HHS Public Access

Author manuscript

Mol Psychiatry. Author manuscript; available in PMC 2015 December 01.

Published in final edited form as:

Mol Psychiatry. 2015 June ; 20(6): 677–684. doi:10.1038/mp.2015.30.

Noncoding RNAs and neurobehavioral mechanisms in psychiatric disease

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Abstract

The human genome project has revolutionized our understanding of the underlying mechanisms in psychiatric disease. It is now abundantly clear that neurobehavioral phenotypes are epigenetically controlled by noncoding RNAs (ncRNAs). The microRNA (miRNA) class of ncRNAs are ubiquitously expressed throughout the brain and govern all major neuronal pathways. The attractive therapeutic potential of miRNAs is underscored by their pleiotropic capacities, putatively targeting multiple pathways within a single neuron. Many psychiatric diseases stem from a multi-factorial origin, thus conventional drug targeting of single proteins may not prove most effective. In this exciting post-genome sequencing era, many new epigenetic targets are emerging for therapeutic investigation. Here we review the reported roles of miRNAs, as well as other ncRNA classes, in the pathology of psychiatric disorders; there are both common and unique ncRNA mechanisms that influence the various diagnoses. Collectively, these potent epigenetic regulators may clarify the disrupted signaling networks in psychiatric phenotypes.

Introduction

A groundbreaking paradigm shift, the discovery of noncoding RNAs (ncRNAs), established the conventional “one gene, one protein” model to be an oversimplified view of gene regulation. Numerous ncRNA classes are now implicated in central nervous system (CNS) functions; microRNAs (miRNAs), natural antisense transcripts (NATs) and long intergenic RNAs (LincRNAs) all have reported regulatory activities in the brain [1-4]. While pleiotropic ncRNAs, including miRNAs, can target large numbers of genes and signaling pathways simultaneously [5, 6], there are also ncRNAs, such as NATs [2], which hybridize to a limited

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Conflict of Interest: The authors declare no conflict of interest.

and precise subset of candidates. Growing evidence indicates that distinct neuronal ncRNA mechanisms, particularly miRNAs, likely influence the development of psychiatric disease. Here we review the role of miRNAs in the neurobehavioral deficits of CNS disorders and also discuss the reported contributions of other ncRNA classes.

Neuronal and synaptic miRNA biology

miRNAs have recently emerged as a global regulator of gene expression and, ultimately, effector of synaptic physiology. These miRNAs function by several mechanisms, including ribosomal RNA modifications, repression of mRNA expression by RNA interference, alternative splicing, and regulatory mechanisms mediated by RNA-RNA interactions. The processing from a primary (pri) transcript to precursor (pre) and mature miRNA in the brain requires the standard miRNA biogenesis machinery, including Drosha, Dicer, DGCR8, and argonaute (Ago) proteins [7, 8]. Functional knockdown of Dicer, which processes the pre-miRNA to its mature transcript, leads to reduced neuronal size and branching as well as aberrant axonal pathfinding [9-11]. Correspondingly, mice with genetic knockout of the pri-miRNA processing protein DGCR8 display a loss of synaptic connectivity and reduced number and size of dendritic spines [12, 13]. At the behavioral level, these mice display impaired spatial working memory-dependent tasks [12]. Interestingly, it has been shown that miRNAs are formed in part by processing of pre-miRNAs locally within dendritic spines [14, 15]. Furthermore, synaptic stimulation leads to local processing of pre-miRNAs in proximity to the synapse [16-18]; a cohort of miRNAs are localized within the synapse, including miR-219-5p, miR-124, miR-134, miR-138, and miR-125b [19, 20]. These miRNAs directly impact learning and memory behaviors, neurotransmission, neurogenesis among other functions [1, 21-24] and their disruption contribute to psychiatric impairments [25].

A subset of miRNAs mediate neuronal specification, maturation and function. The transition from neural stem cells (NSCs) to neural progenitors and ultimately to fully differentiated neurons is highly regulated by a complex interaction of miRNAs and other factors [24]. In general, let-7 [26, 27], miR-124 [28-30] and miR-9 [31] are thought to reduce NSC proliferation and promote neuronal differentiation. It is typically held that miR-134 [32] and miR-25 [33] induce the proliferation and/or inhibit the differentiation of NSCs and neural progenitors. In parallel, miR-137 both decreases [34, 35] and increases [36, 37] NSC proliferation, either enhancing or opposing neuronal maturation. There is an intricate overlap and feedback occurring between these key miRNAs, mediated in part by their target genes. Notably, miRNAs may mediate neurogenesis throughout development from embryo to adult. Adult neurogenesis is reportedly decreased in neurodegenerative disease [38, 39] and depression [40], and is modulated by antidepressant therapeutics [41]. Thus, the following discussions regarding miRNA pathways in psychiatric disorders (outlined in Table 1) may involve neurons derived at all stages of brain maturity.

miRNA modulation of behavioral phenotypes in psychiatric diseases

Schizophrenia and bipolar disorder

Substantial evidence indicates that miRNAs mediate schizophrenia phenotypes through a variety of mechanistic pathways. The copy number variant (CNV) at 22q11.2, resulting in

DiGeorge syndrome, is the most common rare variant identified in schizophrenia, occurring in approximately one percent of patients [42]. Many children with 22q11.2 deletion syndrome have developmental delays and learning disabilities, with a substantially elevated risk of developing schizophrenia (30%) [43]. Though the 22q11.2 region contains 30 to 40 genes, many have not been well characterized; one notable gene is DiGeorge syndrome critical region gene 8 (*DGCR8*), an essential contributor to microRNA biogenesis [8]. Microdeletion of 22q11.2 in mice results in the downregulation of a cluster of miRNAs with corresponding changes in cognitive and behavioral functions[12].

