Histone acetylation: molecular mnemonics on the chromatin

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Abstract | Long-lasting memories require specific gene expression programmes that are, in part, orchestrated by epigenetic mechanisms. Of the epigenetic modifications identified in cognitive processes, histone acetylation has spurred considerable interest. Whereas increments in histone acetylation have consistently been shown to favour learning and memory, a lack thereof has been causally implicated in cognitive impairments in neurodevelopmental disorders, neurodegeneration and ageing. As histone acetylation and cognitive functions can be pharmacologically restored by histone deacetylase inhibitors, this epigenetic modification might constitute a molecular memory aid on the chromatin and, by extension, a new template for therapeutic interventions against cognitive frailty.

By definition, a mnemonic is a device that is intended to assist memory. As human memories outlast the half-life of most biological molecules, any molecular mnemonic — if there is one — should be situated on biologically enduring material. One such molecule is DNA, which carries information across generations. In 1984, Francis Crick (1916–2004) speculated that "memory might be coded in alterations to particular stretches of chromosomal DNA"[1]. Although Crick himself qualified his speculation as "not very likely", we now know that chromatin, the carrier of chromosomal DNA, can assist in storing memory-related information by epigenetic modifications[2]. Epigenetic modifications are defined as "the structural adaptation of chromosomal regions so as to register, signal, or perpetuate altered activity states"[3]. By this definition, epigenetic modifications fulfil two fundamental characteristics of a mnemonic: they react to learning (that is, neuronal activity triggered by new information); and they can convey such information into specific gene expression programmes, which are a prerequisite for long-lasting memories[4].

Of the several types of epigenetic modifications that have been associated with cognitive functions — including post-translational modification of histone proteins by acetylation, methylation, phosphorylation, DNA methylation and RNAi[5] — histone acetylation is most robustly associated with promoting memory formation. Here, we review the growing body of evidence that histone acetylation marks function as molecular mnemonics; describe the implication of increased and decreased histone acetylation in enhancing and constraining cognitive functions, respectively; and discuss the potential of histone deacetylase inhibitors (HDACis) as therapeutic agents against cognitive impairments in several neurological disorders.

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doi:10.1038/nrn3427
Published online
17 January 2013

Histone acetylation as memory aids

The role of histone acetylation. In histone acetylation, a negatively charged acetyl group is added to lysine residues on histone proteins. Histone acetylation is regulated by the opposing action of histone acetyl transferases (HATs) and HDACs. The addition of acetyl groups is catalysed by HATs, which are divided into the GNAT, MYST and p300/CBP subfamilies[6], whereas the removal of acetyl groups is catalysed by HDACs, which, in mammals, are divided into four groups[7]: the zinc-dependent class I, II and IV HDACs, and the NAD-dependent class III HDACs, which are also known as sirtuins.

Histone acetylation diminishes the electrostatic affinity between histone proteins and DNA, and thereby promotes a chromatin structure that is more permissive to gene transcription[8–11]. Moreover, as histone acetylation readily increases following neuronal activity, it is well suited to sustain gene expression changes that are important for long-term synaptic plasticity and memory[4]. It should be noted that although this Review focuses primarily on histone acetylation, this epigenetic modification does not occur independently of other histone modifications[12] or of DNA methylation[13] in the brain (FIG. 1) but instead is part of a highly interwoven network of co-occurring epigenetic changes ('crosstalks')[14]. Two well-characterized crosstalks for memory-related

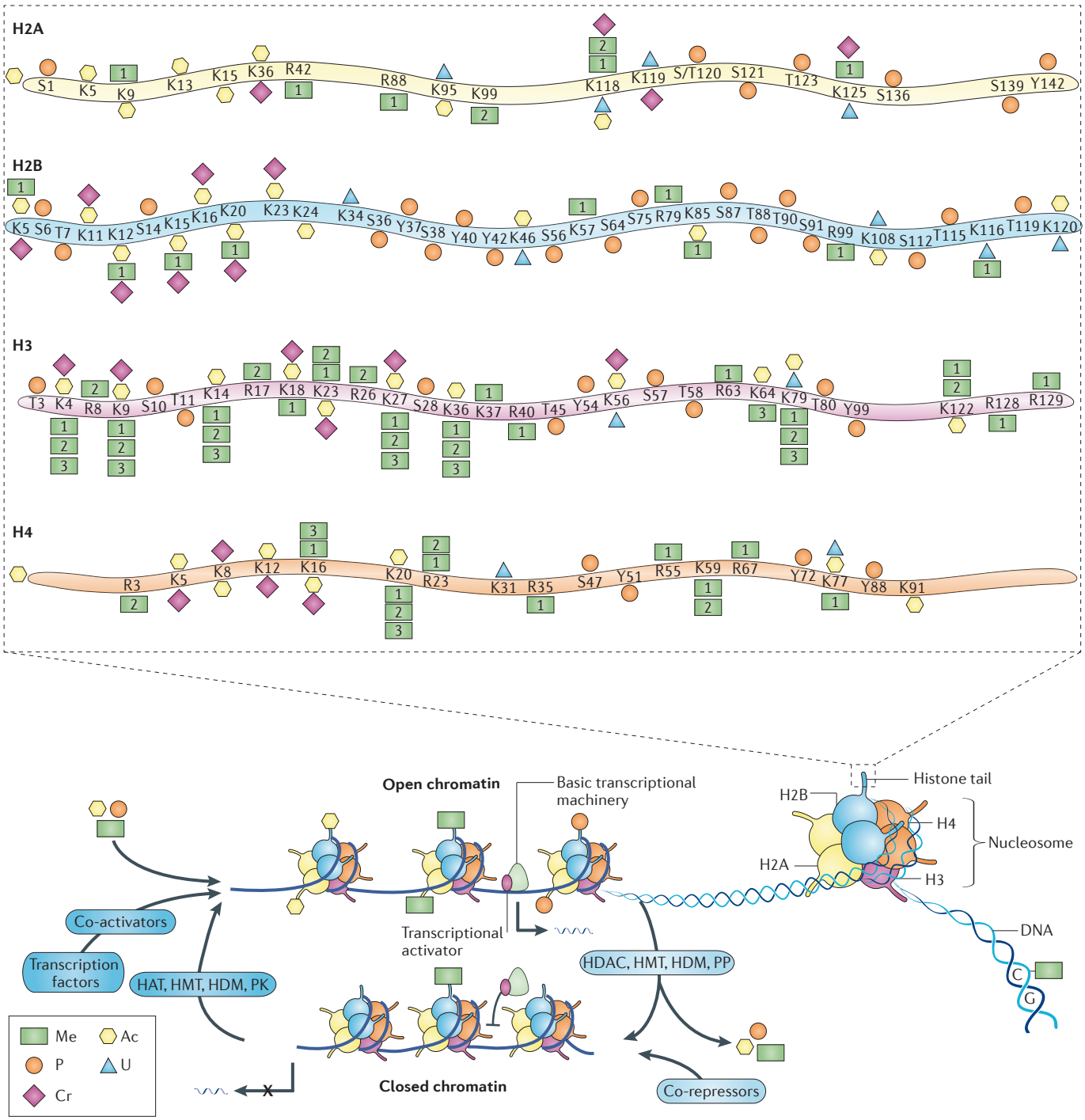

Figure 1 | **The complexity of the epigenetic code in the brain.** The upper panel shows an overview of known post-translational histone (H) modifications on H2A, H2B, H3 and H4 in the mouse brain[12]. The letters and numbers represent histone amino acids and their positions relative to the N terminus. The lower panel is a simplified schematic depicting the relationship between open and closed chromatin. In an open, transcriptionally permissive state, chromatin is characterized by hyperacetylated and hyperphosphorylated histones, the reaction of which is catalysed by protein kinases (PKs) and histone acetyl transferases (HATs). These post-translational modifications create a repulsive force between neighbouring histones and the DNA, which structurally loosens the chromatin to give access to the transcriptional machinery and transcriptional activators. In a closed state, chromatin is characterized by hypoacetylated and hypophosphorylated histones, the reaction of which is catalysed by protein phosphatases (PPs) and histone deacetylases (HDACs). These enzymes also recruit transcriptional co-repressors, which prevent the transcriptional machinery from binding and genes from being expressed. The relationship between histone methylation, which is catalysed by histone methyl transferases (HMTs), and histone demethylases (HDMs) and their influence on gene transcription is residue-specific. DNA methylation (depicted on the far right) occurs on CpG-dinucleotides, and its influence on gene transcription depends on the chromosomal area in which it occurs. Ac, acetyl; Cr, crotonyl; Me, methyl; Me1, mono-methyl; Me2, dimethyl; Me3, trimethyl; P, phospho; U, ubiquityl. The figure is modified, with permission, from REF. 180 © (2012) John Wiley and Sons.

processes are the co-occurrence of the acetylation of lysine (K) residue 14 on histone (H) 3 with the phosphorylation of serine (S)10 and the trimethylation of H3K36 (REFS 15–17), and of H3 acetylation with DNA methylation[13]. Both crosstalks favour learning and memory when increased.

