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A Putative Role for lncRNAs in Epigenetic Regulation of Memory

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Introduction

Few biological processes are as fundamental to individuality or collective identity as memory. Understanding the mechanisms underlying memory formation is dependent on our increased understanding of how gene transcription in the nucleus produces specific proteins underlying synaptic function (Figure 1). The synapse is hypothesized to be the physiological unit of memory, and the singular role of epigenetic modifications in regulating dynamic changes at the synapse during memory and neurodegeneration has been recently review in [1–3]. Nuclear reprograming by epigenetic mechanisms is a process indispensable for memory function [4], and the study of these mechanisms has led to the emergence of the field of neuroepigenetics. Encompassing not only the classic stable, Warrington epigenetic marks necessary for cellular differentiation, neuroepigenetics is the study of epigenetic modifications that enable gene transcription programs necessary for cellular function in response to environmental stimuli [5–7]. Though a complete understanding of the fundamental mechanisms underlying memory continues to elude us, the study of epigenetic regulation of gene transcription in brain regions such as the hippocampus, has begun to shed light on the underpinning of memory formation and maintenance.

Considerable progress has been made in our understanding of how certain epigenetic mechanisms, including DNA methylation and posttranslational modification of histones, contribute to memory formation. Long considered a static mark with the ability to sustain enduring cellular phenotypes, these epigenetic modifications are now known to be dynamically regulated in non-dividing and terminally differentiated neurons, and responsible for established transcriptional regulation of memory associated genes [8–13]. For example, inhibition of DNA methyltransferases (DNMTs), which are responsible for the addition of a methyl group to the 5’ position of the cytosine ring, have been shown to attenuate expression of *Bdnf* in area CA1 of the hippocampus and interfere with contextual fear memory formation [14]. Another example involves a diverse group of histone post-translational

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modifications, impacting chromatin structure around gene regions to contribute to the formation and maintenance of memory. One study found that contextual fear conditioning (CFC) resulted in increases in the transcriptionally repressive dimethylation of histone H3 at lysine 9 (H3K9me2) in CA1 of the hippocampus [15]. Interestingly, inhibition of the G9a/GLP methyltransferase complex in the entorhinal cortex enhanced memory in a CFC paradigm via H3K9me2-mediated silencing of the memory-related gene *COMT* in hippocampal CA1 [16]. Likewise, methylation of histone H3 at lysine 4 (H3K4me), associated with an open chromatin state, has been found to be necessary for the CFC memory formation process, reviewed extensively in [17].

Over the past 15 years, transcriptional programs necessary for synaptic function and memory formation have been demonstrated to be influenced by epigenetic mechanisms[18–20]. Despite our progress in the epigenetics research field, much remains to understand about the role of long non-coding RNAs (lncRNAs) in mediating epigenetic regulation of memory. Less than 2% of the genome contains protein coding transcripts [21], the remainder consisting of noncoding transcripts that were originally believed to be “junk” DNA. Though initially overlooked, the biological significance of non-coding RNAs (ncRNAs) appears indisputable as increased appreciation is gained for the profound regulatory capacities of lncRNAs. NcRNA, categorized as lncRNAs or small non-coding RNAs (which include microRNAs, ribosomal RNAs, small nuclear RNAs, piwi-interacting RNAS, transfer RNAs and small interfering RNAs; Figure 2), play a significant role in both normal cellular function and disease [22–25]. Very recently a handful of studies have begun to show that lncRNA targeting to the synapse influences synaptic plasticity and likely learning and memory[26–28]. As it seems is often the case, our understanding of the role of ncRNAs in the brain has lagged behind other fields such as cancer biology, however a growing body of literature now implicates ncRNAs as potent regulators of cognition [29–32]. The significance of lncRNAs in memory in particular, is an area ready for further exploration.

LncRNAs are endogenous regulatory RNA molecules defined somewhat arbitrarily as transcripts greater that 200 base pairs [33]. Lacking an open reading frame, and thus protein coding capacity, lncRNAs are involved in numerous biological functions and regulate gene expression through a diverse array of mechanisms [34,35]. LncRNAs display temporal, spatial and cell-type specific expression in the brain [36–38], suggesting the potential for unique functional roles. The diversity of mechanisms linked to lncRNA mediated gene transcription has led to the examination of epigenetic crosstalk across the genome. In this review we define epigenetic crosstalk as the ability of one epigenetic mechanism (e.g., lncRNAs) to modify or direct additional epigenetic marks (e.g., histone modifications) with indirect effects on gene expression and subsequently on memory formation. Prior investigations on how modification of chromatin structure by epigenetic enzymes are targeted to gene loci have been unclear. However, the predominantly nuclear localization of lncRNAs, which are heavily enriched in chromatin fractions [21], suggests a role for lncRNAs in chromatin restructuring. In fact, lncRNAs have been shown to bind to numerous chromatin-modifying enzymes, resulting in lncRNA modification or the guiding of regulatory complexes to specific genomic sequences by lncRNAs [39]. Moreover, numerous studies have shown a significant role for lncRNAs in behavior [40], cognitive function [41,42], and disease [43–45].

In this review we will place a specific focus on lncRNA crosstalk with other epigenetic mechanisms both in the brain and neurological disease, with the goal of increasing understanding of lncRNA function such that it might be applied to a better understanding of learning and memory.

First, we discuss lncRNA interactions with two epigenetic mechanisms which are critical to normal memory function (see Figure 3): 1) modifications directly to genomic DNA (DNA methylation), 2) mechanisms effecting chromatin availability via histone modification This is followed by an examination of what little is currently known about how lncRNAs are themselves regulated, specifically by epigenetic crosstalk. Next, we consider the role of lncRNA dysregulation in memory disorders, including age-associated memory impairment, Alzheimer's disease (AD) and epilepsy. Finally, we discuss what, in our view, are critical gaps in the current knowledge in terms of lncRNA regulation of memory, as well as the promise of novel therapeutic options for memory disorders.

The emerging importance of lncRNA function in the brain has recently been highlighted by a number of quality reviews. Thus far there is significant evidence to demonstrate a role for lncRNA function in neural development[46–49] and aging[50–53]. Even more data is available exploring the association of lncRNAs with psychiatric disorders[54–59] and neurological disorders such as CNS/PNS injury and inflammation[60–64], ischemic stroke[65–70], gliomas[71–73], and neurodegenerative disease[74–78]. In a recent review, Grinman et al., nicely summarizes the conservation, evolution and expression of lncRNAs in the brain, as well as what little is known about lncRNA and the neurobiology of learning and memory, including transcriptional and post-transcriptional regulation. In particular, they emphasize the critical role of cis or trans-acting lncRNA regulation of gene expression via either direct interaction or as part of transcriptional complexes[26].

What is missing from the literature is a comprehensive understanding of how lncRNAs influence gene transcription programs necessary for learning and memory, both in the healthy brain and in disease. Thus, in this review we attempt to specifically address a potential role for lncRNAs and epigenetic crosstalk in regulation of gene expression that may in turn be applied to the study of learning and memory.

Epigenetic regulation by lncRNAs

To understand the mechanisms underlying memory, and to develop treatments for disorders of memory, it is necessary to understand how large-scale gene transcription changes are unlocked to allow for memory formation. While our understanding of how lncRNA function to epigenetically control memory-associated gene expression is still in its infancy, much more is known about the function of lncRNA in other fields. Here we will review the known epigenetic cross talk between lncRNA, histone modifications and DNAme in a variety of contexts in the hopes of driving further study and providing insight into how these molecules are directing gene expression changes to enable memory function.

The significant enrichment of many lncRNAs within chromatin identified through the ENCODE transcriptome analysis [21] strongly suggests a role for lncRNA in epigenetic

regulation of gene transcription. Indeed, higher order chromatin structure requires RNA-chromatin interactions [79–81]. This is particularly true in the brain where lncRNA frequently act to direct chromatin modifying enzymes to specific genomic locations, thus altering chromatin state and inducing changes in gene expression necessary for cellular function [82,83]. While the whole of epigenetics includes numerous different mechanisms, this review focuses on the interaction between lncRNA and two significant epigenetic mechanisms responsible for gene expression changes, post-translational histone modification and DNA methylation, as well as how lncRNA themselves are regulated by epigenetic crosstalk.

