapitulate amyloid deposition and are based on the rare familial form of AD. Thus, it is interesting to note that a number of studies found that HDAC inhibitors also improve memory function in aged rodents (Fontán-Lozano *et al*, 2008; Peleg *et al*, 2010; Reolon *et al*, 2011).

A role for histone-acetylation and the zinc-dependent HDACs in models for TAU pathology (Box 1) has not been investigated in detail. I predict that this will be a very interesting line of future research, taking into account that reduction of TAU expression has emerged as a promising therapeutic strategy in AD (Roberson *et al*, 2007) and findings showing that the epigenetic state of the *mapt* gene (which encodes the TAU protein) as well as the *app* gene (which encodes APP) is altered in human AD brains (Iwata *et al*, 2013). Furthermore, the function of TAU itself was found to be regulated via acetylation. TAU acetylation was found to inhibit the turnover of phosphorylated TAU species via a mechanism that involves the HAT p300/KAT3B and the class III HDAC SIRT1 (Min *et al*, 2010), indicating that increased TAU acetylation contributes to disease pathogenesis. In contrast to this view, recent studies suggest that targeting TAU acetylation or related processes could be a beneficial strategy to treat AD. For example, TAU interacts with HDAC6 (Ding *et al*, 2008; Perez *et al*, 2009) which has been linked to Tau clearance (Cook *et al*, 2012). It was furthermore shown that HDAC6-mediated loss of Tau acetylation renders the protein

vulnerable to toxic phosphorylation events (Cook *et al*, 2013). Further evidence that inhibition of HDAC6 might attenuate TAU pathology in AD stems from a Drosophila model (Xiong *et al*, 2013). Here, hyper-phosphorylated Tau protein resulted in microtubule instability and neurodegeneration which was rescued by knock-down of HDAC6 (Xiong *et al*, 2013). Such findings are supported by recent data showing loss of HDAC6 rescues memory function in a mouse model for Alzheimer's disease (Govindarajan *et al*, 2013).

In conclusion, there is substantial evidence that HDAC inhibitor treatment can improve memory function in mouse models for AD even at an advanced stage of pathology. This phenomenon is mechanistically however not well understood.

Two questions need to be addressed in future research: (i) Via which cellular mechanisms do HDAC inhibitors ameliorate AD-related cognitive decline? and (ii) through which specific HDAC proteins do HDAC inhibitors mediate their therapeutic effects? Obviously, these questions are closely linked to research that aims to better understand the role of HATs and HDACs during memory formation. It is also critical to elucidate the question whether targeting the epigenome is symptomatic or whether indeed disease-causing epigenetic mechanisms are affected by therapeutic strategies such as HDAC inhibitors.

The best evidence that altered histone-acetylation is mechanistically linked to memory decline stems from a study in which age-associated memory impairment was investigated in mice (Peleg *et al*, 2010). Here, the onset of cognitive decline during aging was linked to deregulated acetylation of H4K12 (H4K12ac). While memory training induced a transient increase in various histone-acetylation marks in the hippocampus of young and aged mice, H4K12ac did not respond anymore to such a stimulus in old animals. ChIP-Seq was combined with transcriptome analysis, and the data suggest that H4K12ac is critical for the initiation of a learning-induced gene expression program via mechanisms that involved transcriptional elongation (Peleg *et al*, 2010). Intrahippocampal injection of SAHA to aged mice was able to partially restore H4K12ac-linked gene expression and memory function (Peleg *et al*, 2010).

Several HDAC proteins have been linked to cognitive decline. For example, HDAC1 has been implicated with AD, but the current data do not yet allow for a conclusion if inhibition of HDAC1 would be detrimental or beneficial for AD pathology. Recent data suggest that HDAC1 activity contributes to AD pathology since it appears to be a critical mediator of genome stability. Loss of HDAC1 has been linked to DNA damage (Kim *et al*, 2008; Wang *et al*, 2013; Dobbin *et al*, 2013), which represents most likely a loss of nuclear HDAC1 function. Such data suggest that future therapeutic approaches using HDAC inhibitors should avoid targeting HDAC1. However, it was found that in response to axonal damage, which is also a hallmark of AD, HDAC1 is exported from the nucleus to the cytoplasm where it dysregulates mitochondrial transport. In this context, inhibition of HDAC1 was beneficial and could reinstate axonal transport (Kim *et al*, 2010). In contrast, the role of HDAC2 is better understood. HDAC2 expression was found to increase in AD patients and in AD mouse models. Reducing HDAC2 levels in AD mouse models via siRNA approaches was able to reinstate memory function (Gräff *et al*, 2012).

As for the class II HDACs, it was shown that loss of HDAC5 accelerated memory decline in APPPS1-21 mice (Agis-Balboa *et al*, 2013). A recent study found that HDAC5 plays a role in axonal regeneration (Cho *et al*, 2013). Upon axonal damage HDAC5 is transported out of the nucleus which allows the expression of genes that orchestrate a neuronal regeneration program. The only other HDAC that has been studied for its role in AD is HDAC6, which is elevated in post-mortem brain tissue from AD patients (Ding *et al*, 2008). Reducing HDAC6 levels in mice rescues memory impairment in an AD mouse model via a mechanism that involves mitochondrial transport (Govindarajan *et al*, 2013).

In summary, the knowledge of HDAC proteins in learning and brain diseases has significantly increased in the last 5 years. It is however obvious that more research is needed. For example, HDACs mediate their biological function as components of larger complexes that include transcription factors and other proteins, offering another layer for pharmacological interventions. The question how chromatin-modifying enzymes act in the context of protein complexes in the adult brain will be an interesting question for future research.

Taking into account that deregulated acetylation of histone and non-histone proteins is implicated with memory decline and AD, in addition to the role of HDACs, it is important to elucidate the role of HATs in brain diseases. Most of the current knowledge is focused on CBP/KAT3A. Mutations in CBP cause Rubinstein–Taybi syndrome (RTS, see Box 1), and there is some evidence that CBP is implicated in AD pathogenesis, since it was found that phosho-levels of CBP/KAT3A are down-regulated in a mouse model for amyloid deposition. Overexpression of CBP/KAT3A ameliorated memory impairment in this model (Caccamo *et al*, 2010). Further evidence stems from findings suggesting that CBP/KAT3A and the close homologue P300/KAT3B are activated by wild-type presenilin 1, but not by the AD-associated presenilin 1 mutant protein (Francis *et al*, 2007).

