Review Article

Epigenetic mechanisms of major depression: Targeting neuronal plasticity

Shusaku Uchida, PhD 1,2*, Hirotaka Yamagata, MD, PhD 1,2 Tomoe Seki, MD 1,2 and Yoshifumi Watanabe, MD, PhD 1

1Division of Neuropsychiatry, Department of Neuroscience, Yamaguchi University Graduate School of Medicine, Ube, and 2Core Research for Evolutional Science and Technology, Japan Science and Technology Agency, Kawaguchi, Japan

Major depressive disorder is one of the most common mental illnesses as it affects more than 350 million people globally. Major depressive disorder is etiologically complex and disabling. Genetic factors play a role in the etiology of major depression. However, identical twin studies have shown high rates of discordance, indicating non-genetic mechanisms as well. For instance, stressful life events increase the risk of depression. Environmental stressors also induce stable changes in gene expression within the brain that may lead to maladaptive neuronal plasticity in regions implicated in disease pathogenesis. Epigenetic events alter the chromatin structure and thus modulate expression of genes that play a role in neuronal plasticity, behavioral response to stress, depressive behaviors, and response to antidepressants. Here, we review new information regarding current understanding of epigenetic events that may impact depression. In particular, we discuss the roles of histone acetylation, DNA methylation, and non-coding RNA. These novel mechanisms of action may lead to new therapeutic strategies for treating major depression.

Key words: depression, DNA methylation, histone acetylation, non-coding RNA, stress.

GENETIC AND ENVIRONMENTAL FACTORS IN DEPRESSION

More than 350 million people across the globe are affected by major depressive disorder (MDD), a long-term, disabling disease that is ranked second globally in terms of disease burden.1 Although MDD is a serious medical illness and a major public health issue, researchers do not understand what causes the disorder. A meta-analysis of twin studies estimated that MDD heritability is only 37%.2 In contrast, the heritability of other psychiatric diseases, including schizophrenia and bipolar disorder, is approximately 70–80%.3 Identical twin studies have shown a high discordance rate for MDD of 50%, indicating the importance of non-genetic factors.4 Supporting this notion, human genome-wide association studies have largely failed to identify reproducible gene loci that contribute significantly to the disease.5 Epidemiological studies have suggested that stressful life events are associated with a high risk for MDD.6 The current working hypothesis is that variably penetrant, highly complex genetic differences and environmental factors work together to determine resilience and susceptibility to MDD7 (Fig. 1).

THE NEURONAL PLASTICITY THEORY OF DEPRESSION

Increasing evidence has demonstrated altered neuronal and structural plasticity in patients with MDD. Studies utilizing brain-imaging methods have shown that cortical and limbic region atrophy, including decreased volumes in the prefrontal cortex (PFC) and hippocampus, is associated with the duration of
The size of pyramidal neurons in the dorsal lateral PFC and hippocampus was decreased in autopsy samples from patients with MDD. In addition, electron microscopic studies have revealed reduced numbers of dendritic spines within the dorsal lateral PFC of patients with MDD. In animal models of depression and stress, neuronal atrophy, changes in synaptic density, and cell loss have been reported. Various types of chronic stress (e.g., chronic unpredictable stress, repeated restraint stress, or chronic social defeat stress) in rodents lead to abnormal behavior, including the inability to experience pleasure, which is one of the main symptoms of depression. Chronic stress results in decreases in the length and branching of apical dendrites as well as in the quantity and function of synapses at spines of pyramidal neurons of the medial PFC, the CA3 region of the hippocampus, and granule cell neurons of the dentate gyrus. These preclinical studies together with human studies suggest that dysregulation of neuronal and synaptic plasticity caused by chronic stressful life events may contribute to the pathophysiology of MDD. Moreover, if homeostatic mechanisms that control synaptic plasticity are disrupted, synaptic connections that mediate mood and emotions may become lost or destabilized, contributing to disease development and progression.

WHY EPIGENETICS?

Experience-dependent neuronal plasticity allows organisms to adapt and respond to changes in the environment. Neuronal plasticity includes sustained modifications in synaptic structure and function that require de novo gene expression. The regulation of gene expression is a critical molecular mechanism mediating stable adaptations and maladaptations in the brain. Indeed, disruptions in transcription occur in various brain areas in preclinical models of depression and in MDD patients. The pathophysiology of MDD and response to antidepressants are suggested to be controlled by epigenetic modulation of transcription. Epigenetics refers to multiple processes that can induce both transient and potentially heritable lasting changes in gene expression. Epigenetic mechanisms alter the affinity of genomic DNA for various regulatory proteins and/or the association of genomic DNA with proteins that maintain the higher-order structure of the chromosome (e.g., chromatin remodeling). Epigenetic mechanisms include various histone modifications as well as changes to the DNA itself, such as DNA methylation and hydroxymethylation. A newly recognized important group of regulators of epigenetic mechanisms is non-coding RNA, including microRNA (miRNA).

Several perplexing features of MDD, including high discordance rates between identical twins, the chronic relapsing nature of the illness, and the higher prevalence of depression in females, may be explained by epigenetic mechanisms, which can be long lasting. It should be noted that epigenetic regulation of gene transcription is influenced by chronic stress episodes, suggesting that environmental factors may affect neuronal plasticity via epigenetic regulation within the brain, which in turn leads to depression.

In this review, we briefly address the contributions of epigenetic pathways and molecules to neuronal plasticity. Then, we discuss recent studies that have shown that the aberrant neuronal plasticity caused by epigenetic dysregulation of gene expression is pivotal for depression and antidepressant actions.

HISTONE ACETYLATION IN NEUROPLASTICITY, STRESS RESPONSES, AND DEPRESSION

Chromatin remodeling plays a role in multiple physiological and pathological processes in the brain, including circadian rhythms, learning and memory, drug addiction, and depression. Acetylation and deacetylation, which are covalent histone modifications, affect chromatin structure and hence modulate gene expression. Acetyl moieties are added to cationic lysine (K) residues of N-terminal tails of core histones by histone...
acetyltransferases, which decreases the ionic interactions between DNA and histones. Gene expression is thus increased because of enhanced accessibility of transcription factors to promoters. On the other hand, the enzymes responsible for removing acetyl moieties from K residues are called histone deacetylases (HDAC). HDAC increase ionic interactions between histones and DNA, resulting in more tightly packed DNA, more highly condensed chromatin, reduced access of transcription factors to promoters, and finally, reduced transcription.

HDAC are classified into two families: classical HDAC and the SIR2 family of HDAC, which are NAD+ dependent. Three phylogenetic classes of classical HDAC family members have been identified: I, II, and IV. Class I HDAC (HDAC1, 2, 3, and 8) are most similar to RPD3, a regulator of transcription in yeast. Class II HDAC (HDAC4, 5, 6, 7, 9, and 10) share similarity with a yeast deacetylase called HDA1. The single class IV HDAC, HDAC11, is quite different from RPD3 and HDA1. The SIR2 family of HDAC, also known as class III HDAC or SIRT, deacetylates both histones and non-histone proteins and thus modulates multiple cellular functions and affects gene expression. Mammalian sirtuins SIRT1–7 modulate various cellular processes, including gene silencing, cell cycle, apoptosis, metabolism, energy homeostasis, and age-related processes. Here we summarize recent findings regarding the functions of HDAC2, 4, 5, and SIRT1, which are well-characterized HDAC in the brain, in neuronal plasticity, the stress response, and depression.

**HDAC in neuronal plasticity**

Enhancement of neuronal plasticity is essential for adaptive intracellular changes within the brain during the normal stress response. However, severe or chronic stressors are detrimental and can disrupt the ability of the brain to respond to stress normally, eventually leading to depression. Stress and depression may reduce the expression of neurotrophic factors required for synaptic plasticity. Long-term treatment with typical antidepressants leads to an increase in neurotrophic factors and improves synaptic plasticity. For example, a previous study showed that selective serotonin reuptake inhibitors increased long-term potentiation (LTP), a type of heterosynaptic plasticity that is likely involved in learning and memory, as well as synaptic transmission. Other studies have concluded that long-term use of antidepressants can increase spine density or decrease atrophy of spines and dendrites after chronic stress.