Modulation by neuronal activity. Histone acetylation can be triggered by several forms of neuronal activity. For instance, potassium chloride-mediated neuronal depolarization led to increased acetylation of the core histone H2B in rat hippocampal cultures[18], and stimulation of dopaminergic, cholinergic and glutamatergic pathways by receptor-specific agonists increased acetylation of H3K14 and H3S10 in the mouse hippocampus[19]. In all of these cases, the changes in histone acetylation were paralleled by phosphorylation-mediated activation of the extracellular regulated kinase (ERK), a member of the mitogen-activated protein kinase (MAPK) pathway[20], and direct activation of the MAPK–ERK pathway increased histone acetylation, whereas its inhibition blocked it[21]. These findings imply that one pathway by which histone acetylation can be triggered by neuronal activity is via the activity-dependent MAPK pathway, probably through a crosstalk with H3S10 phosphorylation, which often co-occurs with H3K14 acetylation[9,22] (FIG. 2).

Neural activity can also alter histone acetylation by dissociating HDAC2 from the chromatin. Stimulation of cortical neurons with brain-derived neurotrophic factor (BDNF), which promotes neuroplasticity[23], resulted in nitrosylation of HDAC2 on cysteine 262 and cysteine 274, its dissociation from the chromatin, subsequent histone hyperacetylation and a concomitant increase in neurotrophin-dependent gene expression[24]. The expression of one such neurotrophin, *BDNF*, is known to be increased by neuronal activity-driven calcium-dependent de-repression by methyl-CpG-binding protein 2 (MECP2)[25] but is negatively regulated by HDAC2 (REF. 26). Therefore, a burst of neuronal activity is likely to engage a positive-feedback loop centred around HDAC2 and BDNF that can lead to histone acetylation-mediated, self-sustaining gene expression programmes that underlie synaptic plasticity and memory (FIG. 2).

Modulation by synaptic plasticity. Long-lasting forms of synaptic plasticity involve changes in the expression of genes involved in synaptic maintenance and communication[27], and there is substantial evidence that histone acetylation promotes these changes (TABLE 1). For example, at sensory–motor neurons in the marine mollusc *Aplysia californica*, long-term facilitation (LTF) was accompanied by increased binding of the HAT cyclic AMP-responsive element-binding (CREB)-binding protein (CBP) and enhanced histone acetylation at the promoter region of CCAAT/enhancer binding protein (*CEBP*), a transcriptional co-activator of the memory-sustaining protein CREB, which also showed increased transcription[28]. Similar changes were observed at the promoter region of synapsin[29], another gene implicated in LTF. Long-term depression (LTD), by contrast, was accompanied by reduced histone acetylation at *CEBP*. Importantly, LTF normally requires strong electrical stimulation, but administration of the HDACi trichostatin A (TSA) enabled even weak electrical stimulation to induce LTF[28]. This finding indicates that the extent of histone acetylation might co-determine the extent of synaptic plasticity and that HDACis have the potential to enhance naturally occurring synaptic processes.

In mammals, the molecular equivalent of LTF is long-term potentiation (LTP)[30]. Here, too, histone acetylation levels correlate with LTP. LTP induction was paralleled by increased H3 and H4 acetylation, and facilitated by the application of the HDACi TSA[21,31–34] and sodium butyrate (NaB)[21,35]. Notably, LTP-promoting histone acetylation changes occurred specifically at the promoter regions of genes involved in synaptic transmission, such as the extracellular matrix protein reelin[35] and *Bdnf*[33,35], which is consistent with the possibility that there is a positive-feedback loop for self-sustaining changes in histone acetylation that are driven by neuronal activity (FIG. 2).

Complementarily, studies involving the HAT CBP further support the notion that enhanced histone acetylation promotes LTP (TABLE 1): mice that were partly or completely deficient in CBP function showed decreased histone acetylation and impaired induction of transcription-dependent late-phase LTP, whereas the transcription-independent early phase of LTP remained unaffected[32,36–38]. Together, these genetic and pharmacological studies suggest that histone acetylation and late-phase LTP are causally linked.

Modulation by memory formation. The first evidence that learning and memory are also associated with histone acetylation surfaced when Levenson *et al.* examined acetylation of H3 and H4 after contextual fear conditioning or latent inhibition, two paradigms of associative learning. After contextual fear conditioning, acetylation of H3K14 was significantly increased in hippocampal area CA1, whereas acetylation of H4 was unchanged. Conversely, H4 acetylation was selectively increased after latent inhibition training[21]. These early results highlighted two important concepts regarding the relationship between histone acetylation and memory formation. First, changes in histone acetylation accompany memory consolidation; and second, different learning paradigms are likely to elicit distinct epigenetic signatures in the brain.

Many follow-up studies have further corroborated the implied link between histone hyperacetylation and memory formation for fear conditioning[16,39–43], different types of memory[15,17,44–47], different phases of a memory (such as reconsolidation or extinction)[42,48–53] and in species other than rodents[54,55] (TABLE 1). Although such acetylation changes could be detected on a gross scale by western blot or immunohistochemistry, more refined studies using chromatin immunoprecipitation have revealed that memory-induced histone acetylation is specific to certain genes. These include genes that are important for learning and memory, such as the immediate-early genes *Zif268* (also known as *Erg1*), *Creb* and *Bdnf*, which showed an increase in expression concomitant with the increase in histone acetylation[15,41,49,56]. Similar to neuronal

Histone proteins
Basic proteins with a globular core and loosely structured N- and C-terminal tails that form part of the chromatin. Doublets of the four core histones H2A, H2B, H3 and H4 constitute a histone octamer, which is wrapped around by DNA to form the nucleosome. Post-translational histone modifications modulate the compaction of the DNA around histones and thereby the three-dimensional chromatin structure.

Histone deacetylase inhibitors
(HDACis). Small molecules that inhibit the activity of HDACs, most of them by binding to the HDAC catalytic domain.

Synaptic plasticity
The ability of a synapse to change in strength, which is considered to be a cellular correlate of learning and memory.

Long-term facilitation
(LTF). Transcription-dependent facilitation of electrical transmission across synapses.

Long-term depression
(LTD). Transcription-dependent deterioration of electrical transmission across synapses.

Long-term potentiation
(LTP). An increase in synaptic transmission efficiency as a result of presynaptic high-frequency stimulation.

Fear conditioning
A form of associative learning in which an aversive stimulus (for example, an electric shock) is paired with a neutral context (for example, a chamber) or neutral stimulus (for example, a tone), resulting in the expression of fear responses to the originally neutral context or stimulus in the absence of the aversive stimulus.

Latent inhibition
A decrease of the conditioned response in an associative memory task when the conditioned stimulus is presented alone before the conditioning session.

Consolidation
A time-limited process that allows newly acquired memories to be stabilized and permanently stored.

Reconsolidation
A time-limited process that allows reactivated memories to be updated with new information and to be stored in a modified form.

activity, therefore, learning-induced changes in histone acetylation are likely to trigger a positive-feedback loop involving *BDNF* and possibly other genes (FIG. 2).