LncRNA regulation of posttranslational histone modifications

The role of histone modifications in learning and memory is now well-established and has been review extensively[17,84–93]. However, only relatively recently has the role of ncRNAs in epigenetic control of gene expression been appreciated [94–96]. The past few years have seen a rapid advancement of our understanding of how lncRNA interact with a variety of histone modifications [97] including histone methylation [98], acetylation [99,100], and ubiquitination [101]. Perhaps the most well-studied role of lncRNA is X-chromosome inactivation (XCI) via the lncRNA Xist. During XCI, a “Xist cloud” coats one X chromosome, recruiting polycomb repressive complex 2 (PRC2) and inducing heterochromatin confirmation via PRC2 as a mechanism of dosage compensation [102]. Interestingly, Xist has recently been shown to play a role in maintaining repressive histone marks (H3K27me3 and H2AK119 monoubiquitylation) for purposes of sustained XCI in both neurons and a smaller fraction of astrocytes into adulthood [103]. Here we have a prime example of how lncRNA mechanisms associated with development are subsequently coopted for additional purposes across time and in a cell type-specific fashion.

The mechanisms by which lncRNA direct histone modification are diverse and include acting as scaffolds and tethers by binding chromatin modifying enzymes (CME), as well as guiding CME to specific targets [39,97]. Polycomb Repressive Complex 2 (PRC2) is responsible for mediating the addition of largely transcriptionally repressive di or tri-methylation of Lys 27 of histone H3 [104,105] and several studies have suggested regulation and recruitment of PRC2 by various lncRNA including *HOTAIR* [106–108], *XIST* [109,110] and many others [111–113]. For example, the long intergenic non-coding RNA (lincRNA) *HOTAIR* serves as a scaffold for PRC2 (5’) and LSD1/CoREST/REST complex (3’) and the tethering of these complexes results in coupled H3K27methylation and K4 demethylation at target genes [114]. These same mechanisms have the potential to play a role in memory formation as this kind of intricate regulation of gene expression by epigenetic mechanisms is critical for memory. Indeed, histone demethylase LSD1 is necessary for synaptic plasticity and hippocampus dependent memory[115–120] and has been shown to be dysregulated in memory-related diseases[121,122]. REST is a significant transcriptional regulator in a variety of neurodegenerative diseases[123], while CoREST has recently been shown to mediate memory cosolidation in Drosophila[124]. Similarly, a component of the PRC2, the histone lysine methyltransferase EZH2, is a critical regulator of gene expression during fear memory[125,126]. Evidence for the direct interaction of Polycomb repressive complexes and lncRNA is still under debate with many elaborate RNA interactions believed to play a role in

PRC2 direction of gene expression [127], however compelling evidence for a direct association with PRC2 by at least some lncRNA was recently reviewed in [128].

Much of what is known about epigenetic regulation of gene expression profiles by lncRNAs has been derived through the study of lncRNAs in cancer. Several lncRNAs are differentially expressed in glia-derived tumors and many studies are examining their capacity to serve as biomarkers. One such example, AGAP2-AS1, interacts with the active component of the polycomb repressive complex, EZH2 to direct them to the promoter region of TFPI2 and inhibiting transcription [129]. The lncRNA TUG1 with an EZH2 binding domain has also been shown to recruit PRC2 in glioma cells repressing differentiation relevant genes through increased H3K27me [130]. Similarly, the lncRNAs HOTAIRM1 and PXN-AS1 have been found to promote proliferation and migration of glioblastoma cells via sequestration of G9a and EZH2, mediating dimethylation of H3K9 and H327 at the transcription start site of the HOXA1 and DKK1 promoter genes respectively [131,132]. While these interactions are described in the context of glioma cells, EZH2 is a key mediator of memory associated gene expression during fear memory[125,126].

Extending mechanisms observed in neoplastic tissues to other disease processes or healthy tissues must of course be done with caution. However, recent studies demonstrate that lncRNA interaction with chromatin remodeling mechanisms is not limited to oncogenic processes. With improved sequencing technologies, the ability to probe deeper and more thoroughly into the functions of these transcripts in the brain has advanced considerably. Recent RNA immunoprecipitation (RIP) sequencing studies show extensive binding of various lncRNA to the catalytic subunit of PRC2, EZH2, in numerous tissues including the brain [133], and that many of these interactions may be significant for neurological disease [134]. For example, H19 knockdown reverses hypoxic stroke induced upregulation of HDAC1 and downregulation of acetyl-histone H3 and acetyl-histone H4, whereas HDAC1 overexpression negated the beneficial effects of H19 knockdown on infarct volume and brain edema [135]. It is well-established that histone acetylation and deacetylation driven regulation of gene expression contributes to memory function, and the use of HDAC inhibitors to treat neurological disorders characterized by memory dysfunction has garnered significant interest[88,91,136,137]. Given known interactions between HDACs and lncRNAs in other neurological conditions, it appears prudent to explore their likely role in regulating key memory-related epigenetic mechanisms. Indeed, as will be discussed in greater detail below, the lncRNA *Neat1* which has been studied extensively in cancer biology, is now known to transcriptionally represses *c-fos* via H3K9me2, possibly through interaction with the histone methyltransferase G9a in the context of fear memory [37]. Collectively, these studies demonstrate a significant role for lncRNA in directing histone post-translational modifications and subsequent gene transcription.

LncRNA regulation of DNA methylation

The dynamic regulation of DNA methylation is often choreographed and influenced by the expression of various lncRNA [138–140]. For example, during development, the lncRNA *Evf2* both recruits DLX and Methyl CpG binding protein 2 (MeCP2)[141], and inhibits DNA methylation, modulating competition between the DLX1/2 activator and MeCP2 repressor,

enabling differential control of adjacent genes with shared DNA regulatory elements [142]. MeCP2 regulation of transcription has a well-established impact on synaptic function[143] and learning and memory[144–146].

Beyond development, lncRNA continue to mediate gene expression throughout the normal lifespan, as well as in the case of disease. Regulation of gene expression by DNAme and its associated readers, writers and erasers, is critical for synaptic plasticity and in vivo measures of memory[10,147–152]. Thus, any potential recruitment or regulation of these mechanisms by lncRNA in the brain is likely to impact memory-associated gene expression.

In one such example, Diabetes Mellitus associated reduction in neurogenesis is followed by cognitive decline that can be linked to upregulation of the lncRNA *H19*. *H19* binds specifically to the IGF2 gene promoter region, resulting in hypermethylation through enrichment of DNA methyltransferase and ultimately silencing IGF2 expression [153]. Similarly, decreasing expression of the lncRNA *PCA1* can protect against neuroinflammation induced cognitive impairment, and does so via negative regulation of SUZ12, which in turn serves as a recruiting platform for DNA methyltransferases [154].

While there are few other examples from the field of learning and memory, the study of cancer has yielded significant insights into the role of lncRNA in epigenetic control of gene transcription profiles. Recruitment of DNA methyltransferases by lncRNA to promoter regions significantly alters proliferation and invasion-permissive genes, as that seen by the lncRNA *MCM3AP-AS1* which recruits DNMT1/3 (A/B) to the promoter region of NPY1R resulting in its down regulation and activation of the MAPK pathway in prostate cancer [155]. Interestingly, NPY1R expression has recently been shown to mediate spatial learning in adult mice[156]. It may then be reasonable to ask if, in the context of memory formation, the lncRNA *MCM3AP-AS1*, which is also expressed in the brain, might contribute to NPY1R transcription regulation through control of DNA methylation at its promoter. Beyond recruitment and direction of DNMTs, lncRNAs have also been shown to modulate the stability of methyltransferases, inhibiting expression of tumor suppressors via increased DNAme [157].