Of the common genetic variants enriched in patients with schizophrenia, there is a well-established signal at miR-137 and several of its target genes [44-46]. Schizophrenia patients with a miR-137 risk allele exhibit greater symptom severity [47], significantly altered functional connectivity [48], reduced white matter integrity, smaller hippocampi and larger lateral ventricles [49]. Functionally validated targets of miR-137 include such schizophrenia risk genes as CACNA1C [50], TCF4 [50] and ZNF804A [51], while additional putative targets include ERBB4, GABRA1, GRIN2A, GRM5, GSK3B, NRG2, and HTR2C [52]. Overexpression of miR-137 in a human NSC line identified direct and indirect miR-137 targets in neural cells. While direct miR-137 targets were enriched for transcription factors and cell cycle genes, indirect targets included pathways enriched in schizophrenia genome wide association studies, particularly major histocompatibility complex, synapses, FMRP interacting RNAs and calcium channels [53]. More recently, the largest study of common variance identified 108 regions significantly associated with schizophrenia, including significant hits at miR-137 and miR-548 [46].

Post-mortem profiling of miRNA expression in the prefrontal cortex of schizophrenia patients identified a global increase in miRNA expression compared to control populations [54]. More specifically, although the mature and pre-miRNA species were increased (particularly of miR-181b and miR-26b), there was no significant difference in transcription of the source pri-miRNA. These results suggest that the changes were due to increased miRNA biogenesis rather than altered miRNA transcription. The authors further observed upregulated expression of Drosha and DGCR8, both of which are involved in pri-miRNA processing, and speculate this is the ultimate cause of aberrant miRNA levels. Additionally, human analyses have started to reveal a profile signature of miRNA dysregulation in peripheral tissues such as plasma and serum of schizophrenia patients. Intriguingly, plasma levels of miR-181b (discussed above) were found to predict response to antipsychotic treatment [55]; correspondingly, miR-30e has also been postulated as a plasma biomarker of schizophrenia [56].

NMDA-R signaling, one of the most consistently implicated pathways in schizophrenia, is strongly controlled by miR-219 [57]. Notably, miR-219 is the most enriched miRNA in the human synapse, the most downregulated in cortical synaptosomes of schizophrenia patients [20], and was dysregulated in cortical tissue from two patient cohorts [20, 54]. Moreover, neuronal inhibition of miR-219-5p in mice significantly altered the precipitation of schizophrenia behavior by NMDA-R antagonists [57]. Taken together, miR-219-5p actively mediates synaptic functions and the development of psychiatric phenotypes. NMDA-R also regulates miR-132 [21, 58-63], which is implicated in learning and memory functions [21, 59],

long-term potentiation [58-61] and neurotransmission [61]. miR-132 expression is repressed in mice with genetic disruption of the enzyme which produces the NMDA-R co-agonist D-serine [64], and these D-serine deficient mice recapitulate some of the neurobehavioral and cognitive impairments presented in patients with schizophrenia. Expression of miR-132 was dysregulated in human cortical tissue from two schizophrenia datasets but those expression changes were in opposite directions [20, 21]; it remains possible that miR-132 is disrupted in specific neuronal cell types or distinct subcellular regions of neurons in schizophrenia. Interestingly, the NMDA-R regulated transcripts miR-132 and miR-219-5p (discussed above) [65, 66] regulate circadian rhythm, which is frequently disrupted in schizophrenia and other psychiatric disorders [67]. In addition, a subset of other miRNAs also reportedly regulate circadian functions, including miRs – 279, 142-3p, 185, 138, let-7b, 125a, 206 and 182 [68-76]. Indeed, miRNA regulators of NMDA-R signaling and circadian rhythm could yield new therapeutic targets for treatment of neurobehavioral deficits.

miRNA expression is responsive to current therapeutics administered for bipolar disorder, which is known to share overlapping genetic links with schizophrenia [77]. In rats treated with either lithium or valproate, there are a cohort of miRNAs altered in the hippocampus, including let-7b, let-7c, miR-128a, miR-24a, miR-30c, miR-34a, miR-221 and miR-144 [78]. Additionally, miR-134 is altered in the plasma of treated bipolar disorder patients [79]. Valproate and lithium significantly modulate Brain-Derived Neurotrophic Factor (BDNF) levels, a critical regulator of neuronal homeostasis [80, 81], which is itself regulated by both short and long ncRNAs [82-84], such as miR-124a. Notably, miR-124a is linked to depression-related behaviors [83], as discussed in the section below.