In support of the notion that histone acetylation acts as a molecular memory aid, several studies showed that the administration of HDACis was capable of facilitating memory formation[26,32,34,43,45,46,48,57–63], whereas HAT inhibition impaired it[36–38,64–67] (TABLE 1). Importantly, such manipulations had little or no effect on short-term (hour-old) memories but selectively altered long-term (day-old) memories, which is consistent with the involvement of gene expression changes in long-term memory formation.

These findings lead to two conclusions. First, histone acetylation mnemonics are triggered by learning and are a crucial part of memory formation. Second, HDACis seem to have memory-promoting potential

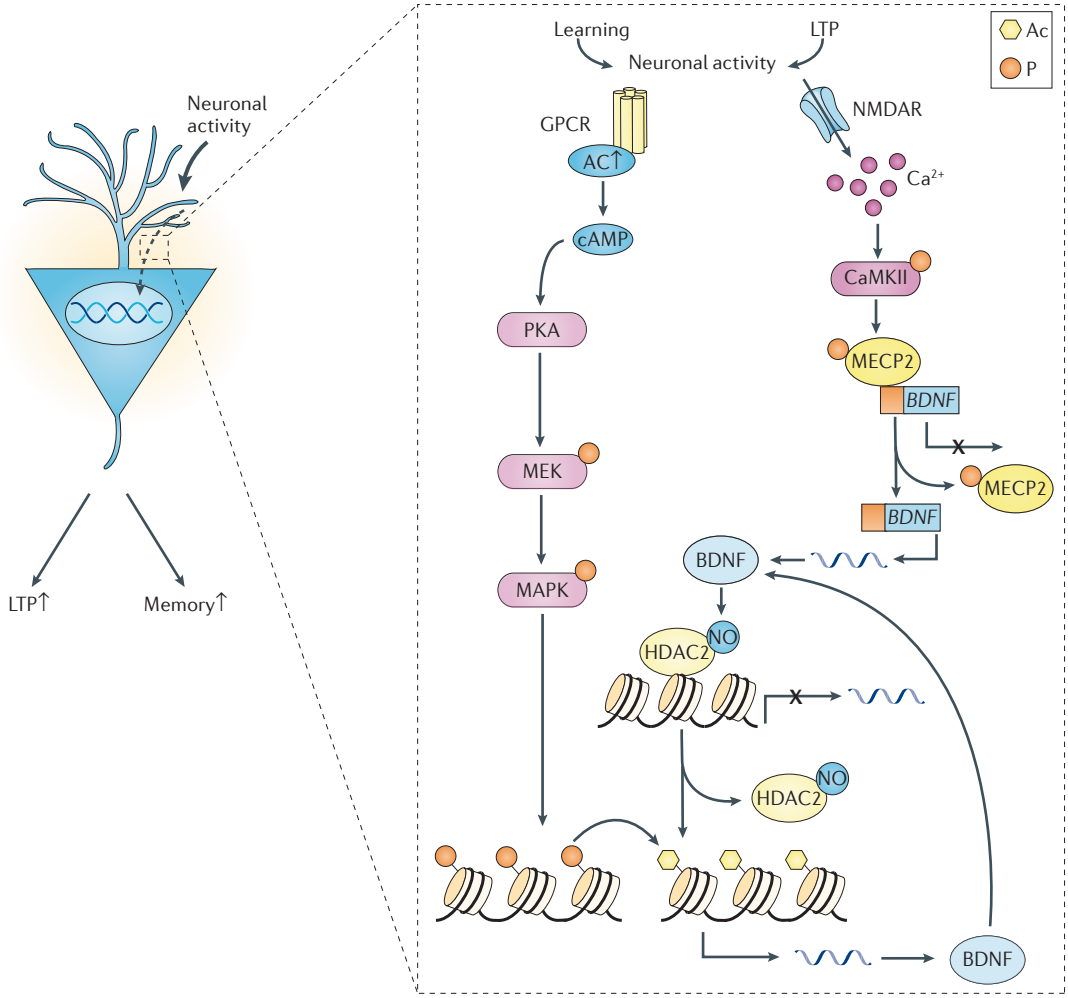

Figure 2 | **Neuronal activity induces histone acetylation.** The left panel shows how neuronal activity signals to the nucleus to induce epigenetic modifications that sustain learning and memory. The inset on the right schematizes two experimentally investigated pathways that induce such epigenetic modifications in terms of histone acetylation. One of these pathways, depicted on the left side of the inset, shows how neuronal activity, in terms of long-term potentiation (LTP) and learning, activates G protein-coupled receptors (GPCRs), which in turn activate adenylyl cyclase (AC) that converts ATP to cyclic AMP (cAMP). cAMP stimulates the activity of protein kinase A (PKA), which phosphorylates mitogen-activated protein kinase kinase (MEK), itself phosphorylating members of mitogen-activated protein kinases (MAPKs) such as extracellular signal-related kinase 1 (not shown). Members of the MAPK family can directly phosphorylate histones, which can subsequently trigger histone acetylation[22]. On the right side of the inset, neuronal activity can also lead to cellular depolarization via calcium influx, which activates calmodulin (not shown) and results in the phosphorylation-dependent activation of calcium/calmodulin-dependent kinase II (CaMKII). CaMKII phosphorylates methyl-CpG-binding protein 2 (MECP2), which triggers the dissociation of MECP2 from the promoter region of brain-derived neurotrophic factor (*BDNF*; represented by the orange square) thereby stimulating the transcription of the latter. BDNF then activates nitric oxide (NO) synthase (not shown), which can lead to the nitrosylation of histone deacetylase 2 (HDAC2). Upon nitrosylation, HDAC2 dissociates from the chromatin, which results in increased histone acetylation at the promoter region of its target genes (including *BDNF*). As a result, BDNF expression is stimulated and likely to engage in a positive-feedback loop to reinforce the nitrosylation of HDAC2, thereby promoting memory-sustaining gene expression changes. Ac, acetyl; NMDAR, NMDA receptor; P, phospho. The left panel is modified, with permission, from REF. 2 © (2005) Macmillan Publishers Ltd. All rights reserved.

because they support naturally occurring molecular events — specifically, learning-induced increases in histone acetylation. As we discuss below, this observation is reminiscent of a phenomenon called 'epigenetic priming' in cancer research[68], in which HDACis potentiate the efficacy of chemotherapeutic agents by, for example, facilitating the expression of previously silenced tumour-suppressor genes[69,70].

The role of HDACs in cognition

Given the implication of histone acetylation in various memories and the capacity of HDACis to further potentiate these molecular mnemonics, it is important to understand the involvement of the different HDACs in cognitive processes, as these might be suitable pharmacological targets to enhance cognition. Here, we focus exclusively on zinc-dependent HDACs and refer the reader to other

Table 1 | **Histone acetylation mnemonics in cognitive processes**

Process	Mechanism	Brain area	Organism	Refs
Synaptic plasticity	LTF is accompanied by increased H3 and H4 acetylation and facilitated by TSA	Sensory–motor neurons	*Aplysia californica*	28,29
	LTP and H3 acetylation are enhanced by PKC activation and the HDACis TSA and SAHA	Amygdala and hippocampus	Mouse and rat	13,21,32,34
	LTP and H2B acetylation are impaired by HAT CBP deficiencies	Hippocampus	Mouse	32,36-38
Fear memory: contextual	Contextual fear memory is accompanied by increased H3 acetylation and enhanced by the HDACis TSA and SAHA	Hippocampus	Mouse and rat	21,26,32, 39–41
	Contextual fear memory is impaired by CBP deficiencies	Hippocampus	Mouse	37,38,67
Fear memory: cued	Cued fear memory is accompanied by increased H3 acetylation and enhanced by the HDACis TSA and VPA	Amygdala	Mouse and rat	42,43,48
	Cued fear memory is impaired by CBP deficiency	Whole body	Mouse	65
Fear potentiated startle	Fear potentiated startle is enhanced by the HDACis NaB and TSA	NA	Rat	34
Eyeblink conditioning	Eyeblink conditioning is accompanied by increased H3 acetylation and enhanced by the HDACis NaB and TSA	Hippocampus	Mouse	45
Latent inhibition	Latent inhibition training is accompanied by increased H4 acetylation	Hippocampus	Rat	21
Object recognition memory	Object memory is accompanied by increased H3 acetylation and enhanced by the HDACis NaB, TSA, MS-275 and RGFP136	Hippocampus	Mouse	15,17,45,63
	Object memory is impaired by CBP and p300 deficiencies	Hippocampus and forebrain	Mouse	36,37,64,66, 67,179
Spatial memory	Spatial memory is accompanied by increased H2B, H3, and H4 acetylation and facilitated by the HDACis NaB and VPA-derivatives	Hippocampus	Mouse and rat	44,47,57,60, 61
	Spatial memory is impaired by CBP deficiencies	Hippocampus and forebrain	Mouse	36,38,64
Social transmission of food preference	Learnt food preference is accompanied by increased H3 acetylation and enhanced by the HDACi NaB	Orbitofrontal cortex	Rat	46
Food aversion memory	Food aversion memory is accompanied by increased H3 acetylation	Command neurons	Mollusc	54
Context memory	H3 acetylation is increased by contextual training and enhanced by the HDACis NaB and TSA	Central brain	Crab	55
Memory reconsolidation	Fear memory reconsolidation is accompanied by increased H3 acetylation	Amygdala and hippocampus	Mouse	42,48
		Central brain	Crab	53
	Extinction training following reconsolidation is facilitated by HDACis NaB, TSA and VPA	NA	Mouse, rat and crab	42,48–50, 52, 53