Understanding the role of lncRNA-mediated epigenetic mechanisms in the context of behavior is still in its infancy. However much remains to be learned about how lncRNA mediation of DNA methylation contributes to learning and memory, and how these mechanisms are disrupted in cognitive impairment.

Regulation of lncRNA expression by epigenetic mechanisms

It can be safely surmised based on the studies described above, and the work of many others, that lncRNA are critical players in the control of gene expression. Less however is known about the signaling pathways that facilitate expression of lncRNAs themselves. The tissue, and time specific expression of many lncRNA argues for a tightly controlled regulation of lncRNA transcription. Once again there are few explicit examples of how regulation of lncRNA expression impacts memory formation. Instead, we must explore what has been elucidated from cancer biology and neurological disease to form a starting point

from which to investigate the role of lncRNA regulation in memory. For example, in breast cancer tissue, IGF/Insulin signaling arbitrates expression of a subset of lncRNA including SNHG7, which is downregulated by IGF via MAPK-driven post transcriptional mechanisms [158]. Interestingly, transcriptional control of SNHG7 also appears to occur through C-myc binding of the promoter region increasing expression and governing glycolysis through the miR-34a-5p/LDHA axis in breast cancer cells [159]. These studies demonstrate multiple levels of transcription regulation of a single lncRNA.

Indeed, there are many broad potential mechanisms by which lncRNA expression including can be regulated including second messenger signaling[160–162], drugs of abuse[163–165], neuronal activation[166–169], and many others which have been described elsewhere[170,171]. Perhaps unsurprisingly then, lncRNAs are subject to regulation themselves by various epigenetic mechanisms. In fact, it is likely that multiple levels of epigenetic regulation will be affected in the case of disease, such as the H3K27me3 facilitation of the lncRNA HOTAIR, leading to altered HOXA1 DNA methylation in chemoresistant small cell lung cancer [172]. Complex governance of lncRNAs expression appears to play a role normal healthy development, such as Ezh2-mediated H3K27me of various lncRNAs in embryonic stem cells [173], as well as in disease. Interestingly, in some cases this regulation appears to be bidirectional with differential DNAme at promoter and transcriptional start sites of lncRNAs. For example, decreased DNAme at the promoter region of the lncRNA SNHG12 results in upregulation of its expression and development of TMZ resistance in glioblastoma cells [174,175]. In a number of human cancers, loss of MEG2 due to hypermethylation and promoter and intronic regions is associated with tumor growth [176]. Similarly, aberrant methylation patterns at multiple lncRNA have been linked to both paranoid and undifferentiated schizophrenia [177]. Four lncRNAs (UCA1, ADARB2-AS1, LINC324 and MAP3K14-AS1) were found to be differentially methylated (hypermethylated) in temporal lobe epilepsy, further showing transcriptional control of lncRNA by DNAme [178]. In reality, multiple epigenetic mechanisms undoubtedly converge to maintain the delicate homeostasis necessary for cellular function and potentially memory formation.

LncRNAs in Memory disorders

Prior sections of this review attempted to impart the significance of lncRNA in regulating gene expression and the general mechanisms by which this might occur. A growing body of literature implicates aberrant lncRNA expression with cellular dysfunction in memory associate diseases (Figure 4; Table 1). It is imperative to obtain a solid understanding of lncRNA mediated gene expression changes in the healthy brain in order to target these transcripts for therapeutic manipulation under pathological conditions. The following is a discussion of lncRNA involvement in three highly prevalent disorders of memory. Taken together, age-related memory impairment, Alzheimer’s disease and Epilepsy represent a monumental global health burden for which there are currently very limited therapeutic options, and for which exploitation of lncRNAs holds particular promise.

Age-associated memory impairment

Why some individuals age with cognition relatively intact and others slip precariously into dementia is a question that has intrigued and beleaguered the scientific community and layperson alike. In translating external experience or stimuli into functionally relevant gene expression changes, epigenetics mechanisms are a critical component of the aging process [179–181]. Studies investigating the various hallmarks of aging have revealed significant differences in lncRNA expression [182]. Differential lncRNA expression is particularly pronounced in the brain, including thousands of novel lncRNA identified as "altered" in the synaptosomes of aging mice [183], as well as age-related expression of two lincRNAs (LINC-RBE and LINC-RSAS) described in the rat brain [184,185]. These findings are consistent with trends seen in humans during aging; for example, post-operative cognitive dysfunction is particularly significant in elderly patients, and has been correlated with 868 differentially expressed lncRNAs, as well as 690 differentially expressed mRNAs related to inflammation and apoptotic pathways [41]. Similarly, studies of post-cardiac arrest cognitive impairment revealed significant changes in hippocampal expression of the lncRNA RNANONMMUT113601.1 and the mRNA Shc1, also an inflammation and apoptosis coupled gene [186]. From these data we have two significant takeaways: first, differentially expressed lncRNA or groups of lncRNA have the potential to serve as biomarkers for age-associated cognitive impairment depending on the timeline with which their expression changes. Second, exosomes or membrane nanovesicles secreted by most cell types including those in the CNS [187], are carriers of a variety of RNAs, including lncRNA [188]. This means there is the potential for minimally invasive (e.g., blood draw) means of measuring brain-derived lncRNA in order to identify those with or predisposed to age-associated cognitive decline.

One lncRNA that has been well studied in the context of aging is *Neat1*. There is an increase in lncRNA *Neat1* expression in the brain of both humans and animal modes of normal aging [37]. *Neat1* mediates age-related impairment in hippocampus dependent memory formation [37]. Downregulation of *Neat1* (via nimodipine used to treat subarachnoid hemorrhage) resulted in upregulation of miR-27a and subsequent downregulation of MAPT, contributing to improved cognitive function [42]. Interestingly, *Neat1* knockout mice showed no deficits in memory [189] likely indicating redundant pathways capable of compensatory function in the case of constitutive knockout.

Alzheimer's disease

The most significant risk factor for developing Alzheimer's disease is aging. Therefore, with our rapidly aging population, significant funding and research effort has been devoted to the study of the mechanisms underlying AD in hopes of identifying novel therapeutic targets. Clinical trials targeting the accumulation of A β have been largely unsuccessful [190] necessitating a different approach. A number of lncRNAs have been implicated in the pathophysiology of AD and were well reviewed recently by [43,76,77,191–193]. For example, 16 age-associated and 12 gender-associated lncRNAs were identified as dysregulated in AD; Specifically, SNHG19 and LNC00672 were significantly correlated with Braak stage, while AS1, LY86-AS1 and LINC00639 were negatively correlated with Braak stage [194]. Interestingly, dysregulated lncRNA expression appears to be consistent across various AD

models, including Intranasal LPS-mediated AD disease model in mice [195]. Likewise, 315 lncRNAs and 311 mRNAs showed significantly altered expression in the hippocampus of a rat model of AD [196]. However, understanding the mechanisms that result in differentially expressed lncRNA largely remains a mystery, although at least one study suggests that expression of many lncRNA may be dependent on histone modifications in AD [197].

Extensive research in humans and animal models suggests a role for epigenetic regulation of gene transcription in the development and progression of AD[198–204]. Altered DNA methylation[205,206] and hydroxymethylation[207] patterns have been described in humans with AD, including at known susceptibility genes including APOE[208], BIN1,[209] and TREM2[210,211]. Likewise, alterations in post-translational histone modification patterns are associated with synaptic dysfunction and memory impairment in AD[212–215]. Further, studies using a mouse model of AD indicated that a substantial number of differentially expressed lncRNAs and subject to transcriptional regulation by histone modifications[197]. Based on our previous discussion regarding lncRNA regulation gene expression through via epigenetic crosstalk, it stands to reason that this aberrant lncRNA expression likely contributes to AD pathology. As argued earlier, there is a long way to go towards understanding the governance of lncRNA expression both in the healthy brain and disease.