Whether CBP/KAT3A or P300/KAT3B control gene expression programs that might mirror the deregulation seen in AD has not been addressed in detail, but novel computational approaches might help to shed light on such questions (Poirel *et al*, 2013). Data for other HATs in neurodegenerative disease are sparse. Loss of PCAF/KAT2B was found to ameliorate the phenotypes induced by the injection of amyloid-beta peptides injected into lateral ventricles (Duclot *et al*, 2010). Moreover, TIP60/KAT5 activity can rescue amyloid-beta-induced neurotoxicity (Pirooznia *et al*, 2012) and axonal transport deficits in a Drosophila model (Johnson *et al*, 2013). There is evidence that TIP60/KAT5 mediates such effects by regulating gene expression, especially of genes linked to apoptotic cell death (Pirooznia *et al*, 2012) and axonal transport (Johnson *et al*, 2013). However, unbiased approaches to decipher the gene expression program controlled by TIP60/KAT5 in the adult brain are missing. A direct link of TIP60/KAT5 to AD pathogenesis is suggested by findings showing that TIP60/KAT5 regulates gene expression in a complex with the amyloid precursor protein intracellular domain (AICD; Cao *et al*, 2004; Müller *et al*, 2013). Moreover, TIP60/KAT5 plays a critical role in orchestrating the cellular response to DNA damage (Kaidi & Jackson, 2013) which is emerging as another critical player in AD pathogenesis (Mao & Reddy, 2011; Herrup *et al*, 2013). There is also evidence that TIP60 mediates microtubule-acetylation (Sarthi & Elefant, 2011), suggesting that it might act as a counterplayer of HDAC6, which has however not been tested so far.

While the role of HATs in neurodegenerative disease is only emerging and from a pharmacological point of view it might be easier to inhibit rather than to activate an enzyme, there is an

Box 2.

Histone-modifying enzymes in other neurodegenerative diseases

A number of chromatin-modifying enzymes have been linked to other neurodegenerative diseases than AD, of which the most important ones are briefly mentioned here. For more information on the role of such enzymes in psychiatric diseases, the reader is referred to some recent review articles on this topic (Labrie *et al*, 2012; Jakovcevski & Akbarian, 2012; Mahgoub & Monteggia, 2013).

HDAC1

A recent study found that HDAC1 levels are increased in mouse models for Chorea Huntington and in CK-p25 mice and showed that elevated HDAC1 induces neuronal cell death in a HDAC3-dependent manner (Bardai *et al*, 2012). However, the same study provides evidence that HDAC1 promotes cell survival via interaction with histone deacetylase-related protein (HDRP), suggesting that rather than inhibiting HDAC1 activity it could be a suitable therapeutic approach to block HDAC1–HDAC3 interactions. Nevertheless, a recent study employed the HDAC1/HDAC3 inhibitors 4b and 136 and found that these compounds were able to ameliorate disease phenotypes in drosophila and mouse models for Huntington's disease (Jia *et al*, 2012). Taking also into account that HDAC1 is required for specific forms of learning (Bahari-Javan *et al*, 2012; Jakovcevski *et al*, 2013) and is deregulated in schizophrenia patients (Sharma *et al*, 2008) suggests that more research is needed to evaluate the potential of this HDAC as a drug target in brain diseases.

HDAC9

Genome-wide association studies identified HDAC9 as a genetic risk factor for ischemic stroke (Traylor *et al*, 2012; Markus *et al*, 2013). Moreover, hemizygous loss of HDAC9 has been linked to schizophrenia (Lang *et al*, 2011). Another study found that an intronic single nucleotide polymorphism in the HDAC9 genes was linked to male-pattern baldness (Brockschmidt *et al*, 2011), which is undeniably a disease of the head, but clearly more research on HDAC9 is needed to evaluate its role in memory function and brain diseases. An issue not discussed yet is alternative splicing. It is thus interesting to note that histone-deactylase-related protein (HDR) is an alternative splice version of the HDAC9 gene that gives rise to a truncated HDAC9 protein linked to neuroprotection (Zhang *et al*, 2008).

HDAC10 and HDAC11

These HDACs have not been linked to a neurodegenerative diseases yet, but there are in general only very little data available for these enzymes. An interesting observation was made in mice subjected to caloric restriction, which is known to improve synaptic plasticity and learning in mice. Fasting led to a down-regulation of the *hdac10* and *hdac11* genes in the hypothalamus (Funato *et al*, 2011). Similar explorative studies reported increased levels of HDAC11 in the cingulate cortex and the striatum of mice after cocaine self administration (Host *et al*, 2011) and in the cortex of mice in a ischemic stroke model (Chen *et al*, 2012).

CBP/KAT3A

Rubinstein–Taybi syndrome (RTS) is an autosomal dominantly inherited form of mental retardation that affects 1 in 125,000 individuals (Petrij *et al*, 1995; Oike *et al*, 1999). It is caused by mutations in CBP/KAT3A and in line with these data, mice that lack CBP show RTS-like phenotypes (Bourtchouladze *et al*, 2003) which can partially be restored by administration of an HDAC inhibitor (Alarcon *et al*, 2004).

CREB-binding protein/KAT3A also appears to play a role in the pathogenesis of Huntington's disease (HD), where it was found that mutant Huntingtin protein interacts with CBP/KAT3A and thereby deregulates gene expression (Steffan *et al*, 2000; Steffan *et al*, 2001; Cong *et al*, 2005; Jiang *et al*, 2006). Although CBP/KAT3A and P300/KAT3B are close homologues, the available data suggest that P300/KAT3B does not bind to mutant huntingtin (Cong *et al*, 2005).