HDAC-mediated epigenetic regulation of transcription impacts neuronal plasticity and behavior. The earliest data supporting this concept came from experiments that investigated the contribution of chromatin remodeling to learning and memory. Administration of an HDAC inhibitor increased histone acetylation, enhanced LTP, and led to greater memory performance. Conversely, Guan et al. found that HDAC2 overexpression reduced synapse number, decreased synaptic plasticity, and impaired memory. This group also demonstrated that HDAC2 bound to the promoters of several genes involved in synaptic plasticity or whose expression was activity dependent. Importantly, the detrimental effects of HDAC2 overexpression on plasticity and memory are reversed by the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA), whereas SAHA was unable to further enhance memory in HDAC2 knockout mice.

**Figure 2.** Epigenetic regulation of gene transcription. Histone acetylation catalyzed by histone acetyltransferases (HAT) is associated with decondensed chromatin, increasing the activity of transcriptional complexes. Conversely, histone deacetylation by histone deacetylases (HDAC) represses target gene transcription. DNA methylation by DNA methyltransferases (DNMT) generally represses transcription by recruiting methylated DNA-binding protein complexes. Me, DNA methylation; Ac, acetylation; TF, transcription factors; RNA polII, RNA polymerase II.

© 2017 The Authors. Psychiatry and Clinical Neurosciences published by John Wiley & Sons Australia, Ltd on behalf of Japanese Society of Psychiatry and Neurology.
mice. Thus, these finding suggest that HDAC2 inhibition may enhance synapse number and memory. Supporting this notion, viral-mediated knockdown of Hdac2 restores synaptic plasticity deficits, enhances synapse number, and improves behavioral abnormalities in a mouse model of neurological disease.53 Thus, HDAC2 plays a critical role in the epigenetic control of neuronal and synaptic plasticity.

HDAC4 is expressed at high levels in the neuronal cytoplasm and dendritic spines.54 Phosphorylation of HDAC4 by Ca2+/calmodulin-dependent protein kinases (CAMK) maintains cytoplasmic localization of HDAC4, leads to its nuclear export,55,56 and suppresses the transcription factor MEF2. In contrast, dephosphorylation of HDAC4 by calcineurin allows nuclear translocation.57 HDAC4 binds to chromatin, MEF2A, and CREB, followed by histone deacetylation and suppression of gene expression in neurons.58,59 Interestingly, immunocytochemistry has shown that HDAC is located in dendritic shafts and spines. Studies in primary cultures have shown that neuronal activity induces nuclear export of HDAC4. The subcellular localization of HDAC4 is thought to be regulated by NMDA receptors, as application of the NMDA receptor antagonist AP5 induces nuclear accumulation of HDAC4.60 In the brain, HDAC4 also negatively regulates transcription required for synaptic transmission and information processing.60 Transgenic mice expressing mutant HDAC4 with constitutive nuclear localization showed reduced expression of genes essential for synaptic function, including Camk2a, Homer1, and Snap25.60 Another line of transgenic mice was created that expresses truncated HDAC4 that is retained in the nucleus. These mice in which nuclear HDAC4 functions as a gain-of-function suppressor of transcription showed abnormal acquisition and retention of memory.60 HDAC4 in the nucleus thus negatively regulates learning and memory. In addition, brain-specific HDAC4 knockout mice have memory and LTP deficits.61 Although MDD may be considered primarily an illness of emotional/mood dysregulation, it also involves substantial cognitive dysfunction.62,63 Taken together, HDAC are associated with structural and synaptic plasticity and abnormal behavior in many neurological and psychiatric diseases.

**HDAC in behavioral responses to stress and depression**

Chronic stress increases the risk for depression.64,65 In rodents, chronic stress affects the total levels of acetylated histones in certain limbic regions.66,67 In addition, several types of chronic stress affect chromatin structure in the brain. These structural changes can be genome wide or specific to individual loci. Genome-wide changes may indicate a general trend toward more permissive or restrictive genomic activity.68 In contrast, locus-specific modifications change histone acetylation at a particular gene, thereby altering its expression.15,35,69,70 HDAC play important roles in the response to stress, depression-related behavior, and antidepressant action. We previously reported that enhancement of HDAC2 function in the ventral striatum by 6 weeks of chronic stress drove depression-like behavior in mice (Fig. 3a). Indeed, a gain-of-function HDAC2 mutation leads to increased stress vulnerability, whereas downregulation of HDAC2 induces a stress-resistant phenotype. Systemic administration of SAHA, which inhibits HDAC, during the last 5 days of 6 weeks of chronic stress...
produced antidepressant-like behavior. Given that administration of classical antidepressants, such as imipramine and fluoxetine, during the last 5 days of this same 6 weeks of chronic stress session did not produce antidepressant-like activity, pharmacological suppression of HDAC may be a more rapidly acting therapeutic strategy. As shown in Table 1 and in support of our findings, other reports have also shown that SAHA has a rapid antidepressant action and that SAHA treatment may be effective for depressive-like behaviors in mice that are resistant to conventional treatments.

Another important player in behavioral response to chronic stress is glial cell-derived neurotrophic factor (Gdnf). Chronic stress decreases Gdnf expression in the ventral striatum, whereas knockdown of HDAC2 or SAHA treatment prevents the reduction in Gdnf expression induced by chronic stress, suggesting that Gdnf is a primary target of HDAC2 and is related to depression. Supporting this notion, chronic stress decreases histone acetylation of the Gdnf promoter, whereas genetic and pharmacological inhibition of HDAC2 prevents stress-induced downregulation of histone acetylation at the Gdnf promoter. These findings suggest that chronic stress enhances HDAC2 function and that this can suppress Gdnf transcription, thereby inducing depression-like behaviors. Further, some reports have shown increased HDAC2 expression and reduced GDNF expression in patients with MDD, strongly supporting a contribution of the HDAC2–GDNF pathway to the pathophysiology of depression.

We also recently reported that administration of an HDAC4/5 inhibitor into the hippocampus prevents chronic stress-induced depression-related behaviors (Fig. 3b), suggesting that hippocampal HDAC4/5 is associated with antidepressant action. Another study reported increased hippocampal HDAC4 following chronic stress exposure, whereas suppression of hippocampal HDAC4 abolished the long-lasting behavioral deficits induced by stress. In addition, the authors identified chromatin changes that supported this long-term transcriptional memory. Virus-mediated overexpression of HDAC4 in the hippocampus induced depression-like behavior but not anxiety-like behavior in adult rats. In mice exposed to chronic stress, long-term antidepressant treatment reduced HDAC5 in the hippocampus. Prodepressant effects and reduced histone H3 acetylation were observed in mice with hippocampal overexpression of HDAC5. In addition, in mice exposed to stress, overexpression of HDAC5 blocked the antidepressant-like effects of imipramine. Higher levels of HDAC4 and HDAC5 were found in depressed patients. Thus, dysregulation of HDAC4/5 expression and subsequent abnormal acetylation of histones can produce depression. HDAC inhibitors targeting HDAC2/4/5 may be a valuable new treatment strategy for depression.

Function of SIRT1 in depression

SIRT1 plays an important role in normal brain function and depression. SIRT1 knockout mice or mice expressing catalytically inactive SIRT1 showed defects in cognition and hippocampal synaptic plasticity. Also, SIRT1 knockout mice showed decreased dendritic branching, branch length, and complexity of dendritic arbors. Moreover, SIRT1 knockout mice exhibited altered hippocampal expression of genes with known functions in synaptic and structural plasticity. In addition, recent findings have begun to reveal novel contributions of SIRT1 to higher-order brain functions and pathologies, such as drug addiction, circadian rhythmicity, endocrine regulation, and synaptic plasticity. Thus, SIRT1 activity is a critical regulator of neuroplasticity and adaptive/maladaptive behavior.