In the search for a viable biomarker for AD and potential progression, lncRNA are proving a promising target. For example, cyclin-dependent kinase 5 (CDK5) deregulation is highly correlated with progression of AD [216]. Two lncRNA *NEAT1* and *HOTAIR* have been shown to negatively regulate CDK5R1 while the lncRNA *MALAT1* appears to positively regulate CDK5R1. Together with human data showing positive correlation between CDK5R1 and *NEAT1* in brain tissue from AD patients, these lncRNAs may serve as biomarkers and potential neuroprotective agents against AD progression [217]. An additional potential biomarker for AD identified recently includes *BACE1-AS* has been found to be elevated in the exosomes of AD patient [218].

LncRNA appear to also be involved in the pathology of AD. The neuronal RNA-binding protein HuD stabilizes the lncRNA BACE1AS contributing to enhanced BACE1 expression and APP levels in patients with AD and HuD overexpressing mice [219]. Perhaps unsurprisingly given the significant role *Neat1* appears to play in normal aging, the lncRNA *Neat1* is upregulated in the APP/PS1 transgenic model of AD and interacts with NEDD4L to promote PINK1 ubiquitination and degradation, further promoting the pathogenesis of AD [220]. Neuron-specific lncRNA *neuroLNC* interacts with the RNA-binding protein TDP-43 resulting in the stabilization of mRNAs encoding for presynaptic proteins, thus influencing neuronal excitability [221]. Alterations in expression of several lncRNAs, either endogenously or artificially is also capable of halting the progression or limiting AD-associated pathology. For example, the apolipoprotein A-I mimetic D4F decreases expression of Aβ through up-regulation of long non-coding RNA *SIRT1-AS* [222]. Silencing of the lncRNA *SOX21-AS1* resulted in decreased oxidative stress injury and reduced apoptosis on hippocampal neurons of and AD mouse model [223]. In an A β25–35 treated hippocampal mouse neurons, decreasing expression of the lncRNA *TUG1* limits apoptosis via elevation of miR-15a and suppression of ROCK1[224]

Perhaps most importantly, targeting of various lncRNA appears to hold significant promise for future therapeutics. *BACE1-AS* inhibition via lentiviral siRNA expression improved memory and learning behaviors in SAMP8 mice [225]. Up-regulation of the lncRNA *Meg3* in the hippocampus of an AD rat model improved spatial learning and memory, inhibited apoptosis of hippocampal neurons and oxidative stress injury via the PI3/Akt pathway. [226]. Finally, the lncRNA *BC1* induces APP mRNA translation in an AD mouse model, while inhibition of *BC1* protects against spatial learning and memory deficits [227].

Epilepsy

Epigenetic control of gene transcription contributes to the aberrant network excitability and recurrent seizures [228,229] however, the functional role of lncRNA in the pathogenesis of epilepsy is still not completely understood, although the state of their role in the disease has been recently reviewed [230–232]. Differential expression of 497 lncRNAs have been identified in mesial temporal lobe epilepsy (TLE) patients with hippocampal sclerosis, along with co-dysregulated mRNAs correlated with inflammatory response and neuropeptide receptor activity predicted to play a role in epileptogenesis [233]. For example, hippocampal and serum levels of the lncRNA ILF3-AS1 were increased in TLE patients. Ectopic expression of ILF3-AS1 in astrocytes increased expression of several metalloproteinases connected with epilepsy and decreased expression of miR-212 which is consistent with lower levels observed in TLE patients [234].

Nearly a third of epileptic patients develop resistance to available anti-epileptic drug therapeutic options. As such, there is emergent need to identify novel mechanisms and biomarkers for the progression of epilepsy. LncRNAs are emerging as interesting potential biomarker in in epilepsy as well. To date numerous different lncRNAs have been identified as differentially expressed in epilepsy [235,236], with some displaying additional sex-specific differences [237].

Rodent models of epilepsy have been invaluable in identifying the various roles lncRNA might play in the pathogenesis of epilepsy. For example, H19 is significantly upregulated in the hippocampus of a rat model of TLE and aggravates seizure induced neuronal apoptosis via sponging the microRNA let-7b [238]. In a rat model of epilepsy downregulation of MALAT1 results in activation of the PI3K/Akt pathways decreasing autophagy and apoptosis in hippocampal neurons [239]. Inhibition of the lncRNA PVT1 decreases the loss of neurons and astrocyte activation, as well as increases expression of BDNF in the hippocampus by downregulating the Wnt signaling pathway [240]. Once again, the lncRNA *Neat1* has been shown to be altered in the disease condition, binding epilepsy associated potassium channel interacting proteins and knockdown induces a neuronal hyper-potentiation phenotypes in iPSCs. *Neat1* is also acutely down-regulated in response to neuronal activity, however it becomes unresponsive with chronic stimulation in a rat model of TLE [168].

Cognitive deficits are well-documented in intractable epilepsy [241,242], however mechanisms underlying these cognitive deficits have not been fully elucidated. Expression of the lncRNA UCA1 and NF-□B mRNA are higher in brain tissues of the pilocarpine model of Epilepsy [243]. NF-□B is well-known to mediate the gene expression dependent process of synaptic

function and memory [244], making its regulation of particular interest in terms of identifying novel therapeutic targets. Indeed, lncRNA interaction with NF- B signaling is a reappearing theme, with downregulation of the lncRNA ANRIL restoring learning and memory via the NF-□B signaling pathway in streptozotocin-induced diabetic rats [245].

Future outlook

The studies reviewed here support a significant role for lncRNAs in epigenetic regulation of transcriptional programs; however, our understanding of how lncRNAs function in the brain is still in relative infancy. Here, we discuss critical questions remaining in the field regarding how lncRNAs function in the context of memory and associated disorders. To better understand how specific lncRNAs contribute to memory formation, lncRNAs must be studied in a region-specific, sex-specific and cell-type-specific manner. Finally, we address the available technologies that can serve to probe important remaining research questions in the field, as well as the advantages and limitations of these molecular genetic approaches.

Brain region and sex specificity

In this section, we consider what is known about brain region specific functions in memory, and subsequently how that knowledge can be applied to the study of lncRNAmediated transcription of memory-permissive genes. Differential expression of several lncRNAs exists between various brain regions [36,38,313], and can be altered in the case of disease [74]. It is well established that specific brain regions such as the hippocampus play a critical role in the acquisition and retrieval of memory [314–318]. Furthermore, both human studies and rodent models demonstrate that hippocampal subfields show specialization associated with memory [319–324]. Thus, it seems likely that lncRNA-mediated regulation of epigenetic mechanisms plays a role in the region-specific transcriptome critical for memory formation.

Given that epigenetic integration of stimuli can confer significant differences in gene expression based on sex [325], expression of specific lncRNAs may vary by sex. Indeed, that appears to be the case in humans and animal models, with differential expression of lncRNAs between the sexes occurring in both the healthy brain and disease states [194,326–328]. The examination of sex differences in lncRNAs and influence on memory formation remain to be studied, and further, how functional control of lncRNAs might be leveraged for more precision directed therapeutics.

Cell type specificity

While research evidence has revealed glia specific enrichment of lncRNAs, most studies continue to focus on the role of lncRNAs in neuronal populations. Similarly, numerous studies examining the effects of manipulating lncRNAs in different brain regions did not determine if lncRNAs in specific cell-types is driving behavioral changes.