In line with impaired CBP/KAT3A function in HD, decreased histone-acetylation and corresponding gene expression were found in HD patients and in HD mouse models (Sadri-Vakili *et al*, 2007; McFarland *et al*, 2012; Yeh *et al*, 2013). Mice that lack CBP/KAT3A show accelerated pathology when crossed to a Huntington's disease model (Klevytska *et al*, 2010), while loss of CBP/KAT3A by itself does not cause neuronal cell death (Valor *et al*, 2011). Moreover, administration of sodiumbutyrate or suberoylanilide hydroxamic acid, phenylbutyrate or sodium butyrate ameliorated disease phenotypes in a mouse model for HD (Hockly *et al*, 2003; Ferrante *et al*, 2003; Gardian *et al*, 2005). Data from a *C. elegans* model suggest that especially inhibition of HDAC3 might counteract the loss of CBP/KAT3A in the presence of mutant huntingtin (Bates *et al*, 2006).

Mll2/Mll4/KMT2D

Mutations in Mll2/Mll4/KMT2D have been linked to Kabuki syndrome, a rare disease that is accompanied by cognitive impairment (Ng *et al*, 2010). Aberrant H3K4me3 was also observed in post-mortem human brain tissue from autistic individuals (Shulha *et al*, 2012a).

increasing body of literature pointing to the potential of HAT activators as a therapeutic avenue in brain diseases (Selvi *et al*, 2010; Schneider *et al*, 2013). A recent study employed a novel HAT activator and found that this compound crosses the blood–brain barrier, increased neuronal plasticity and memory function in wild-type mice (Chatterjee *et al*, 2013). It will be interesting to see how such a compound may affect pathology in mouse models of AD.

In conclusion, the recent literature suggests that it is important to further understand the counteracting roles of HATs and HDACs in AD pathogenesis before such findings can be translated into therapeutic approaches. With respect to other histone-modifications, increased histone-phosphorylation was observed in post-mortem tissue from AD patients (Rao *et al*, 2012), but in general little is known on other histone-modifications and their corresponding enzymes in AD or other brain diseases (Box 2).

DNA-methylation in memory formation

The best-studied epigenetic modification is DNA-methylation. There is evidence that DNA-methylation is dynamically regulated during memory formation. For example, neuronal activity altered the DNA-methylation in granule neurons of the dentate gyrus (Guo *et al*, 2011). Moreover, fear conditioning training in mice induced hippocampal expression of DNMT3a and DNMT3b which correlated with increased DNA-methylation of the PP1 and the reeling gene within 1 h after memory training (Miller & Sweatt, 2007). Administration of DNA-methylation inhibitors such as 5-deoxycytidine (5-aza) or zebularine into the hippocampus impaired associative learning and the regulation of PP1 and reeling genes upon memory training (Miller & Sweatt, 2007). Later studies confirmed these findings used enzymatic DNMT inhibitors rather than the base analogs 5-aza or zebularine (Lubin *et al*, 2008).

Nevertheless, the fact that a base analog such as 5-aza, which has to be incorporated into DNA in order to affect DNA-methylation, impairs memory function is fascinating considering that DNA in post-mitotic neurons normally does not undergo replication. It cannot be excluded that such drugs unspecifically impair memory formation by mechanisms other than DNA-methylation. Moreover, the hippocampus undergoes adult neurogenesis. However, such

newborn neurons normally need to mature at least for 2 weeks before they contribute to plasticity and memory function, which is too long to explain the immediate effect of 5-aza and zebularine when injected into the hippocampus (Ge *et al*, 2005; Agis-Balboa *et al*, 2011). Thus, these data indicate that DNA in post-mitotic neurons might be less stable than generally assumed and base pair analogs can integrate to DNA during DNA repair. In fact, neurons are particular sensitive to reactive oxygen species, and it is estimated that each neuron has to repair at least 40,000 single- and double-strand breaks every day (Martin, 2008). Moreover, a recent study found that neuronal activity induces DNA damage in the hippocampus and cortex of mice, which is rapidly repaired. The authors hypothesize that DNA double-strand breaks occur in response to relevant stimuli and contribute to neuronal plasticity, possibly by facilitating chromatin changes at dynamically regulated genes (Suberbielle *et al*, 2013). Since stimulus-induced DNA damage occurred rapidly within 2 h after a stimulus, such a process could explain indeed how 5-Aza or zebularine would impact on memory formation and DNA-methylation in neurons.

In any case, there is now convincing evidence that DNA-methylation in the adult brain is quite dynamic. For example, DNA-methylation was linked to *bdnf* expression within 2 h after memory training, while no difference in DNA-methylation was detectable 24 h later (Lubin *et al*, 2008). Pharmacological inhibition of DNA-methylation also affects reward learning in the ventral tegmental area (Day *et al*, 2013), and there is also evidence that during memory formation, DNA-methylation and histone-acetylation are linked (Miller *et al*, 2008). A role for DNA-methylation in memory formation has also been suggested using genetic approaches. Mice that lack DNMT1 and DNMT3a from the adult forebrain show impaired memory formation, while mice lacking only DNMT1 or DNMT3a did not show any memory deficits (Feng *et al*, 2010). Notably, DNMT3a is expressed from different promoters giving rise to the two variants DNMT3a1 and DNMT3a2, which lacks 219 amino acids at the N-terminus (Chen *et al*, 2002). DNMT3a2 was found to be an immediate early gene that is generally decreased in the hippocampus of 18-month-old mice (Oliveira *et al*, 2012). Increasing the expression of DNMT3a2 in the hippocampus of cognitively impaired aged mice rescued memory function (Oliveira *et al*, 2012). While this confirms a role of DNA-methylation in memory formation, the precise role of DNMTs in learning and memory needs to be further investigated.