As more post-mortem datasets become publicly available, we believe that groups of consistently altered transcripts in schizophrenia and bipolar disorder will emerge and potentially converge. Combining multimodal SNP and exome sequencing genotype information with RNA and miRNA expression datasets will facilitate miRNA-mRNA correlations. Furthermore, *in vivo* studies will allow for comprehensive investigation of identified candidates. Arguably, some of the more persistent miRNA associations in schizophrenia to date implicate miR-137, miR-181b, and miR-219-5p (Table 1).

Depression

There is accumulating evidence for significant contribution of miRNA mechanisms in mood disorders such as depression. In the prefrontal cortex of depressed subjects who had died by suicide [85], 21 miRNAs were significantly down-regulated in the major depressive disorder (MDD) group. More miRNAs were down-regulated than upregulated, implying a global down-regulation of miRNA levels in MDD. Furthermore, almost half of the down-regulated miRNAs were transcribed by the same pri-miRNA gene transcripts (mir-142-5p and 142-3p; mir-494, 376a*, 496, and 369-3p; mir-23b, 27b and 24-1*; mir-34b* and 34c; mir-17* and 20a) or found within the same chromosomal region (mir-424 and 20b at Xq26.2-3, 377 kb apart; mir-142 and 301a at 17q22, 820 kb apart; mir-324-5p and 497 at 17p13.1, 205 kb apart), suggesting that the down-regulated miRNA expression may be due to decreased transcription. In addition, a set of 29 miRNAs formed an inter-connected network in the MDD group: let-7b, mir-132, 181b, 338-3p, 486-5p, and 650 were “hubs”. A recent study of

genotyping polymorphisms from three miRNA processing genes (DGCR8, AGO1, and GEMIN4) found that DGCR8 rs3757 was associated with increased risk of suicidal tendency and improvement response to antidepressant treatment, whereas AGO1 rs636832 showed decreased risk of suicidal tendency, suicidal behavior, and recurrence [86]. Thus, polymorphisms in miRNA processing genes may influence depression risk and treatment.

Molecular targets of anti-depressants frequently engage the transporters of serotonin, a monoamine neurotransmitter [87]. miRNAs regulate the serotonin transporter (SERT) and its response to serotonin reuptake inhibitor (SSRI) therapeutics. Specifically, SSRI antidepressant fluoxetine (Prozac) treatment in mice induces expression of miR-16 while repressing the miR-16 target SERT [88]. Notably, miR-16 mediates the depression-related behavior through precise control of neurogenesis [89]. Another SERT associated miRNA, miR-135, was found to control the onset of co-existing depression and anxiety symptoms in mice [90, 91] as well as the response to anti-depressant treatment [90, 91].

Because of limited studies in depressed patients, it is difficult to pinpoint specific miRNAs consistently implicated in the pathogenesis of depression; nevertheless, miRNAs that influence BDNF, including miR-132 and miR-34, and neuroinflammation, such as the let-7 family[92], may be highly relevant (Table 1). Intriguingly, miR-124a repression of BDNF provokes depression-related behaviors [83] and significantly mediates neurogenesis. Future studies could investigate if current anti-depressant therapeutics signal through miR-124a or other disease-associated miRNAs to enhance adult hippocampal neurogenesis [40, 41, 93, 94].

Stress, anxiety, and fear disorders

The link between ncRNAs and stress, anxiety, or fear related responses opens new avenues for therapeutic intervention[95]. While a range of genetic associations have been loosely implicated in Post-Traumatic Stress Disorder (PTSD) [96], epigenetic factors likely play a defining role in disease progression. A panel of disrupted miRNAs in the blood of military veterans with active PTSD symptoms have been identified [97]; these PTSD-associated miRNAs were significantly associated with immunological pathways, suggestive of their pathogenic mechanisms in the disorder. Indeed, abnormal systemic immune responses are routinely reported in stress-related conditions [98-100], consistent with its regulation by the PTSD-linked miRNAs. Intriguingly, a few of the miRNA transcripts altered in the veterans suffering from PTSD, including miR-19b and miR-223, were also perturbed in the serum and amygdala of a PTSD animal model [101].

Stress and anxiety, however, are not unique behaviors to PTSD and are provoked through many distinct triggers. Overexpression of miR-34c in the central amygdala elicited an anxiolytic-like effect in mice stressed through acute restraint [102]; furthermore, miR-34c directly targets a key mediator of stress responses, the corticotropin releasing factor receptor type 1 (CRFR1) gene. Notably, miR-34a was recently reported to regulate fear related responses through Notch signaling in mice [103]. Although miR-34a didn't alter anxiety-related parameters in the same manner as miR-34c, it is possible that the miR-34 family is central in behavioral manifestations.

In addition to the above mentioned miRNAs, miRs - 608, 124a, 132, 330-3p, and 16 are also implicated in anxiety phenotypes through genetic associations or *in vivo* analyses [104-109]. Specifically, miR-124 is linked to both anxiety and stress related behaviors through glucocorticoid and corticosteroid signaling, respectively [105, 110]. Moreover, ablation of the miRNA biogenesis enzyme Dicer in the central amygdala of mice provoked the onset of anxiety-like symptoms [102]. Mice with Dicer knockout specifically in dopaminoceptive neurons also exhibit behavioral changes, including ataxia as well as front and hind limb clasping [111]. These Dicer-related phenotypes may also be independent of neurodegenerative mechanisms [111].