CBP, cyclic AMP-responsive element-binding (CREB)-binding protein; H, histone; HAT, histone acetyl transferase; HDACi, histone deacetylase inhibitor; LTF, long-term facilitation; LTP, long-term potentiation; NA, not applicable; NaB, sodium butyrate; PKC, protein kinase C; SAHA, suberoylanilide hydroxamic acid; TSA, trichostatin A; VPA, valproic acid. Note that 'histone acetylation' refers to one or several residue-specific acetylation changes on a given histone; for details, see the references.

reviews covering the NAD-dependent class III HDACs, the sirtuins[71,72], whose role in cognitive functions has only recently been addressed. From these studies it emerges that, for example, SIRT1 (silent mating type information regulation 2, homologue 1) has both neuroprotective[73,74] and memory-promoting properties[75,76]. Hence, for the NAD-dependent HDACs, activation rather than inhibition might be the desired outcome.

The zinc-dependent HDACs (TABLE 2) consist of class I (HDAC1–HDAC 3 and HDAC8), class IIa (HDAC4, HDAC5, HDAC7 and HDAC9), class IIb (HDAC6 and HDAC10) and class IV (HDAC11). All class I, II and IV HDACs are expressed in the brain, most abundantly in neurons[77]. HDAC2–HDAC5 and HDAC11 are also expressed in oligodendrocytes, whereas all HDACs show low expression in astrocytes. In brain regions involved in memory formation, such as the amygdala, hippocampus and cortex, class I and IV HDACs are more highly expressed than class IIa HDACs (of which HDAC4 is most abundantly expressed), which in turn are more highly expressed than class IIb HDACs. Within the class I HDACs, HDAC2 and HDAC3 are more abundantly expressed than HDAC1 and HDAC8 (REF. 77). Here, we summarize the experimentally investigated involvement of the different HDACs in memory-related processes.

Class I HDACs. Of the class I HDACs, HDAC2 and HDAC3 have been shown to negatively regulate learning and memory, whereas HDAC1 has a more specialized role in memory extinction. Thus, HDAC2-overexpressing mice showed impaired LTP and decreased associative and spatial memory, whereas HDAC2-knockout mice showed enhanced synaptic density and neuroplasticity[26]. No memory-modifying effect was observed in

Table 2 | **The implication of zinc-dependent HDACs in cognitive processes**

Class	Type	Predominant subcellular localization	Implication in cognitive processes	Mechanism of action	Refs
I	HDAC1	Nucleus	Facilitates memory extinction	Increases H3K9 acetylation at *cFos* promoter	82
			Increased after contextual fear conditioning	TBD	79
	HDAC2	Nucleus	Constrains LTP, associative and spatial memories in the healthy and the neurodegenerated mouse brain	Binds to the promoter region of memory-related genes; associates with co-repressor complexes	26,90
			Constrains EPSCs	TBD	78
			Decreased after contextual fear conditioning	TBD	79
	HDAC3	Nucleus and/or cytoplasm	Constrains object location memory	TBD	59
			Decreased after contextual fear conditioning	TBD	79
	HDAC8	Nucleus and/or cytoplasm	ND	ND	–
IIa	HDAC4	Nucleus and/or cytoplasm	Cytoplasmic fraction constrains thermotaxic memory in *Caenorhabditis elegans*	TBD, but mainly cytoplasmic	84
			Loss of HDAC4 impairs LTP, associative and spatial memories	TBD	85
	HDAC5	Nucleus and/or cytoplasm	Inhibits LTF in *Aplysia californica*	Binds to the promoter region of *CEBP*	28
			Increased in mouse model of schizophrenia with memory deficits	TBD	86
			Decreased after contextual fear conditioning	TBD	79
	HDAC7	Nucleus and/or cytoplasm	Decreased after contextual fear conditioning	TBD	79
	HDAC9	Nucleus	CNV associated with schizophrenia-related cognitive impairments	TBD	87
IIb	HDAC6	Cytoplasm	Unlikely as HDAC6-specific HDACi had no effect on memory	ND	26
	HDAC10	Nucleus and/or cytoplasm	ND	ND	–
IV	HDAC11	Nucleus	Increased after contextual fear conditioning	TBD	79

CEBP, CCAAT/enhancer-binding protein; CNV, copy number variation; EPSC, excitatory postsynaptic current; HDACi, histone deacetylase inhibitor; LTF, long-term facilitation; LTP, long-term potentiation; ND, not determined; TBD, to be determined.

HDAC1-overexpressing mice. Consistent with this result, virus-mediated knock-down of HDAC2, but not of HDAC1, in primary hippocampal neurons led to an increase in excitatory postsynaptic currents[78]. The cognitive enhancement in the *Hdac2*-knockout mice was accompanied by increased hippocampal histone acetylation, specifically at the promoter region of genes involved in synaptic plasticity and memory, such as synaptophysin and *Bdnf*. As HDAC2 does not bind directly to the chromatin but interacts with members of the co-repressor complexes SIN3A, NURD and CoREST[26], it is likely that HDAC2 works together with these repressors to silence neuroplasticity-related genes and thereby to act as a memory constraint.

HDAC3 also impinges on learning and memory. When HDAC3 was focally deleted in the mouse hippocampus, hippocampal histone acetylation increased, as did the animals' object location memory[59]. However, deletion of HDAC3 did not produce cognitive enhancement for object recognition memory. This discrepancy could indicate that HDAC3 has a more refined role in cognitive control than HDAC2 or that the restricted knockdown of HDAC3 in the hippocampus alone was not sufficient to alter object recognition memory.

In line with these genetic studies, a microarray assay found that both HDAC2 and HDAC3 were decreased in the hippocampus of fear-conditioned rats after learning, which is consistent with their role as mnemonic constraints[79]. By contrast, the expression of HDAC1 was increased, suggesting that it has a different role, which could lie in memory maintenance; as HDAC1 regulates cell cycle re-entry and neuronal DNA repair[80], which must be properly controlled for neuronal functioning[81], it might be specifically required for memory consolidation. Alternatively, as a recent study revealed, it could also regulate fear memory extinction[82]; virus-mediated overexpression of HDAC1 facilitated memory extinction, whereas short hairpin RNA (shRNA)-mediated knockdown of HDAC1 impaired it. Future studies are required to further characterize the role of HDAC1 in memory-related processes.

Class IIa HDACs. Of the class IIa HDACs, there is evidence that HDAC4, HDAC5 and HDAC9 might be involved in cognitive processes, although they are likely to act through non-histone substrates, as they have low basal HDAC activity[83]. In the nematode *Caenorhabditis elegans*, deleting *hda-4*, a homologue of the mammalian HDAC4, led to enhanced long-term memory in a thermotaxic memory task, whereas overexpression of *hda-4* impaired long-term memory[84]. Refining the deletion of *hda-4* to its cytoplasmic fraction also improved memory, implying that HDAC4 has an important cytoplasmic function with respect to cognitive capacities. By contrast, in mice, brain-specific deletion of HDAC4 impaired long-term memory and LTP[85], a discrepancy that could arise from species differences.