It was recently found that DNA is not only methylated but can be hydroxymethylated (5hmC) and that this process is particularly prominent in brain tissue (Kriaucionis & Heintz, 2009). Hydroxymethylation of DNA is mediated by the ten-eleven translocation (TET) proteins TET1, TET2 and TET3 that convert 5-methylcytosine to 5-hydroxymethylcytosine and further to 5-formylcytosine and 5-carboxylcytosine and thereby eventually mediate active DNA-demethylation (Pastor *et al*, 2013). All TET proteins are expressed in the adult brain (Kriaucionis & Heintz, 2009; Szulwach *et al*, 2011). A recent study found that constitutive deletion of TET1 results in a minor decrease of bulk 5 hydroxy-methylation in the adult brain. Mice that lack TET1 are viable and able to form new memories. However, fear extinction learning was impaired in TET1 knockout mice which correlated with the hyper-methylation of selected genes such as *Npas4* (Rudenko *et al*, 2013). In a similar study, viral-mediated overexpression of TET1 in the hippocampus impaired associated learning measured by contextual fear conditioning. Interestingly, overexpression of a catalytical inactive TET1 mutant had the same effect (Kaas *et al*, 2013). Neither of these two studies investigated 5-hydroxymethylation at target genes, and although 5-hydroxymethylation of DNA has been implicated with active and inactive DNA-demethylation, 5-hydroxymethylcytosine appears to be more than a simple intermediate in DNA-demethylation. For example, a recent study found a number of proteins that distinctly bind either 5-methyl- or 5-hydroxy-methylcytosine (Spruijt *et al*, 2013). It will be critical for future research to generate genome-wide data for the methylation and hydroxyl-methylation of DNA during brain plasticity to further understand the role of this novel epigenetic mark.

DNA-methylation in Alzheimer's disease

There are a number of studies that have investigated DNA-methylation in post-mortem tissue from AD patients and in corresponding mouse models (Coppieters & Dragunow, 2011) using a variety of approaches such as measurement of global DNA-methylation (Mastroeni *et al*, 2009), PCR arrays (Siegmund *et al*, 2007; Silva *et al*, 2008), bisulfide sequencing (Brohede *et al*, 2010) or methylated DNA immunoprecipitation (Agbemenyah *et al*, 2013) of target genes linked to AD pathogenesis including the *mapt* gene coding for TAU and the genes for *app or presenilin's* (Fuso *et al*, 2012a; Iwata *et al*, 2013). Also genome-wide approaches using array technology have been used to study DNA-methylation in AD (Bakulski *et al*, 2012). Most but not all studies (Barrachina & Ferrer, 2009) found differences between controls and AD patients or AD models. Generally the current picture suggests that AD correlates with hypomethylation of target genes. Interestingly, AD-related changes in DNA-methylation also occur within non-coding regions such as transposable elements (Bollati *et al*, 2011).

It cannot be excluded that genetic risk may explain part of the DNA-methylation changes observed in AD. However, genes linked to DNA-methylation were not found in GWAS studies. Two functional polymorphisms within the promoter of DNMT3B have been investigated, but no altered risk for sporadic AD was detected (Coppedè *et al*, 2012). On the other hand, there is substantial evidence that environmental factors such as diet impact on DNA-methylation. This is explained by the fact that s-adenosylmethionine (SAM) is the major methyl-donor for DNA-methylation and SAM production within the methionine-homocysteine cycle is strongly affected by dietary factors such as folate or vitamine B12. Indeed, folate deficiency in late life has been associated with an increased risk to develop AD, and AD patients with low baseline folate levels appear to benefit from vitamin B treatment (Hinterberger & Fischer, 2013). Such findings have to be however interpreted with care due to differences in clinical trial design and the fact that not all studies observed improvement in cognitive function (Dangour *et al*, 2010; Hinterberger & Fischer, 2013). However, research in animal models supports a key role of methionine-homocysteine metabolism in AD. For example, a diet rich in folic acid ensures high level of the methyl-donor SAM. In fact, it was found that a folic acid-rich diet could further ameliorate disease pathology in a mouse model for amyloid pathology that was treated with memantine (Chen *et al*, 2010b) or in mice that suffer from memory impairment due to

vitamin deficiency (Fuso *et al*, 2012b). Thus, there is a picture emerging in which dietary factors impact on epigenetic mechanisms such as DNA-methylation, altering the risk of AD. This also implies that not everybody would benefit from a corresponding therapeutic approach, but that such knowledge has to be transformed into suitable biomarker signatures that would then allow to stratify patients for specific treatments. It will also be interesting to see how diet affects other epigenetic mechanisms.

The role of DNA-hydroxymethylation in AD has not been addressed in great detail by now. There is evidence from immunohistochemical analysis that DNA-hydroxymethylation changes in the mouse hippocampus in response to age or amyloid pathology (Chouliaras *et al*, 2012; van den Hove *et al*, 2012), but clearly more research in this direction is needed.

Non-coding RNAs in memory formation

Next-generation sequencing approaches have identified non-coding RNAs that represent a novel mechanism to orchestrate gene expression programs. Such RNAs are currently distinguished on the basis of their length in that RNAs below 200 bases are considered small non-coding RNAs, while RNAs above 200 bases are referred to as long non-coding RNAs. One of the best-studied small non-coding RNAs is microRNAs (miRs).

A role for miRs in the nervous system is recently emerging as a number of studies found that miRs are critical regulators of synaptic plasticity (Schratt *et al*, 2006; Karr *et al*, 2009; Schratt, 2009; Siegel *et al*, 2009; Rajasethupathy *et al*, 2009; Edbauer *et al*, 2010; Impey *et al*, 2010; Fiore *et al*, 2011; Lippi *et al*, 2011; Im & Kenny, 2012; Saba *et al*, 2012; Lee *et al*, 2012a). Moreover, *in vivo* manipulation of miRs leads to changes in memory consolidation. For example, in an Aplysia model, miR124 controls serotonin-induced synaptic plasticity and memory formation via the regulation of CREB (Rajasethupathy *et al*, 2009). In the mouse brain, miR134 was found to control CREB levels, and increased expression of miR134 causes memory impairment (Gao *et al*, 2010). Loss of miR-processing protein DICER in the developing neocortex of mice leads to lethality soon after birth (De Pietri Tonelli *et al*, 2008). When DICER was deleted from excitatory forebrain neurons of the adult mouse brain, animals initially exhibited enhanced memory formation and hippocampal synaptic plasticity but eventually developed severe neurodegenerative phenotypes (Konopka *et al*, 2010). Such data suggest that miRs may represent a molecular brake to memory formation processes, which is critical for neuronal homeostasis. This view is supported by a study that identified the microRNAome of the mouse hippocampus via next-generation sequencing and correlated the expression of miRNAs to the expression of learning-induced genes (Zovoilis *et al*, 2011). MiR34c was one of the miRs increased following learning and the induction of gene expression, and it was subsequently shown that chronic elevation of miR34c in the mouse hippocampus impairs memory formation, while inhibition of miR34c enhances learning and memory (Zovoilis *et al*, 2011). This finding is also interesting since miR34c levels are elevated in the hippocampus of AD patients and in mouse models for amyloid deposition (Zovoilis *et al*, 2011). Similar findings were obtained for miR206 (Lee *et al*, 2012b). *In vivo* manipulation of miR34c, miR128, mir182 or miR132 were also found to be essential for the stress-induced plasticity, cued fear conditioning or recognition learning in mice (Haramati *et al*, 2011; Lin *et al*, 2011; Scott *et al*, 2012).