Human genetic linkage studies and animal models also revealed miRNA pathways in panic or fear responses. At least four miRNAs have single- nucleotide polymorphisms (SNPs) in miRNA sequences located within panic disorder associated genes, including miR-22, miR-138-2, miR-148a, and miR-488 [112]. Furthermore, miR-128 expression is increased with the formation of fear-extinction memory in mice, which is the re-conditioning of the memory to overcome established fear behaviors [113].

An individual's ability to cope with stress is critical in the development of MDD. There is contrasting miRNA expression between rats who developed learned helpless (LH), a behavior that resembles stress-induced depression, compared to rats who did not develop depression (non-learned helpless [NLH]) in spite of receiving similar inescapable shocks [114]. One set of miRNAs showed large, significant, and consistent down-regulation in the frontal cortex of NLH rats compared to a blunted response in LH rats (miR-96, miR-141, miR-182, miR-183, miR-183*, miR-198, miR-200a, miR-200a*, miR-200b, miR-200b*, miR-200c, and miR-429). These synaptically enriched miRNAs[16] are encoded at a few shared polycistronic loci, suggesting coordinated control of their transcription, and they share 5′-seed motifs which indicate similar or overlapping sets of target mRNAs. Interestingly, half of this set are predicted to hit Creb1 as a target, and binding sites for CREB lie upstream of miR-96, miR-182, miR-183, miR-200a, miR-200b, miR-200c, miR-220a*, and miR-200b*. This suggests that a feedback loop arrangement may also exist between Creb and Creb-stimulated miRNAs and target genes [115]. Because these miRNAs are down regulated in NLH rats, but not LH rats, this can be interpreted as a homeostatic response intended to minimize repressive effects on Creb1.

Although more studies are needed to identify a list of miRNAs associated with stress, anxiety and fear, some putative candidates are emerging (Table 1). As discussed previously, miR19b and miR-223 were dysregulated in human and animal models of PTSD [97, 101] and should be evaluated further for therapeutic targeting in trauma-induced stress. Notably, these two transcripts share over 80 bioinformatic mRNA targets through Targetscan prediction. Additionally, the miR-34 family may exhibit an overlapping role in anxiety and fear responses [102, 103]. Overall, replication studies in human and animals will further define persistent miRNA mechanisms in these neurobehavioral deficits.

Long ncRNAs and the interaction between ncRNA transcripts in psychiatric disease

Although miRNAs are arguably the most extensively characterized class of ncRNA in neurons, long ncRNAs (lncRNA) are increasingly implicated in CNS functions [4, 116-118]. Long ncRNAs acts as miRNA sponges and can bind proteins and RNAs that regulate transcriptional changes and epigenetic modifications of chromatin. Indeed, these transcripts regulate basic neuronal biology as well as genes with strong disease-association [4, 116-122]. BC1, one of the first lncRNA transcripts characterized in the brain, is now known to modulate metabotropic receptor signaling [123, 124]. Select members of the NAT class of ncRNAs in the brain are functional and modulate expression of their sense partner [2, 82]; NATs are endogenously transcribed and exhibit at least partial sequence complimentarity to protein-coding genes, ranging from short to long in nucleotide length [2]. An emerging area of investigation indicates that long and short neuronal ncRNAs are co-regulatory [125], which is discussed more throughout the following sections. For example, the BACE1 gene linked to psychiatric and cognitive deficits in Alzheimer's Disease (AD)] is reportedly modulated by a network of competitive ncRNA interactions [126]. More specifically, it was shown that miR-485-5p binding sites in BACE1 are masked through a long antisense transcript, BACE1-AS [126].

Evidence demonstrates that lncRNAs participate in neural plasticity, supported by the expression of a large number of these transcripts in dendrites [127]. In addition, a genome-wide analysis show that lncRNAs are modulated by neuronal activity in human brain [128]. LncRNAs also mediate neurogenesis, neurodevelopment and related pathways [129, 130]. Reports suggest that fine-tuned regulatory control of the embryonic brain by these transcripts is required for development of mature CNS functions [130]. Mouse knockout studies involving long-intergenic ncRNAs (lincRNAs) found that loss of function for linc–Brn1b results in a reduction of cerebral cortex progenitor cells and abnormal cortical lamination amongst other pathologies [3]. Furthermore, a subset of lincRNAs bind miRNAs and inhibit their functions (i.e. miRNA sponge), which can reportedly disrupt brain development [125]. Circular ncRNAs (circRNA) were also recently reported to function as miRNA sponges in neurons. For example, a circRNA was found to have multiple miRNA binding sites, including for miR-7, and both were co-expressed in neocortical and hippocampal neurons [131]. These studies further indicate the importance of interactions between ncRNAs in the brain and the need to uncover their epigenetic networks.