Recent experiments in which we targeted non-histone proteins revealed new functions for SIRT1 in structural plasticity in the hippocampus and depression-like behavior (Fig. 3b). SIRT1 activity is decreased in the dentate gyrus following chronic stress. Blocking SIRT1 activity in the hippocampus with drugs or a genetic approach increases depression-like behaviors. On the other hand, activation of SIRT1 in the hippocampus during chronic stress blocks depression-like behavior and abnormal dendritic structures and increases phosphorylation of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2). Increasing ERK2 activity in the hippocampus using a virus-mediated approach has antidepressant-like effects, and inhibiting ERK2 promotes depression. Thus, SIRT1 appears to play a critical role in regulating depression-like behaviors, and pharmacological activation of SIRT1 is another possible novel strategy for treating MDD.
**SIRT1** is one of the first genes to show genome-wide significant association with MDD.94,95 A single-nucleotide polymorphism (SNP; rs10997870) in **SIRT1** is associated with a risk for panic disorders and social phobias, and a second SNP in **SIRT1** (rs12413112) is associated with MDD.96 These important findings were replicated in individuals in the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders, a cohort of 9000 adult Caucasian twins.97 A third SNP (rs10997875) in **SIRT1** is

| Drug          | Role       | Target            | Species | Findings                                                                 | References       |
|---------------|------------|-------------------|---------|--------------------------------------------------------------------------|------------------|
| Sodium butyrate | Inhibitor  | Class I and II HDAC | Mice    | Repeated administration exerts antidepressant-like effects.              | Schroeder et al.71 |
|               |            |                   |         | Repeated administration prevents both stress-induced reduction of histone acetylation and depression-like behaviors. | Han et al.72     |
| MS-275        | Inhibitor  | Class I HDAC      | Mice    | Repeated administration exerts antidepressant-like effects.              | Yamawaki et al.73|
|               |            |                   |         | Upregulation of histone acetylation in the nucleus accumbens and prefrontal cortex. | Covington et al.66,74|
| SAHA (vorinostat) | Inhibitor  | Class I and II HDAC | Mice    | Rapid-acting antidepressant effects (superior to imipramine).            | Uchida et al.15  |
|               |            |                   |         | Rapid-acting antidepressant effects (superior to desipramine).            | Meylan et al.75  |
|               |            |                   |         | Repeated administration exerts antidepressant-like effects in stressed mice. | Covington et al.66|
| Cpd60         | Inhibitor  | HDAC1/2            | Mice    | Increased histone acetylation in cortex, ventral striatum, and hippocampus. | Schroeder et al.76|
|               |            |                   |         | Repeated administration improves mood-related behaviors.                 |                  |
| LMK-235       | Inhibitor  | HDAC4/5            | Mice    | Repeated administration into the hippocampus exerts antidepressant-like effects in stressed mice. | Higuchi et al.17 |
| SRT2104       | Activator  | SIRT1              | Mice    | Repeated administration into the hippocampus exerts antidepressant-like effects in stressed mice. | Abe-Higuchi et al.16|
|               |            |                   |         | Repeated administration prevents stress-induced spine loss.              |                  |
| 33i           | Inhibitor  | SIRT2              | Mice    | Repeated administration increases serotonin levels and glutamate receptor subunit expression. | Erburu et al.77  |
|               |            |                   |         | Repeated administration prevents stress-induced spine loss.              | Munoz-Cobo et al.78|
| Zebularine    | Inhibitor  | DNMT               | Mice    | Repeated administration exerts antidepressant-like effects in stressed mice. | Uchida et al.15  |
| RG108         | Inhibitor  | DNMT               | Mice    | Repeated administration exerts antidepressant-like effects in stressed mice. | Uchida et al.15  |
|               |            |                   |         | Single administration exerts antidepressant-like effects.                | Sales and Joca79 |
|               |            |                   |         | Repeated administration exerts antidepressant-like effects in stressed mice. | LaPlant et al.80 |
associated with MDD in Japanese individuals. Furthermore, Abe et al. reported that Japanese MDD patients currently in a depressive state expressed lower levels of SIRT1 mRNA in peripheral white blood cells than healthy subjects, whereas MDD patients in remission exhibited expression levels that were comparable to healthy subjects. These results suggest that reduced SIRT1 expression is a potential state-dependent biological marker for MDD. In addition, Lo Iacono et al. found reduced SIRT1 levels in patients with MDD and an inverse correlation between SIRT1 levels and Hamilton Rating Scale for Depression scores. Moreover, Luo and Zhang reported reduced SIRT1 levels in MDD, in agreement with the results of Abe et al. Collectively, these human and preclinical studies showing that SIRT1 regulates depression highlight the possibility that activating SIRT1-dependent pathways may be an important strategy for new therapies for treating depression.

DNA METHYLATION IN THE STRESS RESPONSE AND DEPRESSION

DNA methylation, which generally reduces gene expression, is a major epigenetic mechanism and involves covalent addition of a methyl group to cytosine residues of CpG dinucleotides. Histone modifications and the status of DNA methylation are closely linked (Fig. 2). Abnormal DNA methylation at specific genes has been observed in patients with neuropsychiatric disorders and in animal models of depression and anxiety. The DNA methyltransferases (DNMT) DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L catalyze DNA methylation. DNMT1 maintains the methylation pattern by using pre-existing methylation marks to replicate the methylation pattern onto the new strand during replication. Most of the other DNMT are de novo methyltransferases, meaning that they methylate previously unmethylated CpG regions. DNMT3L, which is enzymatically inactive, recruits or activates de novo DNMT. DNMT2 has weak or no detectable methyltransferase activity in vivo and in vitro.

DNA methylation likely modulates synaptic and structural plasticity and memory formation and may be involved in vulnerability to stress and depression. Environmental factors produce changes in DNA methylation levels at specific promoters, and medications may exert their effect by altering these epigenetic marks. Thus, DNA methylation may explain why many pharmacological interventions for MDD are effective only in specific patient subgroups. Analysis of the DNA methylation status may allow treating physicians to predict clinical outcomes in treatment-resistant patients. The effectiveness of antidepressants may vary over time in the same patient because of the tendency of DNA methylation to change.

DNA methylation in stress vulnerability

Stress at an early age is associated with increased vulnerability to stress and depression at later ages. Epigenetic modifications that occur early in life may last for a lifetime and increase vulnerability to stress. Weaver et al. showed that rat pups reared by females that exhibited high levels of nurturing behavior, such as licking, grooming, and arched-back nursing (high-LG-ABN), had less anxiety, a reduced stress response (activation of the hypothalamic–pituitary–adrenal [HPA] axis), and higher expression of mRNA for the glucocorticoid receptor gene Nr3c1 (specifically the alternatively spliced variant GR1F) in the hippocampus than offspring reared by females with low-LG-ABN. GR1F is driven by a brain-specific promoter with a consensus sequence for binding nerve growth factor inducible factor A (NGFI-A). NGFI-A expression is increased in offspring reared by high-LG-ABN dams. Pups from low-LG-ABN dams showed increased methylation at these sites. In human post-mortem specimens, epigenetic differences were found in methylation of the neuron-specific NR3C1 promoter (GR1F) in the hippocampus between suicide victims with a history of childhood abuse and those who committed suicide but had no abuse history and non-suicide controls. The authors reported lower levels of both glucocorticoid receptor mRNA and GR1F splice variant mRNA but higher cytosine methylation of the GR1F promoter in the group with abuse. These observations show a common effect of parental care between humans and rodents in terms of the epigenetic regulation of NR3C1 expression in the hippocampus.

DNA methylation in depression

DNMT play a role in depression in animals. In mice exposed to chronic stress, Dnmt3a levels in the nucleus accumbens were higher than in control
animals.\textsuperscript{80} Dnmt1 and Dnmt3a were expressed at higher levels in the nucleus accumbens in mice exposed to chronic stress with severe depression-like behaviors; and DNMT inhibitors reversed such behaviors.\textsuperscript{15} An association is likely present between DNMT activity and depression.

Women are twice as likely to experience depression as men.\textsuperscript{119} Men and women show different symptoms of depression and methods of coping.\textsuperscript{120} Although the mechanisms underlying these sex-based differences remain unclear, a recent preclinical study suggested an important role for DNA methylation in stress vulnerability. Hodes et al.\textsuperscript{121} reported that female mice exposed to subchronic stress showed depression-like behavior, whereas male mice did not develop abnormal behavior in response to the same stress episode. Among the genes displaying differential expression between sexes in the nucleus accumbens following a subchronic stress episode is Dnmt3a, which is expressed at higher levels in females than males. Dnmt3a knockout specifically in the nucleus accumbens causes female mice to become more resistant to subchronic stress, whereas overexpression renders male mice more susceptible, directly implicating this gene in stress resistance. Thus, DNA methylation may be associated with sex-based differences in the development of stress vulnerability and in the pathophysiology of depression.