In addition to micro RNAs, a number of other small and long non-coding RNAs such as endogenous small interfering (endo-si) RNAs, PIWI-interacting (pi)RNAs or long intergenic non-coding (linc)RNAs have been identified and the diversity of such RNAs appears to be particularly prominent in the brain (Qureshi & Mehler, 2012). There is at present very limited knowledge on the role of such non-coding RNAs in the adult brain. One interesting finding is that piRNAs, which were originally thought to be only present in germ cells, regulate learning in an Aplysia model (Rajasethupathy *et al*, 2012) and might be important regulators of brain plasticity that counteract the function of miRs (Landry *et al*, 2013). Tsx is a long non-coding RNA that has been linked to germ cell function, but interestingly mice that lack Tsx show enhanced short-term memory function (Anguera *et al*, 2011).

In conclusion, non-coding RNAs are a fascinating new research area in the neurosciences that may help to further understand how the brain orchestrates gene expression during memory formation.

Non-coding RNA in Alzheimer's disease

The best-studied non-coding RNAs in brain disease are miRs that have gained increasing interested as potential biomarker and novel therapeutic strategies. A number of studies identified miRs that are up or down-regulated in post-mortem brain tissue from AD patients or in AD mouse models. While most of these studies are descriptive, there is also evidence that miRs deregulated in AD are mechanistically linked to the pathogenesis. For example, there is now substantial evidence that the miR29 cluster is down-regulated in AD brains (Hébert *et al*, 2008). The beta-secretase BACE1 is a direct target of miR29 and thus decreased miR29 levels lead to elevated BACE1 levels that promotes amyloid pathology (Hébert *et al*, 2008). Interestingly, other miRs that target BACE1 such as miR107, miR298, miR328 have also been linked to AD (Wang *et al*, 2008a; Boissonneault *et al*, 2009; Nelson & Wang, 2010). Moreover, SNPs located within miR29 binding sites of the *bace1* gene correlated with sporadic AD (Bettens *et al*, 2009). Notably, such SNPs were also found for the *app* gene (Bettens *et al*, 2009) and also other miRs such as miR16 and miR101 were linked to app expression (Vilardo *et al*, 2010; Long & Lahiri, 2011; Liu *et al*, 2012a,b). However, since one miR targets multiple mRNAs, it will be important to further understand the role of the gene expression and protein networks controlled by individual miRs.

Unbiased screening approaches were employed to identify miRs that are affected by amyloid pathology. For example, treatment of hippocampal neurons with Aß42 peptides led to altered levels of 21 miRs. Cross-correlation with data from a mouse model for amyloid deposition and human brain tissue identified miR9, Mir181c, let7i, miR30c, miR148b and miR20 to be key miRs affected by amyloid (Schonrock *et al*, 2010). Another study could confirm elevated expression of miR146a in five different mouse models for amyloid deposition (Li *et al*, 2011b). Notably, miR146a was also found to be down-regulated in hippocampal neurons after Aß42 treatment in the Schonrock study (Schonrock *et al*, 2010)—albeit not in the APP mouse model—indicating the need to link screening approaches with subsequent mechanistic studies.

Another miR cluster that has been repeatedly linked to AD pathogenesis and age-associated memory impairment is miR34. Cortical miR34a was found to be up-regulated in a mouse model for amyloid deposition. It was furthermore shown that miR34a controls caspase activity via the expression of BCL2, thereby contributing to AD pathogenesis (Wang *et al*, 2009). miR34c was also identified as a key regulator of learning-induced gene expression and is increased in hippocampal tissue from AD patients and in AD mouse models (Zovoilis *et al*, 2011). Targeting the miR34 cluster was able the reinstate memory function in a mouse model for amyloid deposition which was linked to the regulation of the SIRT1 protein (Zovoilis *et al*, 2011), a class III HDAC implicated with life span and brain diseases (Donmez, 2013). Moreover, miR34a was linked to the down-regulation of TREM2 in human AD brains (Zhao *et al*, 2013; Alexandrov *et al*, 2013), a gene that has been recently identified as a risk factor for sporadic AD (Guerreiro *et al*, 2013), further pointing to an important role of miR34 in AD. While the above-described data suggest that elevated miR34 levels contribute to AD pathogenesis, a recent study found that inhibition of miR34a led to elevated TAU expression, suggesting that in such a context increasing rather than inhibiting miR34a should have therapeutic potential in AD (Dickson *et al*, 2013). Moreover, up-regulation of miR34a extends median life span in the fruit fly (Liu *et al*, 2012a,b), indicating that more research is needed to fully appreciate the role of this miR in the adult mammalian brain.