HDAC5 inhibits memory-sustaining processes across several species. When LTF in *A. californica*'s sensory neurons was prevented by the inhibitory neurotransmitter FMRFamide, HDAC5 was recruited to the promoter region of *CEBP*, which showed a concomitant decrease in histone acetylation[28]. Moreover, in a mouse model of schizophrenia in which object recognition memory is impaired, HDAC5 was upregulated in the prefrontal cortex together with a reduction in H3 acetylation[86], and HDAC5 was also decreased in the hippocampus of fear-conditioned rats after training[79].

HDAC9 was among the top hits in a study investigating copy number variation between patients with schizophrenia who had cognitive disabilities and healthy control subjects[87], but whether HDAC9 has a causal role in memory remains to be tested. The only information available about the role of HDAC7 is that it was decreased in the rat hippocampus after fear conditioning[79].

Class IIb and class IV HDACs. Little is known about the involvement of these HDACs in learning and memory — only that HDAC11 expression was increased in the hippocampus of fear-conditioned rats[79] and that the predominantly cytoplasmic class IIb HDAC6 probably does not participate in mnemonic processes, as chronic treatment of wild-type mice with the HDAC6-specific HDACi WT-161 had no effect on memory[26].

Our current knowledge therefore supports the idea that, in mammals, HDAC1–HDAC3 are causally involved in memory consolidation and extinction, with HDAC2 being a major mnemonic constraint. As such, it is not surprising that HDAC2 also plays a pivotal part in constraining cognitive functions upon neurodegeneration, ageing and, possibly, following prolonged periods of stress.

HDAC2 and cognitive decline

Neurodegeneration. Cognitive decline is a devastating feature of most neurodegenerative diseases of the CNS, including Alzheimer's disease (AD). Despite intensive research[88,89], neither the aetiology of AD nor the mechanism of cognitive decline in this disease have been fully determined.

Increased expression of HDAC2 and decreased histone acetylation mnemonics are a decisive factor underlying the cognitive decline associated with AD[90]. In two mouse models of AD-related cognitive impairment and neurodegeneration (CK-p25 (REFS 91–93) and 5XFAD[94,95] mice), HDAC2 was increased in the hippocampus and the prefrontal cortex, which are involved in memory formation and storage[96], respectively. The increase in HDAC2 levels occurred *in vitro* after neurotoxic insults and oxidative stress through mechanisms involving the phosphorylation-mediated activation of the stress hormone glucocorticoid receptor, which bound to the promoter region of *Hdac2* and stimulated its expression (FIG. 3). Such upregulation of HDAC2 in memory centres of the neurodegenerating brain further coincided with greater binding of HDAC2 to the promoter regions of genes implicated in synaptic plasticity and learning, such as synaptophysin and *Bdnf*, which showed reduced histone acetylation and expression. These processes could thus constitute a negative-feedback loop on memory-sustaining gene expression programmes (FIGS 2,3).

Object location memory
Memory for an object's location that is measured by taking advantage of rodents' natural propensity to explore novel objects. The time spent with a novel versus a familiar object serves as an indicator of the memory strength. In object location, the novelty is given by a change in location of a familiar object.

Object recognition memory
The ability to recognize an object as familiar rather than novel. It is measured in a similar way to object location memory but with the novelty given by presenting the animal with an object that is unfamiliar but in the same location..

Fear memory extinction
A decline in conditioned fear responses when there is a reduction in the predictive value of the conditioned stimulus, for example, through repetitive exposure to the conditioned stimulus without the aversive association.

Alzheimer's disease
(AD). The most common type of neurodegenerative dementia. Patients often show impairments in learning and memory. The disease's neuropathology includes neuron loss in the cerebral cortex and in several subcortical regions and the presence of aggregates in the forms of plaques (containing amyloid-β) and neurofibrillary tangles (containing hyperphosphorylated tau).

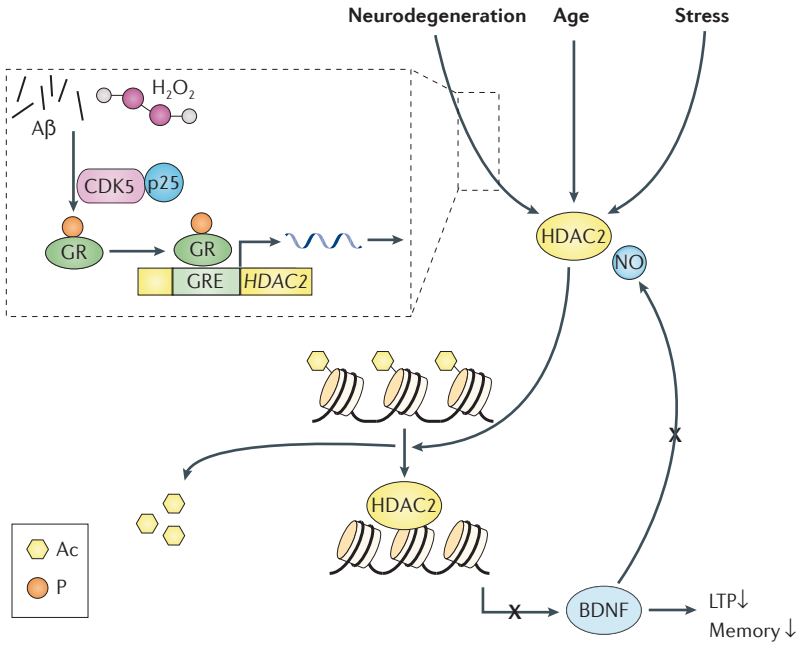

Figure 3 | **The upregulation of HDAC2 in pathological conditions and its relation to cognitive impairment.** Neurodegeneration, ageing and prolonged periods of stress can all induce an increase in HDAC2 expression. In the case of neurodegeneration, neurotoxic insults such as extracellular amyloid-β (Aβ) fibrils, oxidative stress (H_2O_2) and intracellular accumulation of p25 have been found to activate glucocorticoid receptor (GR) by p25–cyclin-dependent kinase 5 (CDK5)-mediated phosphorylation. Phosphorylated GR binds to a GR responsive element (GRE) within the proximal histone deacetylase 2 (*HDAC2*) promoter region and stimulates the expression of *HDAC2*. During both neurodegeneration and ageing, increased levels of HDAC2 in the brain result in its preferential binding to the promoter region of genes that are related to learning, memory and synaptic plasticity, such as brain-derived neurotrophic factor (*BDNF*). There, HDAC2 binding co-occurs with reduced histone acetylation and reduced gene expression, thereby interrupting the BDNF-mediated positive-feedback loop (FIG. 2). Such reduced expression of neuroplasticity genes is correlated with reduced synaptic plasticity and poor memory performance. Note that the involvement of HDAC2 in stress-related cognitive decline has not been experimentally tested yet. Ac, acetyl; LTP, long-term potentiation; NO, nitric oxide.

Braak and Braak stages
A way to categorize the severity of Alzheimer's disease (AD) according to the extent of tau pathology post-mortem. In BB stages I/II (mild AD), tau pathology is mainly restricted to the entorhinal cortex. In stages III/IV (moderate AD), tau pathology has spread to the hippocampal formation and subcortical nuclei. In stages V/VI (severe AD), tau pathology affects the entire brain.

Huntington's disease
(HD). A neurodegenerative disease that is characterized by progressive loss of movement coordination, muscular atrophy and cognitive decline. It is caused by mutations in the huntingtin gene that lead to abnormally high repetitions of the triplet CAG at its 5′-coding region.

Reversing the rise in HDAC2 levels in hippocampal area CA1 of CK-p25 mice by virus-mediated expression of HDAC2-directed shRNAs restored histone acetylation and memory-related gene transcription to normal levels[90]. Remarkably, it also reinstated structural and synaptic plasticity and memory despite persistent neurodegeneration. This indicates that even within a severely degenerated brain, the potential for neuronal plasticity is not lost but might merely be constrained — an important notion for pharmacological treatments aimed at restoring cognition.