For example, overexpression of the lncRNA *MEG3* via third ventricle infusion of overexpression plasmid led to improved learning and memory in a rodent model of AD [226], a significant finding at a time when novel treatments for AD are desperately needed. However, these broad manipulations did not distinguish if the impacts on memory were due to reduced neurodegeneration or limited astrocyte activation, or some combination

thereof. This is an important distinction, as broad overexpression of the lncRNA MEG3 is also reported to play a role in ischemic stroke and may accelerate associated pathological progression [329]. Additionally, determining differences in functional lncRNAs in major brain cell-types (neurons, astrocytes, microglia) should be considered in future studies, as cellular subpopulations exist with distinct lncRNA gene signatures [330]. Moreover, lncRNAs impact microglia activation and associated inflammatory cascades [331–335]. The well-studied lncRNA *Xist* was recently discovered to have microglia-specific functions, downregulating apoptosis and inflammatory associated with microglia following spinal cord injury [336]. The potential functional implications of cell-type specific differences cannot be overstated given the growing body of literature demonstrating the profound impact of altered glia function on synaptic function [337,338], memory, [339–342] and disease [340,343,344]. Therefore, distinguishing cell-type specific contributions of lncRNA during memory formation may lead to novel translational approaches for treating neurological disorders while limiting unintended, off-target effects.

Technological advances and limitations

Recent advances in our understanding of lncRNA are greatly indebt to rapidly progressing sequencing technologies. Despite our expanding catalogue of known lncRNAs, the functional roles of these transcripts will depend on techniques designed to study cell-specific function. Increasing use of single nucleus RNA sequencing (snRNA seq) has already provided an abundance of data, particularly in the context of disease states [345,346]. For purposes of studying the functionality of lncRNA in animal models, innovative techniques are required in order to isolate of cell-type specific nuclear fractions, as well as manipulating transcripts in a cell-type specific manner. Fluorescent activated cell sorting (FACS) and Magnetically activated cell sorting (MACS) are both widely utilize cellular techniques that enable efficient cell-type enrichment and high viability for subsequent culture [347]. In particular, MACS has proven valuable for isolating multiple cell types from the same brain and limiting damage to fragile glia projections which frequently occurs with FACS [348,349]. For the purposes of deep sequencing, FACS has been shown to deliver cleaner microglia fractions [347]. Difficulties arise when attempting to combine region specific and cell-type specific studies, given the relatively small volumes of tissues involved. However, these studies are critical as we have discussed significant differences in both cell type and regional functions of lncRNAs. In cases such as this, in situ hybridization methods provide spatial information and can be combined with cell-type specific markers for further detail.

There are numerous methods used to manipulate lncRNAs for functional studies [350], however cell-type specific manipulation of lncRNAs is a more challenging task. Most RNAi based methods (siRNA or shRNA) are adequate for cell culture designs [351,352], but *in vivo* lack the specificity necessary to exclusively target lesser studies cells such as astrocytes or microglia [353]. There are multiple technological approaches designed to address this problem. Recently, the use of aptamer-siRNA chimeras has gained considerable interest as a treatment strategy, particularly for the treatment of cancer [354]. Aptamers are small single-stranded oligonucleotides which bind with high affinity to their targets which can include lipids, proteins or other small molecules [355]. The development of aptamer-siRNA chimeric RNAs, which can subsequently be internalized by the target cell and processed by Dicer, has

enabled cell type specific delivery of functional siRNA [356]. Despite ongoing challenges to therapeutic application of aptamer-siRNA chimeras, [357,358], initial studies have begun using this technique for treatment of Glioblastoma both *in vitro* [359] and *in vivo* mouse models [360].

There is also great potential for Adeno-Associated Viral (AAV) delivery, which is already capable of targeting specific cell types for many over expression studies using cell-type specific promoters [361]. A more extensive review of the various techniques which can be used in combination with AAVs for targeting neuronal populations can be found in [362]. These cell-type specific promoters are often not however suitable for short siRNA/shRNA sequences necessary for knockdown studies in that they require Pol III recruitment for expression of non-polyadenylated sequences [363,364]. Lentiviral vectors are larger with the potential to house shRNA targeting lncRNA of interest, however lentivirus is already known to result in increased expression of the lncRNA *Neat1* [365], and thus its application used with caution.

Metabolic signaling and lncRNA

An additional research area that deserves further exploration, is investigation of lncRNAs involved in metabolic function, and the reciprocal regulation of lncRNAs by metabolic signaling. Metabolic signaling is mediated at multiple signaling and tissue levels, including the brain [366,367]. There is significant interest in the effect of diet on cognitive function [368] and dietary approaches to disorders of memory [369]. The so-called ketogenic diet has proven promising as an adjuvant or alternative therapy for pediatric patients with intractable epilepsy and other neurological disorder [370,371]. Despite the tentative success of dietary therapeutics, very little is understood about the mechanisms by which these metabolic changes occur, and how they impact memory function. LncRNA have been found to participate in the establishment of metabolic homeostasis [372], representing a promising therapeutic avenue for many diseases. Metabolic reprograming is present with aging [373], cancer [374] and neurodegenerative diseases [375] and we are just beginning to understand the regulatory roles lncRNA may play and the therapeutic applications of targeting these lncRNA [376]. Inspiration can be drawn from the cancer research field that aims to understand how lncRNAs contribute to metabolically relevant gene transcription programming. Thus, there is growing appreciation for similar approaches in understanding how lncRNAs control the epigenome and subsequent transcription programs to impact memory formation in health and in memory impairments.

Concluding remarks

The studies discussed here, and likely many others, demonstrate a complex epigenetic regulatory process driving dynamic and or persistent gene transcription necessary for memory. In this review, we have described how lncRNAs provide a valuable window by which we can view the crosstalk of epigenetic marks both in the healthy brain, and disease states. Finally, we discussed several questions that remain to be answered regarding lncRNAs crosstalk with epigenetic mechanisms in specific brain regions or specialized cell types affects memory, and how this crosstalk may be altered in disorders of memory. The contribution of lncRNAs to this epigenetic crosstalk is only now being fully appreciated,

and much of what we know about lncRNAs, has yet to be fully investigated in the context of memory. Future work should emphasize studies on lncRNA-epigenetic mediated gene transcription changes and determine if these mechanisms are transcript specific. Overall, these lncRNA-epigenetic mechanisms are engaged in an intricate, multi-leveled crosstalk geared towards homeostatic cellular function, with consequences for dysregulation at specific genes, not necessarily bulk changes in epigenetic marks, driving pathology. Importantly, the therapeutic potential of lncRNA-epigenetic transcriptional processes may be harnessed, and additional studies are crucial to elucidating the consequences of differential lncRNAs and the various epigenetic mechanisms by which they function to control large transcriptional programs in the brain to sub serve the process of memory formation.

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Highlights

- Epigenetic mechanisms drive transcriptional programs necessary for memory formation.
- LncRNAs interact with key epigenetic mechanisms to regulate gene expression.
- Aberrant expression of lncRNAs is associated with cellular dysfunction in cognitive disorders.
- Expression of LncRNAs in the brain is region-specific, sex-specific and cell-type specific.