The use of miRs as biomarker is of particular interest in AD research because pathogenesis begins about 20 years before the onset of clinical symptoms (Bateman *et al*, 2012). miRs are very stable compared to other potential biomarker such as proteins or mRNAs. Thus, a number of studies started to investigate miRs in cerebrospinal fluid (CSF) or in blood samples from AD patients and animal models. For example, levels of miR34a were elevated in serum obtained from aged rats when compared to young animals (Li *et al*, 2011a). An early study by Cogswell *et al* used a TaqMan PCR array to study miRs in brain and CSF from AD patients and non-demented controls (Cogswell *et al*, 2008). Interestingly, among other miRs, miR34a and 29a/b levels were increased AD brain tissue. The same study also analyzed miR levels in post-mortem CSF samples from individuals with B&B stage 1 (Braak & Braak staging, Box 1) compared to B&B stage 5. Notably, no CSF changes were observed for miR34 or miR29a/b, and the overall correlation between brain and CSF changes was rather poor. Nevertheless, some interesting observations were made. For example, the miR30 cluster was increased in CSF and decreased in the hippocampus, while miR125b was increased in both, brain and CSF (Cogswell *et al*, 2008). Another recent study used a similar approach and investigated eight selected miRs in post-mortem human hippocampus and CSF from AD patients and controls (Müller *et al*, 2014). Altered levels of miR16, miR34c, miR107, miR128a and miR146a were detected in the hippocampus, which correlates well with previous studies. Analysis of CSF samples was hindered by detection limits and blood contamination, but reliable detection of lower miR146a levels in AD was reported (Müller *et al*, 2014). In a targeted approach, let7-b was found to be increased in the CSF from AD patients (Lehmann *et al*, 2012). These data indicate the changes in miR levels can be detected in CSF, but that the methodological approaches need to be improved and the presently available data should be considered as being preliminary. A recent study employed the array-based nano-string technology to study miR levels in CSF from AD patients and identified miR27-3p to be reduced in the CSF from AD patients (Sala Frigerio *et al*, 2013) while its levels increase in the hippocampus of individuals that suffered from AD (Lau *et al*, 2013). The use of next-generation sequencing to study the entire small non-coding RNAome in CSF from AD patients and controls would be another option that may allow for a complete unbiased and quantitative measurement of CSF miRs. One important issue that needs to be solved is the source of miRs detected in human CSF. For example, miRs can be bound to lipoproteins (Vickers *et al*, 2011) or Argonaute (Arroyo *et al*, 2011) but are also found in cell-derived small vesicles named exosomes or microvesicles (Valadi *et al*, 2007).

A few studies have analyzed miRs in blood samples from AD patients. Using micro array technology, 462 miRs were analyzed in mononuclear blood cells (MBCs) comparing AD patients to healthy controls (Schipper *et al*, 2007). Notably miR34a and miR181b were found to be increased in AD patients (Schipper *et al*, 2007), which is interesting since both have been linked to memory function or AD pathogenesis (Cogswell *et al*, 2008; Wang *et al*, 2009; Zovoilis *et al*, 2011; Saba *et al*, 2012; Zhao *et al*, 2013). Another miR that has been linked to AD and was found to be down-regulated in MBCs from AD patients is miR29b (Villa *et al*, 2013).

In comparison with the data available for micro RNAs, there is limited knowledge on the role of other non-coding RNAs in AD. But not too surprisingly, changes in lincRNAs have been observed in AD. For example, it was found that the non-coding RNA BC200, which is believed to regulate dendritic protein synthesis, is increased in AD patients, while it decreases with normal aging (Mus *et al*, 2007). It has to be mentioned that an early study found down-regulation of BC200 in Brodman area 22 of AD patients (Lukiw *et al*, 1992). Other studies found increased levels of lncRNAs that affect genes linked to amyloid metabolism (Faghihi *et al*, 2008; Ciarlo *et al*, 2013) or neurotransmission (Massone *et al*, 2011). Moreover, SNPs in lincRNAs have been associated with brain structure and cognitive function (Chen *et al*, 2013). While mechanistically little is known on the role of lncRNAs or small RNAs in AD, especially the lncRNAs might be interesting for future research, since they can modulate protein function and at the same time interact in a sequence-dependent manner with DNA or RNA.

Meeting the future in neuroepigenetics

How do chromatin plasticity and the underlying enzymatic machinery contribute to memory formation in health and disease? The current data suggest that, for example, the regulation of gene expression via histone-acetylation or DNA-methylation plays a role, but conclusive data are still lacking. Future approaches must study the genome-wide distribution of enzymes such as HATs and HDACs, as well as other regulators of chromatin structure via ChIP-sequencing, and correlate such data with gene expression, histone-modifications or DNA-methylation. While the basal level of gene expression or gene expression changes linked to chronic disease states often, but not always correlate well with the chromatin state of a given gene (Wang *et al*, 2008b; Peleg *et al*, 2010; Valor *et al*, 2013; Vashishtha *et al*, 2013; Ng *et al*, 2013; Lopez-Atalaya *et al*, 2013; Crepaldi *et al*, 2013), there are little genome-wide data to support the view that transient changes in gene expression as they are, for example, seen in response to memory training indeed

correlate with altered histone-modifications at the corresponding genes in brain cells.

Another key issue the field needs to address in the future is cell type specificity. Most studies still investigate epigenetic processes in heterogenous brain tissue, which can be particularly misleading when interpreting data obtained from AD models or human brain tissue in which the glia/neuron ration is changed due to inflammatory processes and neuronal cell death. There are different options to overcome such problems. Cell type specificity can be obtained, for example, via established methods to isolate cells from complex tissue via fluorescence-activated cell sorting (FACS). Such approaches are especially powerful when fluorescent markers such as GFP are expressed in the cell type of interest, for example, in dopaminergic neurons, which has been successfully used to study epigenetic processes in distinct populations of brain cells (Jordi *et al*, 2013). A disadvantage of isolating intact cells from brain tissue via FACS is the fact that cells need to be dissociated before sorting which usually involves prolonged incubation at 37°C in the presence of proteases such as trypsin or papain. Such protocols are only successful if fresh tissue from early developmental stages is used and even here a substantial amount of cells do not survive the procedure. Taking into account that memory training was found to induce epigenetic changes already within 30–60 min (Levenson *et al*, 2004; Miller *et al*, 2007; Zovoilis *et al*, 2011; Peleg *et al*, 2010), it is difficult to judge whether results obtained by such methods truly reflect the *in vivo* situation. Another approach is of course to isolate cells via laser capture microdissection, which is however very time consuming.