Neurotrophins, which play a key role in maintaining homeostatic activity in the CNS, reportedly respond to lncRNA signaling. For example, the neurotrophin BDNF has sequence complementarity with a conserved NAT, termed BDNF-AS. Functionally, BDNF-AS was reported to modulate neuronal growth *in vitro* and *in vivo* [82]. The sequence complementarity of this noncoding transcript appears to extend into the 3′ untranslated region (3′UTR) of BDNF, which contains regulatory miRNA binding sites such as miR-124a. miR-124, as discussed in previous sections, modulates depression and related neurobehavioral deficits; it is possible that the BDNF-AS partly functions by preventing miR-124 from binding to BDNF.

Susceptibility genes that precipitate psychiatric symptoms are also subject to lncRNA modulation. For example, an endogenous noncoding antisense transcript to the *HTT* gene (HTTAS) functionally regulates *HTT* expression[119], which is the primary genetic aberration in HD and associated cognitive and neurobehavioral pathology. Susceptibility genes for schizophrenia are also epigenetically controlled by lncRNAs. Genetic variations in the Disrupted in Schizophrenia 1 (DISC1) gene are consistently linked with schizophrenia-associated behaviors [132, 133]. A recent report suggests the lncRNA Gomafu mediates DISC1 splicing events, resulting in splice variants linked to schizophrenia [134]. Gomafu, is implicated in neural development [129] and is downregulated in cortical tissue of schizophrenia patients and in activated human neuronal cells [134]. Additionally, DISC1 is regulated by its lncRNA antisense transcript DISC2 [120-122, 132]. Several groups have reported genetic association of DISC2 with schizophrenia as well as other psychiatric disorders [120-122, 132]; however, DISC2 is not conserved among species [132], hampering investigation of its regulatory mechanisms. One intriguing possibility is the existence of regulatory loop between DISC1 and the two ncRNA transcripts DISC2 and Gomafu.

Recent peripheral blood profiling studies also identified significant disruption of lncRNAs in depression, specifically patients with MDD, 17 of which were documented as depression-related gene in previous studies [135]. In parallel, this study uncovered potential miRNA-mRNA networks that are consistent with genes previously associated with depression. Future studies could investigate co-regulatory mechanisms between the dysregulated miRNAs and lncRNAs in the disease. Additionally, the lncRNA antisense transcript coded by LOC285758 has been implicated in violent suicide completers [136], likely triggered through depression or other psychiatric disorders.

Similar to miRNAs, it is possible some of the lncRNAs listed above may mediate the development of the distinct psychiatric symptoms through control of circadian genes. Global transcriptome profiling studies indicate that lncRNAs, including NATs, epigenetically regulate circadian biology [137, 138]. Indeed, an antisense RNA to a circadian gene in Neurospora, termed qrf, is regulated by light and represses the expression of its sense partner frq, through chromatin modifications [139].

Summary

Regulating neural plasticity, neurogenesis, and numerous behavioral phenotypes, it is clear that ncRNAs contribute to the pathogenesis of many psychiatric disorders. Moreover, direct evidence comes from human postmortem brain and animal studies indicating perturbed ncRNA levels in disparate disease such as Huntington's, schizophrenia, depression, PTSD among others.

Despite these findings, one needs to find an integrated view of these ncRNA network(s). It is known that differential co-expression of distinct miRNA groups can directly mediate human disease pathogenesis as well as serve as a biomarker profile for disease diagnosis[140-143]. The disrupted miRNAs, and their corresponding mRNA target genes in each psychiatric disease, are likely to interact with and regulate each other, both directly as targets and indirectly as part of larger regulatory networks. Furthermore, correlated miRNAs and mRNAs may be

coordinately regulated by a (possibly overlapping) set of transcription factors or other epigenetic influences. It remains to be determined whether the changes in the miRNA/mRNA network are i) similar or different across distinct brain regions ii) cell type-specific and iii) reversible mechanisms.

The underlying reasons for altered ncRNA expression remain unresolved and could result from a number of factors, including genetic changes in the promoter region or other locations within the gene. Additionally, defects in RNA editing or epigenetic suppression of the chromosomal region encoding the ncRNAs can also occur. Finally, miRNAs, lncRNAs, and their processing genes are susceptible to regulation by well-established signaling modulators such as BDNF, CREB, calcium, or calcium responsive neurotransmitters. For example, recently it was reported that Dicer is activated by proteolytic cleavage under conditions of elevated calcium levels [14, 16]. The networking of miRNAs and other ncRNAs into critical pathways such as neurotransmission, neurogenesis, and neurodevelopment may open up an entirely new understanding of psychiatric disease. Ultimately, we expect that for many of the complex psychiatric disorders we have considered, novel links between ncRNA mechanisms and the disease pathology will continue to emerge.

Acknowledgements

We would like to acknowledge that some of the studies mentioned in the review were funded by National Institute of Mental Health (R01MH100616) to Dr. Dwivedi. Kristen Brennand is a New York Stem Cell Foundation - Robertson Investigator. The Brennand Laboratory is supported by a Brain and Behavior Young Investigator Grant, National Institute of Health (NIH) grant R01 MH101454 and the New York Stem Cell Foundation. The authors would also like to thank Matthew Daniel for helping to prepare Table 1 on miRNAs in psychiatric disease.