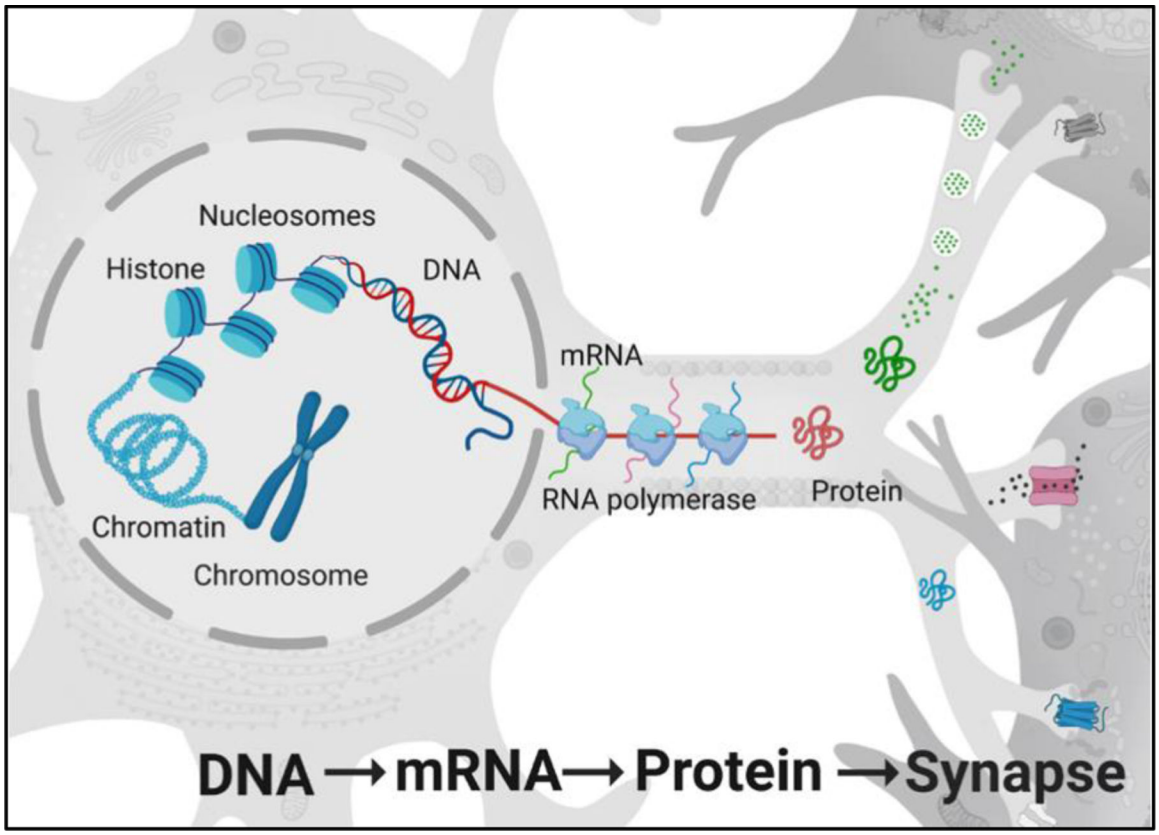

Figure 1.
Schematic representation of the central dogma (DNA → mRNA → protein) of molecular biology in the neuron as it relates to synapse function and memory.

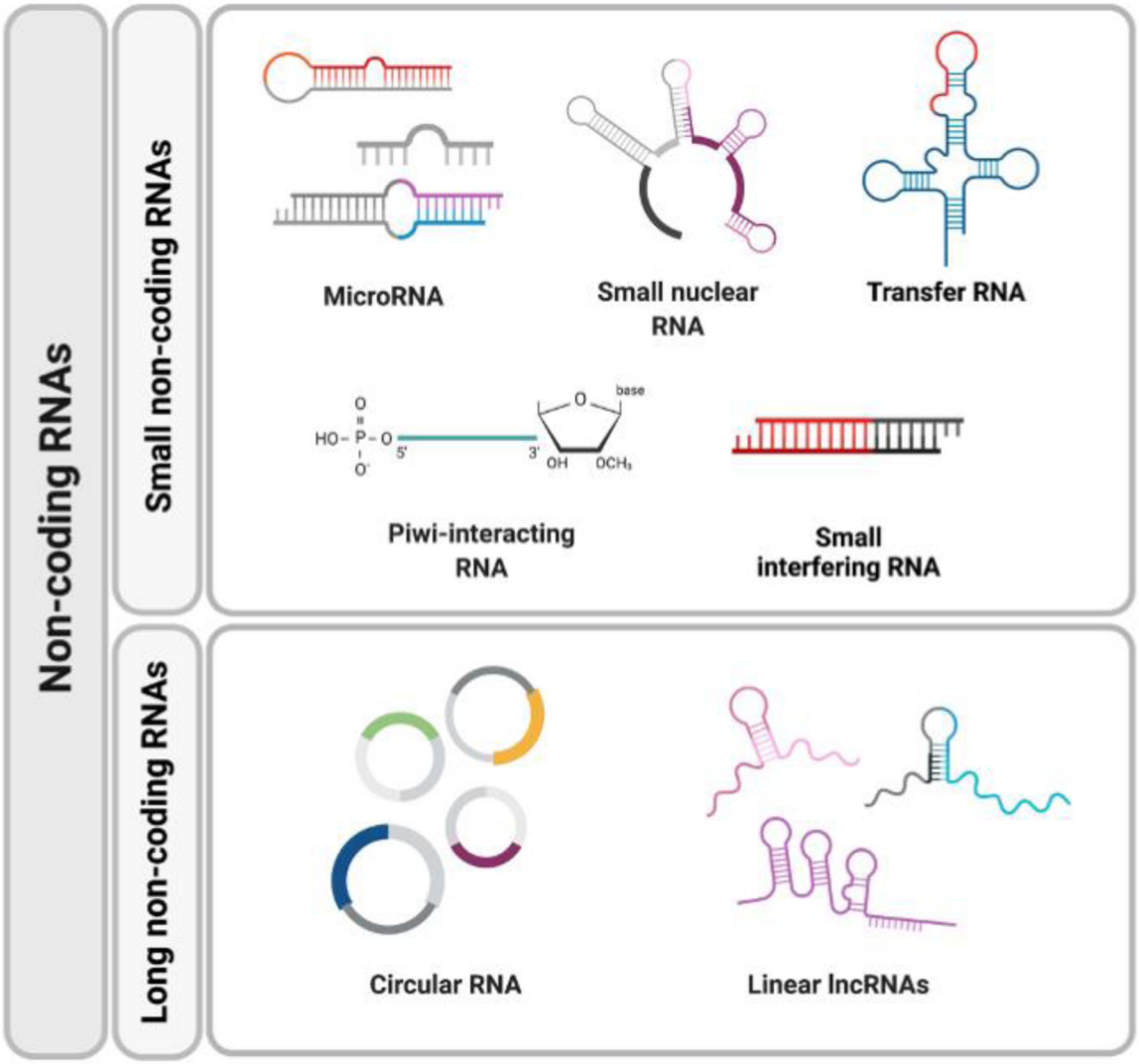

Figure 2. Non-coding RNAs.

Non-coding RNA (ncRNA) are functional RNA molecules that are not translated into proteins. ncRNA can be classified into long ncRNAs (lncRNAs) and Small ncRNAs. Small ncRNAs include many different RNAs, such as microRNAs (miRNAs), small nucleolar RNAs (snoRNAs), transfer RNA (tRNA), piwi-interacting RNAs (piRNAs) and small interfering RNA (siRNA). lncRNAs are the most ubiquitous and functionally diverse class, they include linear lncRNAs and circular RNAs (circRNAs).