Studies of human post-mortem brain tissues have shown decreases in DNMT1 and increases in DNMT3B in the frontopolar cortex of depressed individuals who committed suicide.\textsuperscript{122} DNMT3A mRNA levels were also increased in the nucleus accumbens of individuals with MDD.\textsuperscript{121} DNMT1 and DNMT3B expression was decreased in the amygdala of those who committed suicide, whereas DNMT3B expression was increased in the paraventricular nucleus of such individuals.\textsuperscript{122} Hence, changes in DNMT mRNA expression in depressed suicide victims occur in specific tissues and cells.

Variations in DNA methylation of specific genes in association with depression and/or antidepressant actions have been observed in both humans and rodents. Our previous study showed that DNA methylation at the Gdnf promoter was increased following chronic stress in mice that were both susceptible and resistant to depression.\textsuperscript{15} However, a clear difference in epigenetic modulator complexes on the Gdnf promoter was observed between these two groups (Fig. 3a). In stress-resistant mice, methyl CpG-binding protein 2 (MeCP2)–CREB complexes bound to methylated DNA and presumably increased transcription of Gdnf. In stress-susceptible mice, however, MeCP2–HDAC2 complex binding to methylated DNA on the Gdnf promoter led to transcriptional repression. These data are consistent with another study showing that MeCP2 binding to methylated DNA has a biphasic impact on transcription.\textsuperscript{123} Taken together, these observations indicate that DNA methylation-mediated induction and repression of Gdnf modulate stress resistance and susceptibility, respectively.\textsuperscript{15}

In a related study, adult rats exposed to mistreatment at an early age exhibited higher levels of DNA methylation at CpG sites within the Bdnf promoter as well as decreased levels of Bdnf mRNA.\textsuperscript{124} DNA methylation also appears to regulate hypothalamic corticotropin-releasing factor (CRF), an important modulator of the HPA axis.\textsuperscript{125} In contrast to Bdnf, chronic stress increases CRF expression in susceptible mice along with lower levels of DNA methylation at the Cref promoter. These stress-mediated effects are attenuated by antidepressants. Thus, DNA methylation may be one mechanism of action of the response to stress and effects of antidepressants.

MDD and DNA methylation are significantly linked. Multiplex DNA methylation markers (363 CpG sites) can be used to accurately differentiate MDD patients and healthy controls, a result that was replicated in a separate group of specimens.\textsuperscript{126} Among these 363 sites, several genes, including DGKH, GSK3B, and SGK1, have been identified as playing a role in MDD. The DNA methylation profile of two CpG islands in the BDNF (BDNF-I and –IV) promoter and exon I was significantly different between depressed patients and healthy controls.\textsuperscript{127} Higher DNA methylation at BDNF has been found in patients with MDD and those who committed suicide.\textsuperscript{104,126} SLC6A4 (or SERT) has also been extensively examined for epigenetic changes.\textsuperscript{129} Increased SLC6A4 promoter methylation is significantly associated with childhood trauma, a family history of depression, and more extensive psychopathological problems.\textsuperscript{128} Pharmacogenetics studies have shown an association between certain polymorphisms in SLC6A4 and the response to antidepressants in patients with mood disorders.\textsuperscript{130,131} Methylation at a certain CpG site within SLC6A4 is significantly increased in patients with better therapeutic responses compared to those with worse responses.\textsuperscript{132} Hypermethylation at the CpG island
shore of SLC6A4 was observed in a twin with bipolar. \textsuperscript{133} DNA methylation appears to be an important epigenetic and biological marker that may be useful for both diagnosis and prediction of the response to antidepressants. Substantial progress is currently being made in the area of pharmaco-epigenetics in psychiatry, and the implications for therapeutic treatment are promising. Individualized treatments based on epigenetic information may be an important future advance in psychiatric disease management.

NON-CODING RNA IN STRESS RESPONSES AND DEPRESSION

In addition to mechanisms that disrupt transcription, abnormal post-transcriptional gene regulation by non-coding RNA likely also impacts the etiology of depression. Two groups of non-coding RNA have been described: small (<200 nucleotides) and long non-coding RNA (>200 nucleotides). MicroRNA (miRNA) are a subset of small non-coding RNA that cleave target mRNA or suppress their translation by selective binding to 3′-untranslated regions.\textsuperscript{134,135} miRNA present at high levels in the brain regulate neuronal and synaptic plasticity.\textsuperscript{136,137} miRNA may impact both the pathophysiology of depression and the response to antidepressant drugs, as shown in both animal and human studies.\textsuperscript{138–141} Environmental stress and antidepressant medications change miRNA expression levels in various brain regions that control mood, including the PFC, amygdala, nucleus accumbens, locus coeruleus, and dorsal raphe nucleus.\textsuperscript{115,142–145} For example, miR-34c overexpression in the central amygdala relieved anxiety by decreasing CRF receptor type 1, an important modulator of the response to stress.\textsuperscript{143} Fluoxetine downregulated miR-16 expression in the locus coeruleus, and blocking miR-16 in this region inhibited depression-like behavior due to chronic stress by altering serotonin transporter expression.\textsuperscript{145} In addition, antidepressant administration upregulated miR-135a levels in the dorsal raphe nucleus, and overexpression of miR-135a conferred resilience against chronic social defeat stress by targeting raphe mRNA encoding the serotonin transporter and serotonin receptor 1A.\textsuperscript{142} Importantly, depressed individuals and suicide victims showed reduced miR-135a levels in their blood and post-mortem dorsal raphe nucleus, respectively, and blood miR-135a levels in depressed patients increased after antidepressant treatment.\textsuperscript{142} Thus, post-transcriptional regulation by miRNA networks in various brain regions is likely involved in depression and antidepressant drug actions.

We recently demonstrated that miRNA mediate behavioral responses to chronic stress in rodents by regulating gene expression and synapse number\textsuperscript{137,146} (Fig. 3b). Increased levels of miR-124 in the hippocampus inhibit depression-like behaviors induced by chronic stress and result in stress resilience. In contrast, reduced miR-124 expression enhances behavioral susceptibility to a subthreshold stress episode. These behavioral effects are paralleled by changes in the dendritic structure of dentate gyrus granule neurons. Chronic-stress-induced reduction of spine density is prevented by miR-124 overexpression, and blockade of miR-124 reduces spine density under mild stress. Thus, chronic-stress-induced aberrant structural plasticity may be caused by downregulation of miR-124. miR-124 targets Hdac4, Hdac5, and Gsk3β. Drugs that inhibit HDAC4/5 and GSK3 have antidepressant-like effects on behavior. Taken together, our observations indicate that decreased miR-124 in the hippocampus may affect depression-like behaviors and aberrant structural plasticity induced by chronic stress, at least partially, by increasing HDAC4/5 and/or GSK3β.

A common post-transcriptional process mediated at least in part by miRNA alters the structure of dendrites and neurogenesis.\textsuperscript{137,140,147} MicroRNA-124 is abundantly expressed in neurons, where it regulates adult neurogenesis and promotes dendritic maturation.\textsuperscript{148–150} Thus, our finding that miR-124 overexpression prevents chronic stress-induced dendritic atrophy and spine loss in the dentate gyrus suggests that downregulation of hippocampal miR-124 pathways is a causal mechanism underlying aberrant dendritic remodeling induced by chronic stress. Clinical studies have also reported altered expression of miR-124 in patients with MDD.\textsuperscript{151,152} Our studies and the results of others provide strong evidence for a role for miRNA in depression and show that chronic stress and clinical antidepressants alter miRNA expression. Thus, another novel therapeutic strategy for depression may involve direct manipulation of miRNA pathways.

LIMITATIONS, FUTURE DIRECTIONS, AND CONCLUDING REMARKS

Evidence that epigenetic mechanisms contribute to MDD pathophysiology has accumulated rapidly.
over the last decade. Two unsolved mysteries of MDD are why it is a long-term disease and why patients often display a delayed response to antidepressant medications. The long-term duration of MDD may be due to slowly developing but stable adaptation, processes that are mediated by several epigenetic mechanisms. In fact, the results described in this review support the hypothesis that environmental stressors act through epigenetic mechanisms, including histone acetylation/deacetylation and CpG methylation/demethylation, and interact with an individual’s genetic make-up to determine the risk for depression throughout life.