What is more, HDAC2 was increased in the hippocampus and entorhinal cortex in the brains of people with AD[90] from the earliest Braak and Braak stages of the disease[97], suggesting that increases in HDAC2 levels — and related chromatin compaction — might be an early pathological event in AD. As treatments for cognitive decline in AD should begin as early as possible[98], this constraining epigenetic mechanism, and the means by which to counteract it warrant further investigation.

Intriguingly, earlier studies had already described chromatin compaction in the brains of patients with AD[99,100], including local heterochromatization of neurofilamin[100], which is also a target of HDAC2-mediated hypoacetylation in the neurodegenerating mouse brain[90]. Could such epigenetically mediated downregulation of neuroplasticity genes serve a physiological purpose? General brain functioning[101], and in particular long-term memory[102] and its underlying neuronal signalling cascades[103,104], are energetically costly. The HDAC2-mediated downregulation of the energetically expensive neuroplasticity genes might thereby allow the brain to save energy for other processes, such as cell cycle maintenance and DNA repair, which are crucial in postmitotic neurons[81,105]. Alternatively, HDAC2 increases could merely be pathological.

In addition to the CK-p25 and 5XFAD mice, reduced histone acetylation mnemonics have also been described in other mouse models of AD, namely the Tg2576 (REF. 106) and APP/PS1 mice[107,108]. However, in cultured hippocampal neurons of the 3xTg mouse model of AD, H3 acetylation was increased[109], and in another study of brains from people with AD, HDAC2 was reduced in cortical areas[110]. These discrepancies might arise owing to differences in sources of material or because changes in HDAC2 and histone acetylation do not occur globally but instead are specific to particular genes. Future genome-wide studies of the relationship between HDAC2, histone acetylation and gene expression changes in AD are likely to resolve this issue.

Ageing. Ageing is commonly associated with cognitive decline. In the brain, ageing leads to the transcriptional downregulation of genes involved in synaptic maintenance and function[111–114], and there is increasing evidence that histone hypoacetylation mediates the silencing of neuroplasticity genes in the ageing brain. In the mouse and rat hippocampus, ageing was accompanied by reduced histone acetylation on H3K9 and/or H4K12 (REFS 33,115). Ageing also increased the expression of HDAC2 (FIG. 3), and led to a hypoacetylation at the promoter region of *Bdnf*[33,109]. These findings suggest a perturbed HDAC2–BDNF feedback loop as a common feature of neurodegeneration and ageing (FIG. 3). Importantly, reduced H3K9 and/or H3K14 acetylation also inversely correlated with age in the frontal cortex of the human brain, notably at the promoter regions of several genes involved in neurotransmission[116].

Of note, age-related histone hypoacetylation might not be confined to genes involved in neuronal functions, as it was also detected at repeat-derived transcripts in the mouse brain[117]. As abnormally repeated DNA sequences underlie several brain disorders that include cognitive impairment, such as Huntington's disease (HD)[118] and fragile X syndrome[119], reduced histone acetylation might act protectively by helping to silence these repeats. This is in line with a recent observation that stress-induced increases in repressive H3K9 trimethylation are associated with silenced retrotransposons[120], but the notion of potentially neuroprotective decrements in histone acetylation warrants experimental confirmation.

Box 1 | **LEARning for life**

Early in life, the epigenome can integrate learned information into lasting gene expression changes that can affect adult health. This has been most strikingly demonstrated for the influence of maternal care in infancy on stress responses later in life. Rats that received strong maternal care as pups showed a decreased stress response in adulthood, which was mediated in part by increased H3 acetylation and decreased DNA methylation at the promoter region of the glucocorticoid receptor (*GR*; also known as *Nr3c1*) gene and corresponding higher *GR* transcription. Conversely, pups of low-caring mothers showed hypoacetylation and increased DNA methylation at the *GR* promoter, reduced *GR* expression and a heightened stress response[145]. Similar effects have been found in people with a history of childhood abuse[168].

Intriguingly, early-life events might also influence cognitive health. For instance, in both rats[169] and macaques[170], early-life exposure to lead enhanced the cortical expression of the amyloid precursor protein (*App*) gene, which has been causally implicated in AD-related cognitive decline[171] in adulthood. Such phenomena have been summarized in the 'latent early-life associated regulation' (LEARn) model, which posits that pathological gene expression can occur later in life because of an aversive predisposing incidence early on[172]. As early-life lead exposure also altered cortical DNA methylation and histone acetylation[173], this predisposition is likely to be epigenetic.

Stress. As sustained stress contributes to both neurodegeneration[121,122] and ageing[123,124], and HDAC2 is involved in cognitive decline associated with both conditions, it is conceivable that stress induces cognitive impairment by eliciting HDAC2-mediated epigenetic cascades (FIG. 3). Consistent with this possibility, an adverse environment in adolescent rats decreased hippocampal histone acetylation in the promoter region of *Bdnf* in stress-susceptible animals[125]. Furthermore, early-life stress (maternal separation during postnatal days 2 to 15) increased the expression of HDAC1, HDAC3, HDAC8 and HDAC10 significantly, and that of HDAC2 marginally, in the cortex of adolescent Balb/c mice (but not in the stress-resilient C57Bl/6 strain), an effect that was accompanied by reduced H4 acetylation and that persisted for up to 2 weeks[126]. As such, changes in histone acetylation might be capable of translating early-life stressors into persistent effects in adulthood (BOX 1).

Together, these findings support the idea that reduced histone acetylation contributes to the cognitive decline in AD-related neurodegenerative diseases, in ageing and potentially after prolonged periods of stress. Such reduced acetylation mnemonics have been called an epigenetic 'blockade'[90], 'bottleneck'[127] or 'brake-pad'[128] for cognitive functions. Reversing these epigenetic constraints with HDACis has become a justified and attractive target for pharmacological interventions against cognitive decline.

HDACis against cognitive decline

As a result of the evidence reviewed here, HDAC2 has become the favoured target in attempts to attenuate cognitive decline. No HDAC2-specific HDACis exist, mainly because HDAC2 is structurally nearly identical to HDAC1 (REFS 7,129). Nevertheless, several types of HDACi (all of which inhibit HDAC2) have shown promising results as treatments for cognitive decline in animal models[130,131] (TABLE 3).

Classes of HDACis. HDACis are divided into four major classes based on their chemical structure. The first class are the carboxylic acids NaB, phenylbutyrate (PB), and valproic acid (VPA), which predominantly inhibit class I HDACs[131]. The second class are the hydroxamic acids TSA, suberoylanilide hydroxamic acid (SAHA) and SAHA-related compounds, which inhibit class I and II HDACs with approximately equal potency[131,132], although the inhibition of the class II HDACs might be driven by their association with class I HDACs, which are the primary target of SAHA[133]. The third class contains a benzamide group, and members include MS-275 and RGFP136, which inhibit class I HDACs with an increased selectivity towards HDAC1 and HDAC3, respectively[131]. Last, the fourth class of HDACis contains cyclic tetrapeptides, which display class I HDAC-selectivity *in vitro*, but little is known about their *in vivo* functions.

HDACis and neurodegenerative cognitive decline. Neurodegeneration-associated memory impairments can be rescued by treatment with HDACis. This was first demonstrated in the CK-p25 mouse model, in which daily NaB administration for 4 weeks counteracted associative and spatial memory decline[57]. Remarkably, this occurred despite persistent neuronal loss, as NaB — similar to the virus-mediated reduction of HDAC2 (REF. 90) — had no effect on neuronal survival. Instead, HDACi-treated animals showed increased synaptic density, suggesting that memory-sustaining plasticity in the surviving neurons can be reactivated. Comparable positive results for HDACis in improving structural plasticity and cognitive performance were also obtained in the APP/PS1 (REFS 107,108,133) and Tg2576 (REFS 106,134,135) mouse models of AD (TABLE 3), promoting histone acetylation as a new pharmacological template against cognitive decline. Alternatively, natural regimens have been shown to mimic the positive effect of HDACis on memory performance (BOX 2).