References

1. Kocerha J, Kauppinen S, Wahlestedt C. microRNAs in CNS disorders. Neuromolecular Med. 2009; 11(3):162–172. [PubMed: 19536656]
2. Faghihi MA, Wahlestedt C. Regulatory roles of natural antisense transcripts. Nat Rev Mol Cell Biol. 2009; 10(9):637–643. [PubMed: 19638999]
3. Sauvageau M, Goff LA, Lodato S, Bonev B, Groff AF, Gerhardinger C, et al. Multiple knockout mouse models reveal lincRNAs are required for life and brain development. Elife. 2013; 2:e01749. [PubMed: 24381249]
4. Barry G, Mattick JS. The role of regulatory RNA in cognitive evolution. Trends Cogn Sci. 2012; 16(10):497–503. [PubMed: 22940578]
5. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009; 136(2):215–233. [PubMed: 19167326]
6. Nam JW, Rissland OS, Koppstein D, Abreu-Goodger C, Jan CH, Agarwal V, et al. Global analyses of the effect of different cellular contexts on microRNA targeting. Molecular cell. 2014; 53(6): 1031–1043. [PubMed: 24631284]
7. Gregory RI, Chendrimada TP, Shiekhattar R. MicroRNA biogenesis: isolation and characterization of the microprocessor complex. Methods Mol Biol. 2006; 342:33–47. [PubMed: 16957365]
8. Gregory RI, Yan KP, Amuthan G, Chendrimada T, Doratotaj B, Cooch N, et al. The Microprocessor complex mediates the genesis of microRNAs. Nature. 2004; 432(7014):235–240. [PubMed: 15531877]
9. Davis TH, Cuellar TL, Koch SM, Barker AJ, Harfe BD, McManus MT, et al. Conditional loss of Dicer disrupts cellular and tissue morphogenesis in the cortex and hippocampus. J Neurosci. 2008; 28(17):4322–4330. [PubMed: 18434510]

10. De Pietri Tonelli D, Pulvers JN, Haffner C, Murchison EP, Hannon GJ, Huttner WB. miRNAs are essential for survival and differentiation of newborn neurons but not for expansion of neural progenitors during early neurogenesis in the mouse embryonic neocortex. Development. 2008; 135(23):3911–3921. [PubMed: 18997113]
11. Schaefer A, O'Carroll D, Tan CL, Hillman D, Sugimori M, Llinas R, et al. Cerebellar neurodegeneration in the absence of microRNAs. J Exp Med. 2007; 204(7):1553–1558. [PubMed: 17606634]
12. Stark KL, Xu B, Bagchi A, Lai WS, Liu H, Hsu R, et al. Altered brain microRNA biogenesis contributes to phenotypic deficits in a 22q11-deletion mouse model. Nat Genet. 2008; 40(6):751–760. [PubMed: 18469815]
13. Olde Loohuis NF, Kos A, Martens GJ, Van Bokhoven H, Nadif Kasri N, Aschrafi A. MicroRNA networks direct neuronal development and plasticity. Cellular and molecular life sciences: CMLS. 2012; 69(1):89–102. [PubMed: 21833581]
14. Lugli G, Larson J, Martone ME, Jones Y, Smalheiser NR. Dicer and eIF2c are enriched at postsynaptic densities in adult mouse brain and are modified by neuronal activity in a calpain-dependent manner. J Neurochem. 2005; 94(4):896–905. [PubMed: 16092937]
15. Glanzer J, Miyashiro KY, Sul JY, Barrett L, Belt B, Haydon P, et al. RNA splicing capability of live neuronal dendrites. Proc Natl Acad Sci U S A. 2005; 102(46):16859–16864. [PubMed: 16275927]
16. Lugli G, Torvik VI, Larson J, Smalheiser NR. Expression of microRNAs and their precursors in synaptic fractions of adult mouse forebrain. J Neurochem. 2008; 106(2):650–661. [PubMed: 18410515]
17. Smalheiser NR. Regulation of mammalian microRNA processing and function by cellular signaling and subcellular localization. Biochim Biophys Acta. 2008; 1779(11):678–681. [PubMed: 18433727]
18. Smalheiser NR. Synaptic enrichment of microRNAs in adult mouse forebrain is related to structural features of their precursors. Biol Direct. 2008; 3:44. [PubMed: 18957138]
19. Siegel G, Saba R, Schratt G. microRNAs in neurons: manifold regulatory roles at the synapse. Curr Opin Genet Dev. 2011; 21(4):491–497. [PubMed: 21561760]
20. Smalheiser NR, Lugli G, Zhang H, Rizavi H, Cook EH, Dwivedi Y. Expression of microRNAs and other small RNAs in prefrontal cortex in schizophrenia, bipolar disorder and depressed subjects. PLoS One. 2014; 9(1):e86469. [PubMed: 24475125]
21. Bicker S, Lackinger M, Weiss K, Schratt G. MicroRNA-132, -134, and -138: a microRNA troika rules in neuronal dendrites. Cellular and molecular life sciences: CMLS. 2014
22. Smalheiser NR, Lugli G. microRNA regulation of synaptic plasticity. Neuromolecular Med. 2009; 11(3):133–140. [PubMed: 19458942]
23. Sun AX, Crabtree GR, Yoo AS. MicroRNAs: regulators of neuronal fate. Current opinion in cell biology. 2013; 25(2):215–221. [PubMed: 23374323]
24. Meza-Sosa KF, Pedraza-Alva G, Perez-Martinez L. microRNAs: key triggers of neuronal cell fate. Frontiers in cellular neuroscience. 2014; 8:175. [PubMed: 25009466]
25. Pittenger C. Disorders of memory and plasticity in psychiatric disease. Dialogues Clin Neurosci. 2013; 15(4):455–463. [PubMed: 24459412]
26. Zhao C, Sun G, Li S, Lang MF, Yang S, Li W, et al. MicroRNA let-7b regulates neural stem cell proliferation and differentiation by targeting nuclear receptor TLX signaling. Proc Natl Acad Sci U S A. 2010; 107(5):1876–1881. [PubMed: 20133835]
27. Rybak A, Fuchs H, Smirnova L, Brandt C, Pohl EE, Nitsch R, et al. A feedback loop comprising lin-28 and let-7 controls pre-let-7 maturation during neural stem-cell commitment. Nature cell biology. 2008; 10(8):987–993. [PubMed: 18604195]
28. Cheng LC, Pastrana E, Tavazoie M, Doetsch F. miR-124 regulates adult neurogenesis in the subventricular zone stem cell niche. Nat Neurosci. 2009; 12(4):399–408. [PubMed: 19287386]
29. Liu K, Liu Y, Mo W, Qiu R, Wang X, Wu JY, et al. MiR-124 regulates early neurogenesis in the optic vesicle and forebrain, targeting NeuroD1. Nucleic Acids Res. 2011; 39(7):2869–2879. [PubMed: 21131276]