Epigenetic regulation of gene transcription is important for dendritic development and spine formation. Mounting evidence suggests that aberrant epigenetic regulation within the brain may result in abnormal spine morphology, leading to a depressive state. Indeed, evidence is increasing that suggests spine dysfunction in depression. However, no causal evidence exists for synaptic spines controlling the cellular pathology of disease states and subsequent affective behaviors. Studies using novel investigative tools, such as synaptic optogenetics,\textsuperscript{153,154} may uncover the mechanistic relations between synaptic dysfunction and depression-like behaviors.

As described above, histones can be acetylated, which affects gene expression. Acetylation requires a pool of the metabolite acetyl-CoA in the nucleus.\textsuperscript{155} A very new study showed that acetyl coenzyme A synthetase in the hippocampus of mice is necessary for epigenetic regulation of transcription of genes involved in neuroplasticity dynamics and memory formation.\textsuperscript{156} This is the first evidence for metabolic signaling to chromatin in the brain and indicates a critical role for this type of signaling in cognitive function. Molecules that affect energy homeostasis, such as the epigenetic molecule acetyl-l-carnitine that is produced during normal metabolism, affect and hence provide rapid antidepressant-like activity.\textsuperscript{157,158} These results suggest that metabolic pathways are linked to epigenetic regulation of genes associated with depression. Although further detailed studies are necessary for confirmation, metabolism-dependent epigenetic pathways are likely critical in the pathophysiology of depression and antidepressant responses.

Men and women with MDD show variations in the magnitude, laterality, and direction of volumetric changes in different brain regions,\textsuperscript{159,160} as well as differences in serotonin synthesis and the density of serotonin 5HT1A autoreceptors.\textsuperscript{161,162} Males and females with MDD also differ in terms of activation of the HPA axis following stress.\textsuperscript{163} Thus, sex differences may be present in the etiology and pathophysiology of MDD, although the underlying molecular mechanisms remain largely unknown. A very recent paper reported distinct transcription signatures in multiple brain areas between male and female MDD patients,\textsuperscript{26} suggesting sex-based differences in epigenetic regulation of gene transcription. Additional studies will be needed to elucidate the epigenetic mechanisms responsible for sex-based differences in MDD.

In conclusion, studies addressing the importance of epigenetic mechanisms in susceptibility to stress and depression have provided important information regarding the various genes and biochemical pathways that are changed in particular brain regions, and how these differences may determine the risk of depression and alleviation of symptoms in response to antidepressants. These new data will inform efforts to develop novel strategies for new antidepressant compounds by moving beyond monoamine transporters and receptors. As described in Table 1, given that HDAC inhibitors and DNMT inhibitors exert antidepressant-like actions in several rodent models,\textsuperscript{15–17,66,69,71–80,164} epigenetic molecules themselves may be suitable targets for treatment. Medications targeting epigenetic modifications (e.g., HDAC and DNMT inhibitors) are already in use and are proving effective for cancers and neurodegenerative disorders.\textsuperscript{165–167} However, because HDAC and DNMT are widely expressed, drugs that alter these molecules may be associated with adverse effects. Nonetheless, epigenetic drugs are effective, and they have received a great deal of attention for the possible treatment of multiple diseases.\textsuperscript{168–170} Drugs that specifically target epigenetic modulators that are enriched in the brain may affect HDAC or DNMT and may be useful new therapies for depression.

**ACKNOWLEDGMENTS**

This study was supported in part by Grants-in-Aid from JSPS (15K09807 to S.U. and 15H04895 to Y.W.) and by CREST-JST (to S.U.), and by research grants from the Takeda Science Foundation, the Kanae Foundation for the Promotion of Medical Science, and the Naito Foundation (all to S.U.). The authors declare no competing financial interests.
REFERENCES

1. Smith K. Mental health: A world of depression. Nature 2014; 515: 181.
2. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: Review and meta-analysis. Am. J. Psychiatry 2000; 157: 1552–1562.
3. Kendler KS. Overview: A current perspective on twin studies of schizophrenia. Am. J. Psychiatry 1983; 140: 1413–1425.
4. Fraga MF, Ballestar E, Paz MF et al. Epigenetic differences arise during the lifetime of monozygotic twins. Proc. Natl. Acad. Sci. U. S. A. 2005; 102: 10604–10609.
5. Bosker FJ, Hartman CA, Nolte IM et al. Poor replication of candidate genes for major depressive disorder using genome-wide association data. Mol. Psychiatry 2011; 16: 516–532.
6. Hammen C. Stress and depression. Annu. Rev. Clin. Psychol. 2005; 1: 293–319.
7. Sun H, Kennedy PJ, Nestler EJ. Epigenetics of the depressed brain: Role of histone acetylation and methylation. Neuropsychopharmacology 2013; 38: 124–137.
8. MacQueen G, Frodl T. The hippocampus in major depression: Evidence for the convergence of the bench and bedside in psychiatric research? Mol. Psychiatry 2011; 16: 252–264.
9. Price IL, Drevets WC. Neurocircuitry of mood disorders. Neuropsychopharmacology 2010; 35: 192–216.
10. Rajkowska G, Miguel-Hidalgo II, Wei J et al. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol. Psychiatry 1999; 45: 1085–1098.
11. Stockmeier CA, Mahajan GI, Konick LC et al. Cellular changes in the postmortem hippocampus in major depression. Biol. Psychiatry 2004; 56: 640–650.
12. Kang HJ, Volfii R, Hajsazan T et al. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. Nat. Med. 2012; 18: 1413–1417.
13. Li N, Liu RJ, Dwyer JM et al. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. Biol. Psychiatry 2011; 69: 754–761.
14. Berton O, Nestler EJ. New approaches to antidepressant drug discovery: Beyond monoamines. Nat. Rev. Neurosci. 2006; 7: 137–151.
15. Uchida S, Hara K, Kobayashi A et al. Epigenetic status of Gdnf in the ventral striatum determines susceptibility and adaptation to daily stressful events. Neuron 2011; 69: 359–372.
16. Abe-Higuchi N, Uchida S, Yamagata H et al. Hippocampal sirtuin 1 signaling mediates depression-like behavior. Biol. Psychiatry 2016; 80: 815–826.
17. Higuchi F, Uchida S, Yamagata H et al. Hippocampal MicroRNA-124 enhances chronic stress resilience in mice. J. Neurosci. 2016; 36: 7253–7267.
18. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: Potential therapeutic targets. Science 2012; 338: 68–72.
19. Watanabe Y, Gould E, McEwen BS. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. Brain Res. 1992; 588: 341–345.
20. West AE, Greenberg ME. Neuronal activity-regulated gene transcription in synapse development and cognitive function. Cold Spring Harb. Perspect. Biol. 2011; 3: a005744.
21. Alberini CM. Transcription factors in long-term memory and synaptic plasticity. Physiol. Rev. 2009; 89: 121–145.
22. Uchida S, Martel G, Pavlowsky A et al. Learning-induced and stathmin-dependent changes in microtubule stability are critical for memory and disrupted in ageing. Nat. Commun. 2014; 5: 4389.
23. Uchida S, Shumyatsky GP. Deceivingly dynamic: Learning-dependent changes in stathmin and microtubules. Neurobiol. Learn. Mem. 2015; 124: 52–61.
24. Tsankova N, Renthal W, Kumar A, Nestler EJ. Epigenetic regulation in psychiatric disorders. Nat. Rev. Neurosci. 2007; 8: 355–367.
25. Pena CJ, Bagot RC, Labonte B, Nestler EJ. Epigenetic signaling in psychiatric disorders. J. Mol. Biol. 2014; 426: 3389–3412.
26. Labonte B, Engmann O, Purushothaman I et al. Sex-specific transcriptional signatures in human depression. Nat. Med. 2017; 23: 1102–1111.
27. Yamagata H, Uchida S, Matsuo K et al. Identification of commonly altered genes between in major depressive disorder and a mouse model of depression. Sci. Rep. 2017; 7: 3044.
28. Kouzarides T. Chromatin modifications and their function. Cell 2007; 128: 693–705.
29. Suzuki MM, Bird A. DNA methylation landscapes: Provocative insights from epigenomics. Nat. Rev. Genet. 2008; 9: 465–476.
30. Kriaucionis S, Heintz N. The nuclear DNA base 5-hydroxymethylcytosine is present in Purkinje neurons and the brain. Science 2009; 324: 929–930.
31. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature 2008; 455: 894–902.
32. Etchegaray JP, Lee C, Wade PA, Reppert SM. Rhythmic histone acetylation underlies transcription in the mammalian circadian clock. Nature 2003; 421: 177–182.
33. Guan Z, Giustetto M, Lomvardas S et al. Integration of long-term-memory-related synaptic plasticity involves bidirectional regulation of gene expression and chromatin structure. Cell 2002; 111: 483–493.