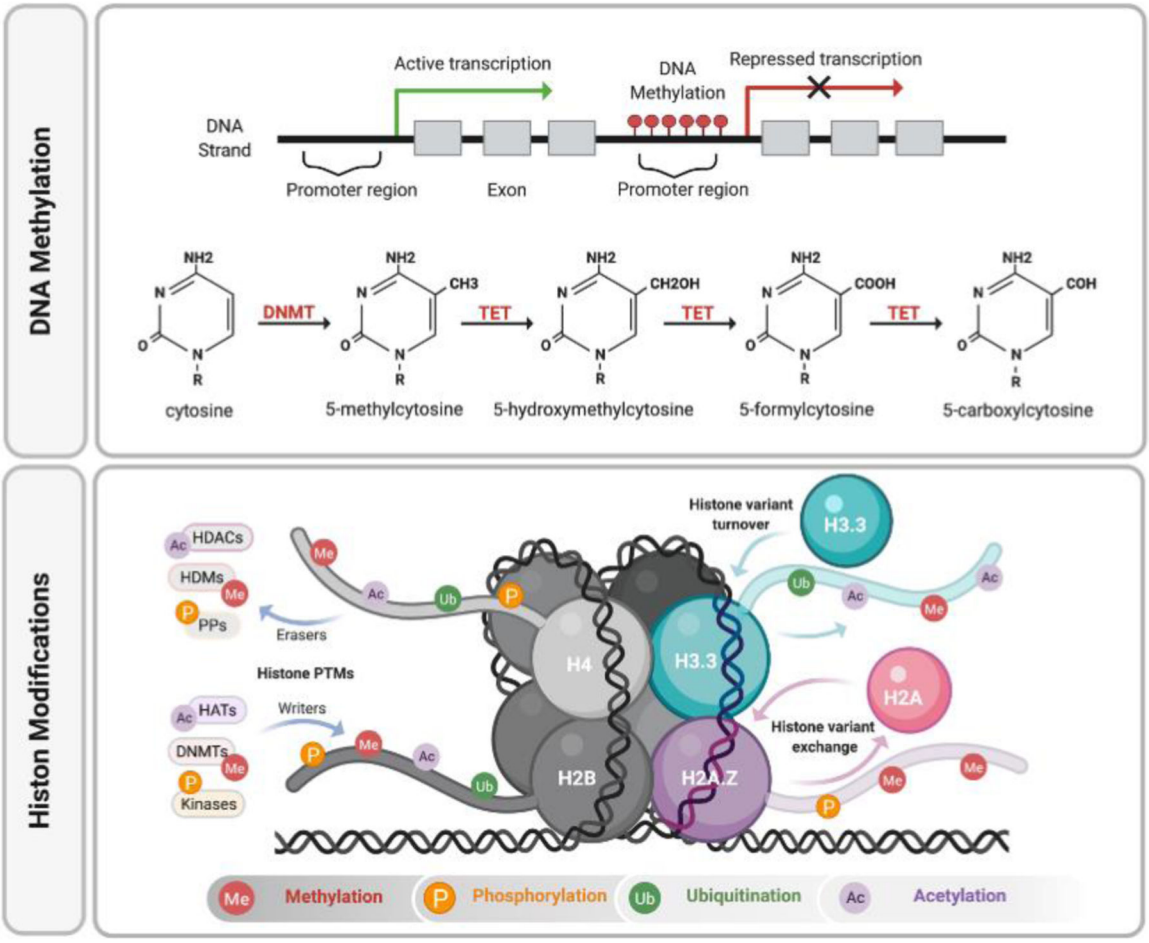

Figure 3. Epigenetic mechanisms of gene expression regulation.

Several types of epigenetic mechanisms play a role in gene regulation, including (1) DNA methylation of gene promoter regions reflect that gene transcriptional activity; if the promoter region is hypermethylated then the gene transcription is repressed, and vice versa, hypomethylated promoter region favors active genes. In this reaction, DNA methyltransferases (DNMTs) modulate gene transcription via the addition of methyl group to the fifth position of cytosines to be converted to 5-methylcytosine (5mC), which then can be demethylated via ten-eleven translocation (TET) dioxygenase to 5-hydroxymethylcytosine (5-hmC) → 5-formylcytosine (5-fC) → 5-carboxycytosine (5-caC). (2) The post-translational modifications (PTMs) of the histone proteins by methylation on lysine or arginine, phosphorylation on serine or threonine residues, ubiquitylation of lysines, acetylation, and deacetylation of lysines. Histone tails can be modified by “writer” enzymes that catalyze the addition of epigenetic marks on histone tails such as histone acetyltransferases (HATs), histone methyltransferases (HMTs), and Kinases, and removed by “eraser” enzymes, such as histone deacetylases (HDACs), histone demethylases (HDMs) and Protein phosphatase (PPs); Histone variant functions is mediated via in histone variant exchange and turnover.

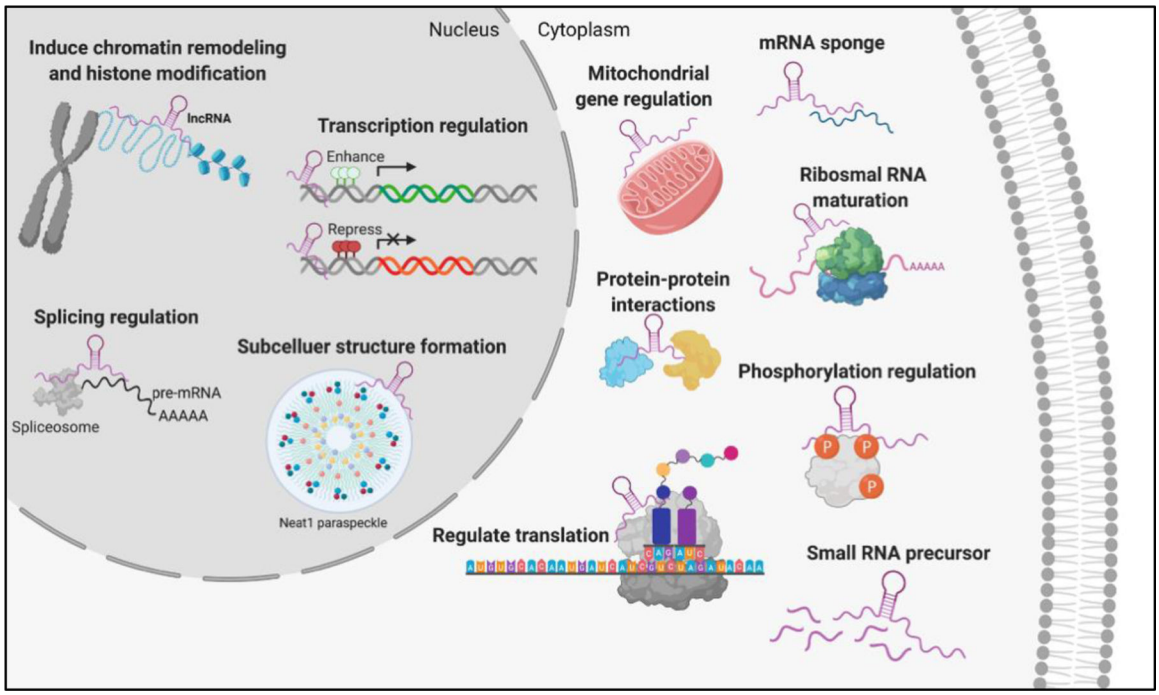

Figure 4. Proposed Molecular Functions of lncRNA in memory disorders.

lncRNAs contribute to numerous processes necessary for cellular function and homeostasis. As a result, aberrant expression of lncRNAs seen in disease can significantly alter cellular function resulting in impaired learning and memory. See text for detailed discussion.

Table 1.

Selected lncRNAs and Their Altered Expression in Memory Related Conditions lncRNA Description Regulation

lncRNA	Description	Regulation	Associated disease	Related Biological Processes	Functions & Implications	References
17A	LncRNA 17A	Up	AD	Cognitive decline, neurodegeneration	Regulates alternative splicing and signaling. Linked to Aβ secretion and elevation of Aβ42 production. Dysregulation leads to deactivation of GABAB signaling, autophagy and neurodegeneration.	246–248
ANRIL	Antisense Noncoding RNA in The INK4 Locus (CDKN2BAS1)	Up	AD	Neurodegeneration	Regulates gene transcription repression. Involved in chromatin modifications via PRC2 recruitment.	249–251
BACE1-AS	Beta-Secretase 1-Antisense RNA	Up	AD	Neurodegeneration, protein aggregation	Involved in post-transcriptional regulation and BACE1 mRNA stability, competes with miR-485–5p for binding to BACE1 and prevents it's targeting on BACE1 mRNA. Increases Aβ 1–42 accumulation.	252–255
BC1	LncRNA BC1 (BC1-FMRP)	Up	AD	Spatial learning and memory impairments, protein aggregation	Involved in mRNA translation and downregulation of BC1. Leads to accumulation of Aβ peptides.	227,256–259
BC200	LncRNA BC200	Soma: Up Dendritic: Down	AD	Cognitive decline	Regulates local translation at the synapse, long-term synaptic plasticity and enhances BACE1 and Aβ1–42 expression.	256–258,260–263
EBF3-AS	Early B Cell Transcription Factor 3-Antisense RNA	Up	AD	Neurodegeneration	Promotes neuronal apoptosis through Aβ25–35- and okadaic acid.	264
GDNF-AS1	Glial Cell Derived Neurotrophic Factor (GDNF Antisense RNA 1)	--	AD	Neurodegeneration	Involved in mRNA translation.	206
GDNF-AS	Glial Cell Derived Neurotrophic Factor -Antisense RNA	down	PD	Cognitive decline; neurodegeneration	Involved in mRNA stability.	263
LRP1-AS	LDL Receptor Related Protein 1-Antisense RNA	Up	AD	Cognitive decline. neurodegeneration	Transcription repression by sequestration of chromatin-regulatory proteins. Linked to the increasing Aβ formation and decreased clearance. Regulate LRP1 expression.	265–268
MEG3	Maternally Expressed 3	Down	AD	Cognitive decline, Involved with spatial learning and memory ability	Upregulation of *MEG3* inhibits the pathological injury and hippocampal neurons apoptosis, decreased Aβ expression, inhibited oxidative stress and inflammatory injury. Involved in induced astrocytes activation through blocking PI3/Akt pathway.	226
MEG3	Maternally Expressed 3	Down	HD	Neurodegeneration	Involved in gene regulation. *MEG3* is a direct target of REST and modulate mHTT aggregation.	251,269–271