30. Papagiannakopoulos T, Kosik KS. MicroRNA-124: micromanager of neurogenesis. Cell stem cell. 2009; 4(5):375–376. [PubMed: 19427286]
31. Zhao C, Sun G, Li S, Shi Y. A feedback regulatory loop involving microRNA-9 and nuclear receptor TLX in neural stem cell fate determination. Nat Struct Mol Biol. 2009; 16(4):365–371. [PubMed: 19330006]
32. Gaughwin P, Ciesla M, Yang H, Lim B, Brundin P. Stage-specific modulation of cortical neuronal development by Mmu-miR-134. Cerebral cortex. 2011; 21(8):1857–1869. [PubMed: 21228099]
33. Brett JO, Renault VM, Rafalski VA, Webb AE, Brunet A. The microRNA cluster miR-106b~25 regulates adult neural stem/progenitor cell proliferation and neuronal differentiation. Aging. 2011; 3(2):108–124. [PubMed: 21386132]
34. Sun G, Ye P, Murai K, Lang MF, Li S, Zhang H, et al. miR-137 forms a regulatory loop with nuclear receptor TLX and LSD1 in neural stem cells. Nat Commun. 2011; 2:529. [PubMed: 22068596]
35. Silber J, Lim DA, Petritsch C, Persson AI, Maunakea AK, Yu M, et al. miR-124 and miR-137 inhibit proliferation of glioblastoma multiforme cells and induce differentiation of brain tumor stem cells. BMC medicine. 2008; 6:14. [PubMed: 18577219]
36. Smrt RD, Szulwach KE, Pfeiffer RL, Li X, Guo W, Pathania M, et al. MicroRNA miR-137 regulates neuronal maturation by targeting ubiquitin ligase mind bomb-1. Stem Cells. 2010; 28(6): 1060–1070. [PubMed: 20506192]
37. Szulwach KE, Li X, Smrt RD, Li Y, Luo Y, Lin L, et al. Cross talk between microRNA and epigenetic regulation in adult neurogenesis. J Cell Biol. 2010; 189(1):127–141. [PubMed: 20368621]
38. Mu Y, Gage FH. Adult hippocampal neurogenesis and its role in Alzheimer's disease. Mol Neurodegener. 2011; 6:85. [PubMed: 22192775]
39. Winner B, Rockenstein E, Lie DC, Aigner R, Mante M, Bogdahn U, et al. Mutant alpha-synuclein exacerbates age-related decrease of neurogenesis. Neurobiology of aging. 2008; 29(6):913–925. [PubMed: 17275140]
40. Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. Cell. 2008; 132(4):645–660. [PubMed: 18295581]
41. Jacobs BL, van Praag H, Gage FH. Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol Psychiatry. 2000; 5(3):262–269. [PubMed: 10889528]
42. Rees E, Kirov G, Sanders A, Walters JT, Chambert KD, Shi J, et al. Evidence that duplications of 22q11.2 protect against schizophrenia. Mol Psychiatry. 2014; 19(1):37–40. [PubMed: 24217254]
43. Karayiorgou M, Simon TJ, Gogos JA. 22 q11.2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia. Nat Rev Neurosci. 2010; 11(6):402–416. [PubMed: 20485365]
44. Ripke S, Sanders AR, Kendler KS, Levinson DF, Sklar P, Holmans PA, et al. Genome-wide association study identifies five new schizophrenia loci. Nat Genet. 2011; 43(10):969–976. [PubMed: 21926974]
45. Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kahler AK, Akterin S, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat Genet. 2013; 45(10):1150–1159. [PubMed: 23974872]
46. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014; 511(7510):421–427. [PubMed: 25056061]
47. Green MJ, Cairns MJ, Wu J, Dragovic M, Jablensky A, Tooney PA, et al. Genome-wide supported variant MIR137 and severe negative symptoms predict membership of an impaired cognitive subtype of schizophrenia. Mol Psychiatry. 2013; 18(7):774–780. [PubMed: 22733126]
48. Liu B, Zhang X, Hou B, Li J, Qiu C, Qin W, et al. The Impact of MIR137 on Dorsolateral Prefrontal-Hippocampal Functional Connectivity in Healthy Subjects. Neuropsychopharmacology. 2014; 39(9):2153–2160. [PubMed: 24625753]
49. Lett TA, Chakravarty MM, Felsky D, Brandl EJ, Tiwari AK, Goncalves VF, et al. The genome-wide supported microRNA-137 variant predicts phenotypic heterogeneity within schizophrenia. Mol Psychiatry. 2013; 18(4):443–450. [PubMed: 23459466]