34. Kumar A, Choi KH, Renthal W et al. Chromatin remodeling is a key mechanism underlying cocaine-induced plasticity in striatum. Neuron 2005; 48: 303–314.

35. Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nat. Neurosci. 2006; 9: 519–525.

36. Grunstein M. Histone acetylation in chromatin structure and transcription. Nature 1997; 389: 349–352.

37. Hsieh J, Gage FH. Chromatin remodeling in neural development and plasticity. Curr. Opin. Cell Biol. 2005; 17: 664–671.

38. Brownell JE, Zhou J, Ranalli T et al. Tetrahydrenoma histone acetyltransferase a: A homolog to yeast Gcn5p linking histone acetylation to gene activation. Cell 1996; 84: 843–851.

39. Ogryzko VV, Schultz RL, Russanova V, Howard BH, Nakatani Y. The transcriptional coactivators p300 and CBP are histone acetyltransferases. Cell 1996; 87: 953–959.

40. Whittle JR, Powell MJ, Popov VM, Shirley LA, Wang C, Pestell RG. Sirtuins, nuclear hormone receptor acetylation and transcriptional regulation. Trends Endocrinol. Metab. 2007; 18: 356–364.

41. Bao J, Sack MN. Protein deacetylation by sirtuins: Delineating a post-translational regulatory program responsive to nutrient and redox stressors. Cell. Mol. Life Sci. 2010; 67: 3073–3087.

42. Sassone-Corsi P. Minireview: NAD+, a circadian metabolite with an epigenetic twist. Endocrinology 2012; 153: 1–5.

43. Michan S, Sinclair D. Sirtuins in mammals: Insights into their biological function. Biochem. J. 2007; 404: 1–13.

44. Herskovits AZ, Guarante L. SIRT1 in neurodevelopment and brain senescence. Neuroen 2014; 81: 471–483.

45. de Kloet ER, Oitzl MS, Joels M. Stress and cognition: Are corticosteroids good or bad guys? Trends Neurosci. 1999; 22: 422–426.

46. Bath KG, Jing DQ, Dincheva I et al. BDNF Val66Met impairs fluoxetine-induced enhancement of adult hippocampus plasticity. Neuropsychopharmacology 2012; 37: 1297–1304.

47. Ampuero E, Rubio FJ, Falcon R et al. Chronic fluoxetine treatment induces structural plasticity and selective changes in glutamate receptor subunits in the rat cerebral cortex. Neuroscience 2010; 169: 98–108.

48. Bessa JM, Ferreira D, Melo I et al. The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. Mol. Psychiatry 2009; 14: 739, 764–739, 773.

49. Magarinos AM, McEwen BS. Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: Comparison of stressors. Neuroscience 1995; 69: 83–88.

50. Levenson JM, Sweatt JD. Epigenetic mechanisms in memory formation. Nat. Rev. Neurosci. 2005; 6: 108–118.

51. Levenson JM, O’Riordan KJ, Brown KD, Trinh MA, Molfese DL, Sweatt JD. Regulation of histone acetylation during memory formation in the hippocampus. J. Biol. Chem. 2004; 279: 40545–40559.

52. Guan JS, Haggarty SJ, Giacometti E et al. HDAC2 negatively regulates memory formation and synaptic plasticity. Nature 2009; 459: 55–60.

53. Graff J, Rei D, Guan JS et al. An epigenetic blockade of cognitive functions in the neurodegenerating brain. Nature 2012; 483: 222–226.

54. Darcy MJ, Calvin K, Cavnar K, Ouimet CC. Regional and subcellular distribution of HDAC4 in mouse brain. J. Comp. Neurol. 2010; 518: 722–740.

55. Schlumm F, Mauerci D, Freitage HE, Bading H. Nuclear calcium signaling regulates nuclear export of a subset of class IIa histone deacetylases following synaptic activity. J. Biol. Chem. 2013; 288: 8074–8084.

56. Uchida S, Shumyataksy GP. Synaptically localized transcriptional regulators in memory formation. Neuroscience 2017. https://doi.org/10.1016/j.neuroscience.2017.07.023

57. Paroni G, Cernotta N, Dello Russo C et al. PP2A regulates HDAC4 nuclear import. Mol. Biol. Cell 2008; 19: 655–667.

58. Bolger TA, Yao TP. Intracellular trafficking of histone deacetylase 4 regulates neuronal cell death. J. Neurosci. 2005; 25: 9544–9553.

59. Chen B, Cepko CL. HDAC4 regulates neuronal survival in normal and diseased retinas. Science 2009; 323: 256–259.

60. Sando R III, Gounko N, Pieraut S, Liao L, Yates J III, Maximov A. HDAC4 governs a transcriptional program essential for synaptic plasticity and memory. Cell 2012; 151: 821–834.

61. Kim MS, Akhtar MW, Adachi M et al. An essential role for histone deacetylase 4 in synaptic plasticity and memory formation. J. Neurosci. 2012; 32: 10879–10886.

62. Taladowska M, Berk M, Maes M, Galecki P. Autobiographical memory dysfunctions in depressive disorders. Psychiatry Clin. Neurosci. 2016; 70: 100–108.

63. MacQueen GM, Memedovich KA. Cognitive dysfunction in major depression and bipolar disorder: Assessment and treatment options. Psychiatry Clin. Neurosci. 2017; 71: 18–27.

64. Kessler RC. The effects of stressful life events on depression. Annu. Rev. Psychol. 1997; 48: 191–214.

65. Pittenger C, Duman RS. Stress, depression, and neuroplasticity: A convergence of mechanisms. Neuropsychopharmacology 2008; 33: 88–109.

66. Covington HE III, Maze I, LaPlant QC et al. Antidepressant actions of histone deacetylase inhibitors. J. Neurosci. 2009; 29: 11451–11460.
67. Hunter RG, McCarthy KJ, Milne TA, Pfaff DW, McEwen BS. Regulation of hippocampal H3 histone methylation by acute and chronic stress. *Proc. Natl. Acad. Sci. U. S. A.* 2009; 106: 20912–20917.

68. Nestler EJ. Epigenetic mechanisms of depression. *JAMA Psychiatry* 2014; 71: 454–456.

69. Covington HE III, Maze I, Sun H et al. A role for repressive histone methylation in cocaine-induced vulnerability to stress. *Neuron* 2011; 71: 656–670.

70. Weaver IC, Cervoni N, Champagne FA et al. Epigenetic programming by maternal behavior. *Nat. Neurosci.* 2004; 7: 847–854.

71. Schroeder FA, Lin CL, Crusio WE, Akbarian S. Antidepressant-like effects of the histone deacetylase inhibitor, sodium butyrate, in the mouse. *Biol. Psychiatry* 2007; 62: 55–62.

72. Han A, Sung VB, Chung SY, Kwon MS. Possible additional antidepressant-like mechanism of sodium butyrate: Targeting the hippocampus. *Neuropharmacology* 2014; 81: 292–302.

73. Yamawaki Y, Fuchikami M, Morinobu S, Segawa M, Matsumoto T, Yamawaki S. Antidepressant-like effect of sodium butyrate (HDAC inhibitor) and its molecular mechanism of action in the rat hippocampus. *World J. Biol. Psychiatry* 2012; 13: 458–467.

74. Covington HE III, Maze I, Vialou V, Nestler EJ. Antidepressant-like action of HDAC inhibition in the prefrontal cortex. *Neuroscience* 2015; 298: 329–335.

75. Meylan EM, Halfon O, Magistretti PJ, Cardinaux JR. The HDAC inhibitor SAHA improves depressive-like behavior of CRTC1-deficient mice: Possible relevance for treatment-resistant depression. *Neuropharmacology* 2016; 107: 111–121.