lncRNA	Description	Regulation	Associated disease	Related Biological Processes	Functions & Implications	References
NEAT1	Nuclear Paraspeckle Assembly Transcript 1	Up	AD	Cognitive decline	Essential for Paraspeckles formation, integrity, gene expression regulation and miRNA sponging.	28
NEAT1, NEAT1-L, NEAT1-S	Nuclear Paraspeckle Assembly Transcript 1	Up	HD	Cognitive decline	Decreasing *NEAT1* expression lowers mHTT aggregates and TP53 expression in HD. *NEAT1* provides neuroprotection against mHtt-induced cytotoxicity NEAT1-L) and oxidative stress-induced injury NEAT1-S).	251,271–273
NEAT1	Nuclear Paraspeckle Assembly Transcript 1	Up	PD	Cognitive decline	Upregulation of *NEAT1* supports Bax/BCl ratio, caspase 3 activity, α-synuclein expression, MPTP concentration, LC3-II/ LC3-I level and promotes PINK1 protein stability. *NEAT1* serves as miR-124 decoy and promotes cell death and apoptosis.	251,274–276
MIAT	Myocardial Infarction Associated Transcript	Down	AD	Cognitive decline, Neurodegeneration, Protein aggregation	*MIAT* regulates Aβ clearance through *LRP1* expression. Downregulation of *MIAT* promotes miR-150–5p/VEGF-mediated fibrillogenesis, reduces the number of microvessels and the expression of tight junction proteins. Loss of *MIAT* increases Aβ40 and Aβ42 levels and promotes neuronal loss.	251,277
NAT-RAD18	Natural antisense transcript against RAD18 E3 Ubiquitin Protein Ligase	Up	AD	Neurodegeneration	Promotes neuron loss through the down regulation of *RAD18* expression.	278
NDM29	Neuroblastoma Differentiation Marker 29	Up	AD	Neurodegeneration, Protein aggregation	Promotes Alu-induced inflammation and processing of APP and amyloid β secretion.	247,279
SORL1-AS	Sortilin Related Receptor 1-Antisense RNA	Up	AD	Protein aggregation, Cognitive decline	Decreases *SORL1* expression by altering mRNA splicing and impairs APP processing.	251,280
SOX2-OT	SRY-Box Transcription Factor 2-Overlapping Transcript	Up	AD, PD	Neurodegeneration	Regulates co-transcribed Sox2 gene expression, reduces Frizzled 3/5 FZD3/5)-mediated Wnt signaling and triggers oxidative stress generation that leads to apoptosis and neuronal loss.	281,282
HAR1A, HAR1F	Highly Accelerated Region 1A, F	Down	HD	Neurodegeneration	Direct targets of REST. Mutated huntingtin gene lead to abnormal nuclear-cytoplasmic REST/NRSF trafficking leading to downregulation of *HAR1* expression and subsequently repression of numerous neuronal genes.	251,283–286
HTT-AS	HTT Antisense RNA	Down	HD	--	Overexpression of *HTT-AS* downgrades endogenous HTT transcript levels.	248,287
LINC00341	SYNE3: Spectrin Repeat Containing Nuclear Envelope Family Member 3	Up	HD	--	Unknown	251,269

lncRNA	Description	Regulation	Associated disease	Related Biological Processes	Functions & Implications	References
LINC00342	Long Intergenic Non-Protein Coding RNA 342	Down	HD	--	Unknown	251,269
RPS20P22	Ribosomal Protein S20 Pseudogene 22	Up	HD	--	*RPS20P22* regulates *RPS20* expression. Reduction of *RPS20P22* leads to accumulation of p53.	251,269
TUG1	Taurine Up-Regulated 1	Up	HD, Aging	Cognitive decline, neurodegeneration	Direct downstream target of p53. Binds to the PRC2 epigenetic regulatory complex of genes and sponge/decoy function.	250,288,289
TUNA (TUNAR)	Tcl1 Upstream Neuron-Associated lincRNA	Down	HD	--	*TUNA* expression declines significantly with increased HD disease grade.	251,290
HOTAIR	HOX Transcript Antisense RNA	Up	PD	Neurodegeneration	*HOTAIR* upregulation is associated with *LRRK2* upregulation and the induction of caspase 3-dependent apoptosis.	291–293
MALAT1	Metastasis Associated Lung Adenocarcino ma Transcript 1	Up	PD	Neurodegeneration	Involved in synapse development by regulating synapse formation and maintenance of genes expression. Modulates the recruitment of SR family pre-mRNA-splicing factors to the transcription site.	294,295
MALAT1	Metastasis Associated Lung Adenocarcino ma Transcript 1	--	AD	Neurodegeneration	Negatively regulates the CDK5R1/p35 complex and promotes cell death by controlling expression of the miR-15/107 family.	217,251
NORAD	Non-Coding RNA Activated by DNA Damage	Down	PD	---	*NORAD* stabilizes the genome through PUMILIO proteins. Downregulation of *NORAD* induces cytotoxicity through caspase3/7, ROS and LDH activity.	251,296
P21	Long non-coding RNA-p21	Up	PD	Neurodegeneration	p21 is a miR-1277–5p decoy and regulates α-Synuclein through miR-1277–5p. Upregulation of p21 inhibits cell viability, promotes caspase 3 activation, and increases Bcl family-initiated apoptosis.	297,298
PINK1-AS	PTEN Induced Kinase 1-Antisense RNA	Up	PD	Neurodegeneration	Regulates the stability of Pink1 transcript, involved in mitochondrial biogenesis and increases the sensitivity to apoptosis.	299
SNHG1	Small Nucleolar RNA Host Gene 1	Up	PD	Neurodegeneration	Upregulation of SNHG1 promotes neuroinflammation.	300–302
SNHG1	Small Nucleolar RNA Host Gene 1	Down	PD	Neurodegeneration	Involved in miR-15 decoy and inhibits miR-15 function.	268,303
UCHL1-AS1	Ubiquitin C-Terminal Hydrolase L1-Antisense RNA 1	Down	PD	Neurodegeneration	Involved in dopaminergic neuron differentiation and maintenance, cellular stress response and miRNA decoy. Promotes Uchl1 expression by upregulating the translation process.	304–306
RMST	Rhabdomyosar coma 2-associated Transcript	--	--	Neurogenesis, Neurodegeneration	Transcriptionally repressed by REST, required for the binding of SOX2 to promoter regions of	307

lncRNA	Description	Regulation	Associated disease	Related Biological Processes	Functions & Implications	References
					neurogenic transcription factors and involved in neurogenesis.	
GAS5	Growth-arrest-specific 5	up	Aging	Cognitive decline, neurodegeneration	Prepares the cell to apoptosis. Upregulation correlates with impaired learning and novelty-induced behavior.	308–310
DGCR5	DiGeorge syndrome critical region gene 5	Down	HD	Neurodegeneration	*DGCR5* is downstream target of REST in HD disease.	269,311,312