An alternative strategy is to directly sort nuclei using endogenous marker proteins (Jiang *et al*, 2008). This method has the advantage that cells do not need to be dissociated during long incubation times. For example, nuclei sorting via staining for the neuronal marker protein NeuN was found suitable to study neuronal versus non-neuronal chromatin marks via ChIP-PCR or NGS analysis (Jiang *et al*, 2008; Shulha *et al*, 2012b). Advanced protocols such as the batch-isolation of tissue specific chromatin for immunoprecipitation (BiTS-ChIP) have been successfully used to isolate chromatin even from fixed nuclei thereby allowing a direct view at the chromatin at the time of tissue isolation (Bonn *et al*, 2012a; Bonn *et al*, 2012b). There is no reason to believe that such an approach should not work for brain tissue. In conjunction with next-generation sequencing technologies and advanced bioinformatics analysis, these methods will allow for an unprecedented insight to cell-type-specific chromatin dynamics in the adult brain. Machine learning approaches appear to be particularly suitable to decipher the epigenetic code from data obtained via genome-wide analysis (Bonn *et al*, 2012a). However, even the most sophisticated bioinformatics analysis of next-generation sequencing data will only describe epigenetic networks. In order to understand such networks, subsequent steps must involve hypothesis-driven mechanistic research (Fig 3).

How much Lamarck is in our memories?

Epigenetic processes are dynamic yet persistent at the same time, and DNA does not replicate in post-mitotic neurons. Thus, there is little chance for altering the genetic code other than by transposon activity or mutations (Muotri *et al*, 2007), which are rare events. DNA-methylation provides another layer to encode information in DNA without changing its nucleotide sequence. Patterns of

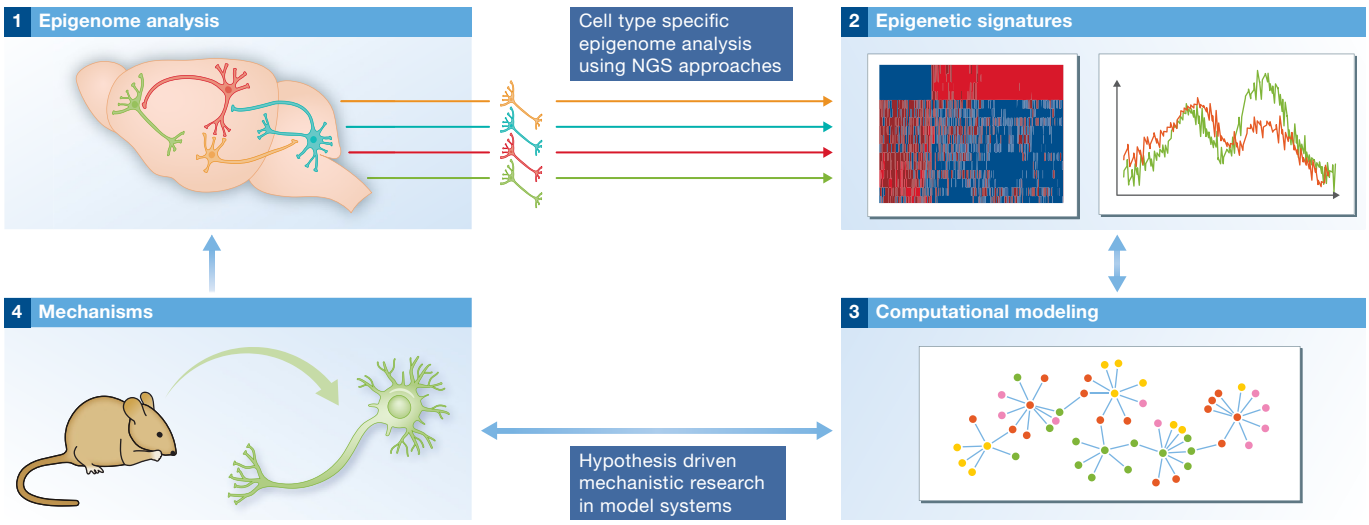

Figure 3. Understanding the epigenome of learning and memory.
1. Experimental approaches to test memory function in model systems should be employed to define the epigenetic landscape of memory formation. Well-studied examples are mice that are subjected to hippocampus-dependent memory training such as contextual fear conditioning. 2. In order to understand how the epigenome shapes neuronal circuitries, it will be essential to isolate distinct cell types for epigenome analysis. This could be achieved in a meaningful manner via fluorescence-activated cell sorting of nuclei that will then be subjected to epigenome profiling using next-generation sequencing (NGS) approaches. 3. Bioinformatic analysis and computational modeling will be an essential tool to understand the molecular networks linked to memory formation in health and disease. 4. This will allow researchers to formulate novel hypothesis about the underlying mechanisms that shall then be tested using suitable models systems. For example, mutant mice that lack or overexpress the hub within a given network. The effect of such manipulation and the epigenetic network can then be tested again using cell-type-specific epigenome profiling.

DNA-methylation can be very persistent and are maintained across generations, yet they are not irreversible, and especially in neurons there is increasing evidence showing that in some genomic regions DNA-methylation is quite dynamically regulated during memory formation. An interesting example of DNA-methylation transmitting acquired information across generations stems from studies that investigate the effect of early life stress on cognitive function. Early life stress is a prominent risk factor for neuropsychiatric diseases, and in rodents it leads to increased anxiety and depressive-like behavior that can be observed even in the offspring, albeit this second generation was never exposed to such stress (Franklin *et al*, 2010). This effect has been linked to altered DNA-methylation of the corticotropin-releasing factors receptor 2 in the brain and in the germ line. Another recent study investigated the consolidation of fear memories for specific odors. This type of learning correlated with neuroanatomical changes in the olfactory system and altered expression of the relevant odor-receptor (Dias & Ressler, 2013). Notably, such changes were also observed in the subsequent generation that consequently showed enhanced odor learning. Mechanistically, this phenotype was linked to altered DNA-methylation of the relevant odor-receptor (Dias & Ressler, 2013).