76. Schroeder FA, Lewis MC, Fass DM et al. A selective HDAC 1/2 inhibitor modulates chromatin and gene expression in brain and alters mouse behavior in two mood-related tests. *PLoS One* 2013; 8: e71323.

77. Ebruru M, Munoz-Cobo I, Diaz-Perdigon T et al. SIRT2 inhibition modulate glutamate and serotonin systems in the prefrontal cortex and induces antidepressant-like action. *Neuropharmacology* 2017; 117: 195–208.

78. Munoz-Cobo I, Belloch FB, Diaz-Perdigon T, Puerta E, Tordera RM. SIRT2 inhibition reverses anhedonia in the VGLUT1−/− depression model. *Behav. Brain Res.* 2017; 335: 128–131.

79. Sales AJ, Joca SR. Effects of DNA methylation inhibitors and conventional antidepressants on mice behaviour and brain DNA methylation levels. *Acta Neuropsychiatr.* 2016; 28: 11–22.

80. LaPlant Q, Vialou V, Covington HE III et al. Dnmt3a regulates emotional behavior and spine plasticity in the nucleus accumbens. *Nat. Neurosci.* 2010; 13: 1137–1143.

81. Hobara T, Uchida S, Otsuki K et al. Altered gene expression of histone deacetylases in mood disorder patients. *J. Psychiatr. Res.* 2010; 44: 263–270.
101. Luo XJ, Zhang C. Down-regulation of SIRT1 gene expression in major depressive disorder. Am. J. Psychiatry 2016; 173: 1046.

102. Portela A, Esteller M. Epigenetic modifications and human disease. Nat. Biotechnol. 2010; 28: 1057–1068.

103. McGowan PO, Sasaki A, D’Alessio AC et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat. Neurosci. 2009; 12: 342–348.

104. Keller S, Sarchiapone M, Zarrilli F et al. DNA methylation of the Crf gene in adult mice. Eur. J. Biochem. 2003; 270: 87–95.

105. Jeltsch A. The human Dnmt2 promoter methylation in the Wernicke area of suicide subjects. Arch. Gen. Psychiatry 2010; 67: 258–267.

106. Jeltsch A. On the enzymatic properties of Dnmt1: Specificity, processivity, mechanism of linear diffusion and allosteric regulation of the enzyme. Epigenetics 2006; 1: 63–66.

107. Pradhan S, Bacolla A, Wells RD, Roberts RJ. Recombinant human DNA (cytosine-5) methyltransferase I. Expression, purification, and comparison of de novo and maintenance methylation. J. Biol. Chem. 1999; 274: 33002–33010.

108. Fatemi M, Hermann A, Gowher H, Jeltsch A. Dnmt3a and Dnmt1 functionally cooperate during de novo methylation of DNA. Eur. J. Biochem. 2002; 269: 4981–4984.

109. Bourchis D, Xu GL, Lin CS, Bollman B, Bestor TH. Dnmt3L and the establishment of maternal genomic imprints. Science 2001; 294: 2536–2539.

110. Xie S, Wang Z, Okano M et al. Cloning, expression and chromosome locations of the human DNMT3 gene family. Gene 1999; 236: 87–95.

111. Hermann A, Schmitt S, Jeltsch A. The human Dnmt2 has residual DNA-(cytosine-C5) methyltransferase activity. J. Biol. Chem. 2003; 278: 37171–37121.

112. Day JJ, Sweat JD. DNA methylation and memory formation. Nat. Neurosci. 2010; 13: 1319–1323.

113. Nusslock R, Miller GE. Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis. Biol. Psychiatry 2016; 80: 23–32.

114. Franklin TB, Saab BJ, Mansuy IM. Neural mechanisms of stress resilience and vulnerability. Neuron 2012; 75: 747–761.

115. Uchida S, Hara K, Kobayashi A et al. Early life stress enhances behavioral vulnerability to stress through the activation of REST4-mediated gene transcription in the medial prefrontal cortex of rodents. J. Neurosci. 2010; 30: 15007–15108.

116. Uchida S, Hara K, Kobayashi A et al. Maternal and genetic factors in stress-resilient and -vulnerable rats: A cross-fostering study. Brain Res. 2010; 1316: 43–50.

117. Poletti S, Aggio V, Brioschi S, Dallaspesia S, Colombo C, Benedetti F. Multidimensional cognitive impairment in unipolar and bipolar depression and the moderator effect of adverse childhood experiences. Psychiatry Clin. Neurosci. 2017; 71: 309–317.

118. Meaney MJ, Szyf M. Maternal care as a model for experience-dependent chromatin plasticity? Trends Neurosci. 2005; 28: 456–463.

119. Kessler RC, McGonagle KA, Zhao S et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch. Gen. Psychiatry 1994; 51: 8–19.

120. Martin LA, Neighbors HW, Griffith DM. The experience of symptoms of depression in men vs women: Analysis of the National Comorbidity Survey Replication. JAMA Psychiatry 2013; 70: 1100–1106.

121. Hodes GE, Pfau ML, Purushothaman I et al. Sex differences in nucleus accumbens transcriptome profiles associated with susceptibility versus resilience to subchronic variable stress. J. Neurosci. 2015; 35: 16362–16376.

122. Poulter MO, Du L, Weaver IC et al. GABAA receptor promoter hypermethylation in suicide brain: Implications for the involvement of epigenetic processes. Biol. Psychiatry 2008; 64: 645–652.

123. Chahrour M, Jung SY, Shaw C et al. MeCP2, a key contributor to neurological disease, activates and represses transcription. Science 2008; 320: 1224–1229.

124. Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the BDNF gene. Biol. Psychiatry 2009; 65: 760–769.

125. Elliott E, Ezra-Nevo G, Regev L, Neufeld-Cohen A, Chen A. Resilience to social stress coincides with functional DNA methylation of the Crf gene in adult mice. Nat. Neurosci. 2010; 13: 1351–1353.

126. Numata S, Ishii K, Tajima A et al. Blood diagnostic biomarkers for major depressive disorder using multiplex DNA methylation profiles: Discovery and validation. Epigenetics 2015; 10: 135–141.

127. Fuchikami M, Morinobu S, Segawa M et al. DNA methylation profiles of the brain-derived neurotrophic factor (BDNF) gene as a potent diagnostic biomarker in major depression. PLoS One 2011; 6: e23881.

128. Kang HJ, Kim JM, Lee JY et al. BDNF promoter methylation and suicidal behavior in depressive patients. J. Affect. Disord. 2013; 151: 679–685.

129. Sugawara H, Bundy M, Ishigooka J, Iwamoto K, Kato T. Epigenetic regulation of serotonin transporter in psychiatric disorders. J. Genet. Genomics 2013; 40: 325–329.
130. Fabbri C, Serretti A. Pharmacogenetics of major depressive disorder: Top genes and pathways toward clinical applications. *Curr. Psychiatry Rep.* 2015; 17: 50.

131. Porelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. *Eur. Neuropsychopharmacol.* 2012; 22: 239–258.

132. Okada S, Morinobu S, Fuchikami M et al. The potential of SLC6A4 gene methylation analysis for the diagnosis and treatment of major depression. *J. Psychiatr. Res.* 2014; 53: 47–53.

133. Sugawara H, Iwamoto K, Bundo M et al. Hypermethylation of serotonin transporter gene in bipolar disorder detected by epigenome analysis of discordant monozygotic twins. *Transl. Psychiatry* 2011; 1: e24.

134. Kosik KS. The neuronal microRNA system. *Nat. Rev. Neurosci.* 2006; 7: 911–920.

135. Bartel DP. MicroRNAs: Target recognition and regulatory functions. *Cell* 2009; 136: 215–233.

136. Rajasethupathy P, Fiumara F, Sheridan R et al. Characterization of small RNAs in Aplysia reveals a role for miR-124 in constraining synaptic plasticity through CREB. *Neuron* 2009; 63: 803–817.

137. Schratt GM, Tuebing F, Nigh EA et al. CREB. *Mol. Psychiatry* 2015; 20: 677–684.

138. Issler O, Chen A. Determining the role of microRNAs in psychiatric disorders. *Nat. Rev. Neurosci.* 2015; 16: 201–212.