In addition to restoring chromatin, synaptic and cognitive plasticity, a new line of evidence suggests that HDACis might also be neuroprotective. In Tg2576 mice, injections of the HDACi PB reduced neurotoxic amyloid-β[134,135], and HDACis have shown promising *in vivo* neuroprotective potential in animal models of HD[136–140] and amyotrophic lateral sclerosis (ALS)[141,142] as well as against seizure-induced neuronal damage[143]. Although the underlying mechanisms of these effects remain unclear, the intriguing possibility that HDACis might constitute a two-pronged approach against both neurotoxicity and memory decline warrants further tests.

HDACis and age-related cognitive decline. As in animal models of neurodegeneration, HDACis are also effective against age-related cognitive impairment[115,144] (TABLE 3). In aged mice with a deficit in H4K12 acetylation[115], acute treatment with SAHA or NaB successfully reinstated histone acetylation, partially rescued gene expression deficits and restored associative memory[115]. Similarly, the HDACis TSA and NaB abolished LTP deficits in hippocampal slices from aged rats and increased spine complexity and H3K9 acetylation, particularly at the promoter of *Bdnf*, which also showed higher transcription[33]. Thus, HDACis might work in part by reinstating

Fragile X syndrome
A common form of neurodevelopmental mental retardation caused by unusual trinucleotide expansions and subsequent gene silencing of fragile X mental retardation 1 (*FMR1*) or *FMR2*.

Amyotrophic lateral sclerosis
(ALS). A progressive neurological disease that is associated with the degeneration of central and spinal motor neurons. This neuron loss causes muscles to weaken, leading to paralysis. About 90% of all ALS cases are sporadic, the remaining 10% being caused by genetic mutations, for example, in superoxide dismutase 1 (*SOD1*).

Table 3 | **The potential of HDAC inhibitors as pharmacological treatments against cognitive decline**

Structural class	Selectivity	HDACi	Disease model	Effect	Refs
Carboxylic acids	Class I	NaB	AD	Rescue of associative and spatial memories in CK-p25 mice; increase of synaptic density	57
				Rescue of associative memories in APP/PS1 mice	108,133
			Age	Rescue of associative memories in aged mice; partial reversal of gene expression deficits	115
				Rescue of object memory in aged rats	144
				Rescue of synaptic plasticity and increase of spine number and spine density in hippocampal slices of aged rats	33
			RTS	Rescue of object location memory	153
		PB	AD	Rescue of associative memories in APP/PS1 mice	133
				Rescue of associative and spatial memories in Tg2576 mice; reduction of amyloid and tau pathologies; restoration of spine density	106,134, 135
		VPA	AD	Rescue of associative memories in APP/PS1 mice	133
Hydroxamic acids	Class I and II	TSA	AD	Rescue of synaptic plasticity and associative memories in APP/PS1 mice	107
			RTS	Rescue of object memories in CBP-deficient mice	64
		SAHA	Age	Rescue of associative memories in aged mice	115
			RTS	Rescue of synaptic plasticity and associative memories in CBP-deficient mice	36
Benzamide group	Class I	MS-275	Not yet tested	–	–
		RGFP 136	Not yet tested	–	–

AD, Alzheimer's disease; CBP, cyclic AMP-responsive element-binding (CREB)-binding protein; HAT, histone acetyl transferase; HDACi, histone deacetylase inhibitor; NaB, sodium butyrate; PB, phenylbutyrate; RTS, Rubinstein–Taybi syndrome; SAHA, suberoylanilide hydroxamic acid; TSA, trichostatin A; VPA, valproic acid.

the positive epigenetic feedback loop involving histone acetylation at *BDNF* (FIG. 2). In future studies, it will be important to evaluate how long the beneficial effects of HDACis last, or if there is an age limit beyond which cognitive capacities cannot be restored.

HDACis and stress-induced cognitive decline. No study has yet investigated the ability of HDACis to prevent or reverse stress-induced cognitive impairment. However, as several studies have shown that HDACis can reverse stress-induced histone acetylation[126,145], they might also yield positive results in terms of cognitive capacities.

Caveats and limitations of HDACis. With respect to the potential usefulness of HDACis as pharmacological treatments against cognitive decline, the relatively unspecific action of HDACis and the associated potential for side effects present a major concern. HDACis can be neurotoxic in neuronal cultures[146,147], and several side effects, such as thrombocytopenia, fatigue, confusion, hepatotoxicity and abnormal heart rhythms, have been reported in tests of HDACis as adjuncts for cancer treatment in humans[132]. In general, however, HDACis are surprisingly well tolerated[148], given that they are administered orally or intraperitoneally and therefore should act systemically.

Such absence of severe side effects in humans and animals alike is even more unexpected because of the complex crosstalk between histone acetylation and other post-translational histone modifications[22], DNA methylation[149] and microRNAs[150]. It is therefore essential to investigate the consequences of artificially increasing histone acetylation on other epigenetic marks. Moreover, the effects of HDACis on other brain functions need to be carefully monitored, as mood, anxiety and depression are also regulated by epigenetic modifications[151].

These limitations notwithstanding, HDACis have shown remarkable potential to rescue cognitive functions in other diseases as well[152]. For instance, in mouse models of the neurodevelopmental disorder Rubinstein–Taybi syndrome, which is caused by mutations in the HAT CBP and characterized by severe cognitive decline, HDACis could rescue synaptic plasticity and cognitive function[36,64,153] (TABLE 3). Likewise, HDACis successfully restored cognitive functions in animals models of addiction[154], depression[155–157] and schizophrenia[158]. However, our understanding of the mechanisms of these effects is limited. Below, we describe a model for the functioning of HDACis that integrates findings about their use in cancer research and that might be applicable to their potential against cognitive decline — epigenetic priming.

Rubinstein–Taybi syndrome
A monogenic neurodevelopmental disorder caused by mutations in the gene coding for the histone acetyltransferase cyclic AMP-responsive element-binding (CREB)-binding protein (CBP). The disease is characterized by skeletal and facial abnormalities, and varying degrees of mental retardation.

Box 2 | **Natural HDAC inhibitors?**

A stimulating environment can mimic the ability of the histone deacetylase inhibitor (HDACi) NaB to rescue cognitive deficits. In the CK-p25 mouse model of neurodegeneration, environmental enrichment, consisting of running wheels, climbing devices, hidden nutrient sources and the possibility for social interaction, reinstated synaptic density as well as associative and spatial memories[57]. This effect was presumably mediated by increased hippocampal and cortical histone acetylation, as environmental enrichment (similar to NaB treatment) increased acetylation of H3 and H4 in wild-type mice[57]. Environmental enrichment can also reverse schizophrenia-associated memory impairments in mice, and this reversal was accompanied by increased H3 acetylation[86]. Thus, environmental enrichment constitutes an attractive natural alternative to HDACis to improve cognition.

It will be interesting to investigate whether other behavioural regimens that are beneficial for cognition have similar HDACi-like properties. One such regimen is calorie restriction. Calorie restriction has shown promising cognitive-enhancing effects in mouse models of AD[174–176] and can also improve memory in elderly humans[177]. Recently, calorie restriction was found to affect the expression of several HDACs in the brain (REF. 178). However, it is not known whether calorie restriction also modifies the histone acetylation landscape in brain areas involved in learning and memory.

Epigenetic priming

In cancer research, epigenetic priming refers to the ability of HDACis or other drugs that target the epigenetic machinery to 'prime' or 'sensitize' cancerous cells to anticancer treatments and thereby to enhance their efficacy. This term was first coined in a study that combined decitabine, a DNA-hypomethylating agent, with chemotherapy against acute myelogenous leukaemia[68]. Chemotherapy response rates were improved by epigenetic priming through DNA hypomethylation, which presumably facilitated the expression of previously silenced tumour-suppressor genes[159]. Although other studies did not use the phrase 'epigenetic priming', they came to similar conclusions[160], in particular for HDACis[70]. For instance, pre-exposure of glioblastoma cells to the HDACi MS-275 sensitized the cells to chemotherapy-induced apoptosis[161]. Likewise, breast cancer cells became more susceptible to apoptosis induced by topoisomerase inhibition after being treated with VPA, which increased euchromatization[162]. The effect of VPA was reproduced by viral-mediated knock-down of HDAC2 (REF. 162), suggesting that HDAC2 targeting is desirable for HDACi-mediated epigenetic priming.