The same principle is true for histone-modifications that can be dynamically regulated in response to environmental stimuli, and changes in histone-modifications have been linked to the transmission of phenotypes across generations. For example, liver damage in rats initiates a hepatic wound healing program that eventually leads to changes in histone-methylation and DNA-methylation in genes linked to fibrosis (Zeybel *et al*, 2012). Notably such changes were also observed in sperm, and indeed the offspring of such rats could better adapt to liver damage (Zeybel *et al*, 2012). An interesting observation of this study was the fact that serum transfer from animals that were exposed to liver damage to a control group caused the same transgenerational phenotypes, suggesting that a factor present in blood must mediate epigenetic changes in the germ cells (Zeybel *et al*, 2012).

How such environmental stimuli mediate epigenetic changes in brain cells and in germ cells is however not well understood.

Similarly, non-coding RNAs are affected by learning processes but can also mediate phenotypic changes across generations. A fascinating example is paramutations that have been well studied, for example, in plants (Cuzin *et al*, 2008) but also occur in mammals. In mice, it was found that presence of miR 221 and miR 222 in germ cells was responsible for the transfer of a specific phenotype linked to tail color to the subsequent generation (Rassoulzadegan *et al*, 2006).

There are other remarkable examples in which epigenetic processes define in a stable yet reversible manner an organisms behavior (Herb *et al*, 2012), and although not all of the above-discussed examples are directly linked to memory formation as we understand it, such findings illustrate that epigenetic processes are in a *bona fide* position when it comes to long-term information storage. Namely, they allow the compromise between the competing needs for flexibility of a system to update existing memories and the necessary stability that is required to maintain a once consolidated memory trace.

In fact, there is a substantial amount of literature investigating how epigenetic processes mediate long-term memory formation in other organisms such as plants that can for example "remember" the previous winter. Vernalization describes the ability of a plant to flower in the spring depending on a cold period during the previous winter. This process critically involves histone-modifications (He *et al*, 2003), DNA-methylation (Bastow *et al*, 2004) but also the action of non-coding RNAs such as the lncRNAs *coolair* and *coldair* (Heo & Sung, 2011; He & Amasino, 2005; Swiezewski *et al*, 2009) that orchestrate the corresponding gene expression programs.

It is thus tempting to speculate that an epigenetic code could be part of the engram. The nature of the engram is still a mystery, but the predominant view suggests that structural changes occurring at synapses which represent specific neuronal networks recruited during memory consolidation are an essential part of it (Routtenberg, 2013). Could it be possible that part of the information processed in such networks is permanently stored within the chromatin of the corresponding cells? Although this is pure speculation, in favor of this view it was shown that formerly lost memories could be reinstated in

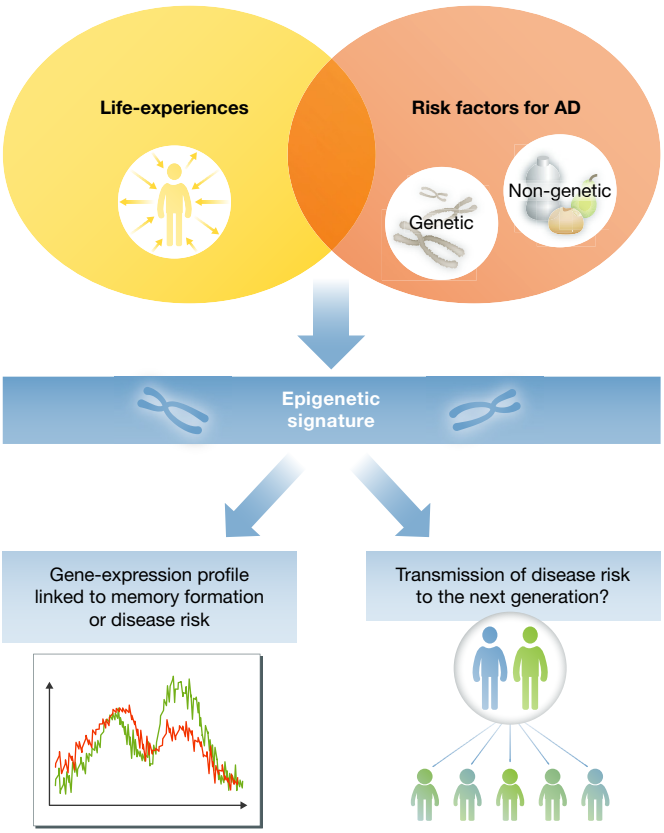

Figure 4. The epigenome as a read out for life experience and disease risk.
Throughout lifetime an organism is exposed to variable environmental stimuli that can initiate memory consolidation processes. On the basis of the existing data, it can be speculated that consolidation of such life experiences into memories critically involve long-term epigenetic changes. Such epigenetic signatures may even be transmitted to the next generation thereby influencing the phenotype of the coming generations. Part of such life experiences represents the interaction of genetic and non-genetic risk factors for brain diseases such as Alzheimer disease. I hypothesize that also such risk factors lead to a disease-specific epigenetic signature and a corresponding gene expression profile that may even affect disease risk in the next generation. As such epigenetic signatures may serve as *bona fide* biomarkers and therapeutic strategies to target, the epigenome may turn out to be more beneficial than directly targeting the multiple risk factors that are believed to contribute to disease pathogenesis.

a mouse model for severe neurodegeneration when mice received an epigenetic drug, in this case an HDAC inhibitor (Fischer *et al*, 2007).

It will therefore be important in future studies to investigate the mechanism by which the synapse within a particular neuronal circuitry communicates to the corresponding nucleus and to understand how the nucleus integrates such signals on the level of the chromatin. Moreover, in order to address such questions, it will be essential to study only the cells that contribute to such networks. This will also be important in the context of brain disease such as loAD that are caused by variable combinations of genetic and environmental risk factors. If the epigenome indeed serves as a molecular read out for life experience—including the exposure to AD risk factors—it might be possible to develop powerful epigenetic biomarkers and disease modifying therapies for such devastating diseases without the necessity to identify or target all possible risk factors directly (Fig 4).

In conclusion, to study epigenetic processes in memory formation during health and disease is a fascinating novel area of research that still offers great challenges but also a unique chance to further understand how the brain stores information and to develop novel therapeutic approaches to treat patients in which memory function is disturbed.

Conflict of interest

The author declares that he has no conflict of interest.

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