139. Dwivedi Y. Emerging role of microRNAs in major depressive disorder: Diagnosis and therapeutic implications. *Dialogues Clin. Neurosci.* 2014; 16: 43–61.

140. Im HL, Kenny PJ. MicroRNAs in neuronal function and dysfunction. *Trends Neurosci.* 2012; 35: 325–334.

141. Issler O, Haramati S, Paul ED et al. MicroRNA 135 is essential for chronic stress resiliency, antidepressant efficacy, and intact serotoninergic activity. *Neuron* 2014; 83: 344–360.

142. Haramati S, Navon I, Issler O et al. MicroRNA as repressors of stress-induced anxiety: The case of amygdalar miR-34. *J. Neurosci.* 2011; 31: 14191–14203.

143. Dias C, Feng I, Sun H et al. Beta-catenin mediates stress resilience through Dicer1/microRNA regulation. *Nature* 2014; 516: 51–55.

144. Baudry A, Mouillet-Richard S, Schneider B, Launay JM, Kellermann O. miR-16 targets the serotonin transporter: A new facet for adaptive responses to antidepressants. *Science* 2010; 329: 1537–1541.

145. Uchida S, Nishida A, Hara K et al. Characterization of the vulnerability to repeated stress in Fischer 344 rats: Possible involvement of microRNA-mediated downregulation of the glucocorticoid receptor. *Eur. J. Neurosci.* 2008; 27: 2250–2261.

146. O’Carroll D, Schaefer A. General principals of miRNA biogenesis and regulation in the brain. *Neuropsychopharmacology* 2013; 38: 39–54.

147. Cheng LC, Pastrana E, Tavazoie M, Doetsch F. miR-124 regulates adult neurogenesis in the subventricular zone stem cell niche. *Nat. Neurosci.* 2009; 12: 399–408.

148. Cao X, Pfaff SL, Gage FH. A functional study of miR-124 in the developing neural tube. *Genes Dev.* 2007; 21: 531–536.

149. Smirnova L, Grafe A, Seiler A, Schumacher S, Nitsch R, Wulczyn FG. Regulation of miRNA expression during neural cell specification. *Eur. J. Neurosci.* 2005; 21: 1469–1477.

150. Roy B, Dunbar M, Shetlon RC, Dwivedi Y. Identification of MicroRNA-124-3p as a putative epigenetic signature of major depressive disorder. *Neuropsychopharmacology* 2017; 42: 864–875.

151. He S, Liu X, Jiang K et al. Alterations of microRNA-124 expression in peripheral blood mononuclear cells in pre- and post-treatment patients with major depressive disorder. *J. Psychiatr. Res.* 2016; 78: 65–71.

152. Hayashi-Takagi A, Yagishita S, Nakamura M et al. Labeling and optical erasure of synaptic memory traces in the motor cortex. *Nature* 2015; 525: 333–338.

153. Shirai F, Hayashi-Takagi A. Optogenetics: Applications in psychiatric research. *Psychiatry Clin. Neurosci.* 2017; 71: 363–372.

154. Wellen KE, Hatizavassiliou G, Sachdeva UM, Bui TV, Cross JR, Thompson CB. ATP-citrate lyase links cellular metabolism to histone acetylation. *Science* 2009; 324: 1076–1080.

155. Mews P, Donahue G, Drake AM, Luczak V, Abel T, Berger SL. Acetyl-CoA synthetase regulates histone acetylation and hippocampal memory. *Nature* 2017; 546: 381–386.

156. Bigio B, Mathe AA, Sousa VC et al. Epigenetics and energetics in ventral hippocampus mediaterapid antidepressant action: Implications for treatment resistance. *Proc. Natl. Acad. Sci. U. S. A.* 2016; 113: 7906–7911.

157. Lau T, Bigio B, Zelli D, McEwen BS, Nasca C. Stress-induced structural plasticity of medial amygdala stellate neurons and rapid prevention by a candidate antidepressant. *Mol. Psychiatry* 2017; 22: 227–234.

158. Hastings RS, Parsey RV, Oquendo MA, Arango V, Mann JJ. Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology* 2004; 29: 952–959.

159. Kong L, Chen K, Womer F et al. Alterations of microRNA-124 expression in peripheral blood mononuclear cells in pre- and post-treatment patients with major depressive disorder. *J. Psychiatr. Res.* 2016; 78: 65–71.

160. Kaufman J, Sullivan GM, Yang J et al. Alterations of microRNA-124 expression in peripheral blood mononuclear cells in pre- and post-treatment patients with major depressive disorder. *J. Psychiatr. Res.* 2016; 78: 65–71.

161. Hayashi-Takagi A, Yagishita S, Nakamura M et al. Labeling and optical erasure of synaptic memory traces in the motor cortex. *Nature* 2015; 525: 333–338.

162. Shirai F, Hayashi-Takagi A. Optogenetics: Applications in psychiatric research. *Psychiatry Clin. Neurosci.* 2017; 71: 363–372.

163. Wellen KE, Hatizavassiliou G, Sachdeva UM, Bui TV, Cross JR, Thompson CB. ATP-citrate lyase links cellular metabolism to histone acetylation. *Science* 2009; 324: 1076–1080.

164. Mews P, Donahue G, Drake AM, Luczak V, Abel T, Berger SL. Acetyl-CoA synthetase regulates histone acetylation and hippocampal memory. *Nature* 2017; 546: 381–386.

165. Bigio B, Mathe AA, Sousa VC et al. Epigenetics and energetics in ventral hippocampus mediate rapid antidepressant action: Implications for treatment resistance. *Proc. Natl. Acad. Sci. U. S. A.* 2016; 113: 7906–7911.

166. Lau T, Bigio B, Zelli D, McEwen BS, Nasca C. Stress-induced structural plasticity of medial amygdala stellate neurons and rapid prevention by a candidate antidepressant. *Mol. Psychiatry* 2017; 22: 227–234.

167. Hastings RS, Parsey RV, Oquendo MA, Arango V, Mann JJ. Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology* 2004; 29: 952–959.

168. Kong L, Chen K, Womer F et al. Sex differences of gray matter morphology in cortico-limbic-striatal neural system in major depressive disorder. *J. Psychiatr. Res.* 2013; 47: 733–739.

169. Kaufman J, Sullivan GM, Yang J et al. Quantification of the serotonin 1A receptor using PET: Identification of a potential biomarker of major depression in males. *Neuropsychopharmacology* 2015; 40: 1692–1699.

170. Underwood MD, Kassir SA, Bakalian MJ, Galfalvy H, Mann JJ, Arango V. Neuron density and serotonin
receptor binding in prefrontal cortex in suicide. *Int. J. Neuropsychopharmacol.* 2012; 15: 435–447.

163. Bangasser DA, Valentino RJ. Sex differences in stress-related psychiatric disorders: Neurobiological perspectives. *Front. Neuroendocrinol.* 2014; 35: 303–319.

164. Fuchikami M, Yamamoto S, Morinobu S, Okada S, Yamawaki Y, Yamawaki S. The potential use of histone deacetylase inhibitors in the treatment of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2016; 64: 320–324.

165. Adwan L, Zawia NH. Epigenetics: A novel therapeutic approach for the treatment of Alzheimer’s disease. *Pharmacol. Ther.* 2013; 139: 41–50.

166. Mack SC, Hubert CG, Miller TE, Taylor MD, Rich JN. An epigenetic gateway to brain tumor cell identity. *Nat. Neurosci.* 2016; 19: 10–19.

167. Qiu X, Xiao X, Li N, Li Y. Histone deacetylases inhibitors (HDACis) as novel therapeutic application in various clinical diseases. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2017; 72: 60–72.

168. Tyler DS, Vappiani J, Caneque T et al. Click chemistry enables preclinical evaluation of targeted epigenetic therapies. *Science* 2017; 356: 1397–1401.

169. Ricq EL, Hooker JM, Haggarty SJ. Toward development of epigenetic drugs for central nervous system disorders: Modulating neuroplasticity via H3K4 methylation. *Psychiatry Clin. Neurosci.* 2016; 70: 536–550.

170. Uchida S, Teubner BJ, Hevi C et al. CRTC1 nuclear translocation following learning modulates memory strength via exchange of chromatin remodeling complexes on the Fgf1 gene. *Cell Rep.* 2017; 18: 352–366.