A common denominator of these and other studies is that the HDACis alone had little or no curative effect[70,160]; they were only effective in combination with other treatments. Thus, HDACis probably act by supporting gene expression programmes that have already been activated. This mode of action could also explain the general absence of side-effects of HDACis; as HDACis need ongoing metabolic activity to have a phenotypical influence, their effect outside the target tissue might be minimal (FIG. 4a). Likewise, their effect on the expression of genes that are not already characterized by increased rates of transcription, such as housekeeping genes, might be minimal. For instance, in the brain, VPA treatment did not alter the histone acetylation of the housekeeping gene *Gapdh* (glyceraldehyde-3-phosphate dehydrogenase), whereas it increased that of *Bdnf* exon I[49].

The concept of epigenetic priming is also applicable to the action of HDACis in cognitive processes. The administration of HDACis alone might have little or no effect — and therefore produce few side effects — but when combined with learning-induced neuronal activity, HDACis support gene expression programmes that are elicited by such activity. On a molecular level, this would result in the facilitation or potentiation of the increases in histone acetylation that already occur after learning (FIG. 4b). This mechanism would also explain why HDACis can boost memory irrespective of whether they are administered before learning or afterwards[2,32,57]. When HDACis are administered before learning, the administration of the HDACi constitutes the epigenetic priming, whereas when HDACis are administered after learning, the learning itself can be considered the priming event (FIG. 4b).

The study that most strongly supports cognitive epigenetic priming found that socially transmitted food preferences were accompanied by increased histone acetylation in the orbitofrontal cortex of rats (the priming event) and that further enhancement of histone acetylation by NaB also improved long-term memory[46]. NaB was only effective when administered within 15 days of training, highlighting the importance of underlying (priming) neuronal activity during this time-limited period of memory consolidation[163].

Intriguingly, epigenetic priming might also explain graded memory acquisition — the temporal integration of new information during multiple trial intervals, which is facilitated when training trials are spaced rather than presented in close temporal proximity[164]. Augmenting the inter-trial interval during an object recognition task not only improved memory consolidation but also increased histone acetylation, alongside other transcription-enabling histone modifications[17]. In future studies, it will be particularly interesting to investigate cognitive epigenetic priming in spaced training paradigms in conjunction with the application of HDACis.

Conclusions and outlook

On the basis of current knowledge, histone acetylation marks can be considered as epigenetic mnemonics because they facilitate cognitive functions when increased and constrain them when reduced. In addition, there is overwhelming evidence that HDACis can enhance memory by promoting histone acetylation.

However, this might be a rather simplistic view, as most studies have analysed histone modifications in whole-tissue homogenates, which consist mainly of excitatory neurons. As nothing is known about histone acetylation dynamics during memory formation in other brain cells, it might be more prudent to say that histone acetylation fulfils the criteria of molecular mnemonics in excitatory neurons, as shown by several immunohistochemical studies[26,37,46,52,115]. More refined studies are needed to investigate the role of histone acetylation in other cell types.

Moreover, although this Review has focused exclusively on histone acetylation, this post-translational modification does not act alone on cognitive functions. Rather, histone acetylation acts with other epigenetic

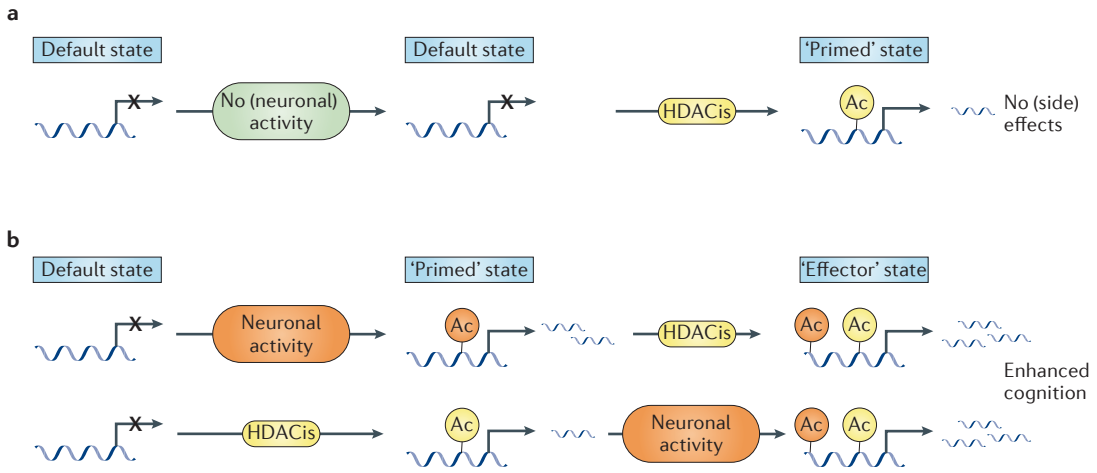

Figure 4 | **Epigenetic priming.** **a** | Theoretical model of epigenetic priming that explains the absence of effects of histone deacetylase inhibitors (HDACis) outside the targeted brain area or tissue. Non-target brain areas and/or tissues do not have default ongoing metabolic (or neuronal) activity, and hence the effect of the HDACi on histone acetylation and further downstream pathways is minimal. **b** | In targeted brain areas and/or tissues, HDACis have a more pronounced effect on histone acetylation and downstream gene expression programmes, as these areas and/or tissues are by default already defined by a metabolic (neuronal)-activity-triggered pre-existing hyperacetylated — that is, relaxed — chromatin structure. Note that this relaxation does not necessarily have to be driven by histone acetylation but could involve other epigenetic mechanisms, which are not shown. In the brain, the epigenetic priming could either be mediated by neuronal activity (top), or by the application of the HDACi (bottom) with the same end result. Ac, acetyl.

modifications that together, presumably, define an epigenetic code for memory[14]. Such codes are far from being deciphered, as new types of epigenetic modifications on DNA[165] and histones[12] are still being identified in the brain, and known histone modifications have been found to occur on hitherto unknown residues[12]. Whole-genome approaches that take epigenetic modifications on both histones and the DNA into consideration are likely to unravel the full complexity of the cognitive epigenetic landscape.

Once these fundamental issues are resolved, it will be interesting to address the following questions. Are there memory type-specific epigenetic codes, and, if so, how do they change during cognitive decline? How do such codes react to adverse influences such as stress? Can pharmacological or behavioural interventions reinstate these codes and, with them, cognitive potential?

With respect to medical applications, histone acetylation dynamics might serve two purposes. First, histone acetylation marks could constitute potential biomarkers for cognitive decline, as histone hypoacetylation accompanies memory deficits across various cognitive disorders[152]. This option is already being tested using biopsy material for different types of gliomas[166]; however, histone acetylation cannot yet be measured non-invasively. Second, re-instating histone acetylation with HDACis has shown promising potential against memory impairments, and the broad applicability and absence of severe side effects of HDACis underscore this potential. In addition to the prevalent targeted approaches aimed at enhancing cognition[167], HDACis might represent a novel 'generic' treatment at the level of chromatin, which makes it theoretically accessible to all genes that are deregulated in cognitive decline. Under the theoretical framework of cognitive epigenetic priming, HDACis might be particularly attractive because they support naturally occurring gene expression programmes, irrespective of the identity of these genes.

In conclusion, the study of histone acetylation and other epigenetic mnemonics has already greatly improved our understanding of the functioning of both the healthy and cognitively impaired brain, and is likely to continue to do so. There is cause for hope that this knowledge will eventually help to counteract cognitive decline characterized by a lack of such mnemonics.

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Acknowledgements
We thank S. Jemielity and A. Mungenast for critical reading of the manuscript and acknowledge support from a Bard Richmond grant to J.G., and the US National Institutes of Health (grants, NS078839 and NS51874) to L.-H.T. L.-H.T. is an investigator of the Howard Hughes Medical Institute.

Competing interests statement
The authors declare no competing financial interests.

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