50. Kwon E, Wang W, Tsai LH. Validation of schizophrenia-associated genes CSMD1, C10orf26, CACNA1C and TCF4 as miR-137 targets. Mol Psychiatry. 2013; 18(1):11–12. [PubMed: 22182936]
51. Kim AH, Parker EK, Williamson V, McMichael GO, Fanous AH, Vladimirov VI. Experimental validation of candidate schizophrenia gene ZNF804A as target for hsa-miR-137. Schizophr Res. 2012; 141(1):60–64. [PubMed: 22883350]
52. Wright C, Turner JA, Calhoun VD, Perrone-Bizzozero N. Potential Impact of miR-137 and Its Targets in Schizophrenia. Front Genet. 2013; 4:58. [PubMed: 23637704]
53. Collins AL, Kim Y, Bloom RJ, Kelada SN, Sethupathy P, Sullivan PF. Transcriptional targets of the schizophrenia risk gene MIR137. Transl Psychiatry. 2014; 4:e404. [PubMed: 24984191]
54. Beveridge NJ, Gardiner E, Carroll AP, Tooney PA, Cairns MJ. Schizophrenia is associated with an increase in cortical microRNA biogenesis. Mol Psychiatry. 2010; 15(12):1176–1189. [PubMed: 19721432]
55. Song HT, Sun XY, Zhang L, Zhao L, Guo ZM, Fan HM, et al. A preliminary analysis of association between the down-regulation of microRNA-181b expression and symptomatology improvement in schizophrenia patients before and after antipsychotic treatment. J Psychiatr Res. 2014; 54:134–140. [PubMed: 24694668]
56. Sun XY, Lu J, Zhang L, Song HT, Zhao L, Fan HM, et al. Aberrant microRNA expression in peripheral plasma and mononuclear cells as specific blood-based biomarkers in schizophrenia patients. Journal of clinical neuroscience: official journal of the Neurosurgical Society of Australasia. 2014
57. Kocerha J, Faghihi MA, Lopez-Toledano MA, Huang J, Ramsey AJ, Caron MG, et al. MicroRNA-219 modulates NMDA receptor-mediated neurobehavioral dysfunction. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106(9):3507–3512. [PubMed: 19196972]
58. Remenyi J, van den Bosch MW, Palygin O, Mistry RB, McKenzie C, Macdonald A, et al. miR-132/212 knockout mice reveal roles for these miRNAs in regulating cortical synaptic transmission and plasticity. PLoS One. 2013; 8(4):e62509. [PubMed: 23658634]
59. Scott HL, Tamagnini F, Narduzzo KE, Howarth JL, Lee YB, Wong LF, et al. MicroRNA-132 regulates recognition memory and synaptic plasticity in the perirhinal cortex. Eur J Neurosci. 2012; 36(7):2941–2948. [PubMed: 22845676]
60. Wibrand K, Pai B, Siripornmongcolchai T, Bittins M, Berentsen B, Ofte ML, et al. MicroRNA regulation of the synaptic plasticity-related gene Arc. PLoS One. 2012; 7(7):e41688. [PubMed: 22844515]
61. Wibrand K, Panja D, Tiron A, Ofte ML, Skaftnesmo KO, Lee CS, et al. Differential regulation of mature and precursor microRNA expression by NMDA and metabotropic glutamate receptor activation during LTP in the adult dentate gyrus in vivo. Eur J Neurosci. 2010; 31(4):636–645. [PubMed: 20384810]
62. Pathania M, Torres-Reveron J, Yan L, Kimura T, Lin TV, Gordon V, et al. miR-132 enhances dendritic morphogenesis, spine density, synaptic integration, and survival of newborn olfactory bulb neurons. PLoS One. 2012; 7(5):e38174. [PubMed: 22693596]
63. Edbauer D, Neilson JR, Foster KA, Wang CF, Seeburg DP, Batterton MN, et al. Regulation of synaptic structure and function by FMRP-associated microRNAs miR-125b and miR-132. Neuron. 2010; 65(3):373–384. [PubMed: 20159450]
64. Balu DT, Li Y, Puhl MD, Benneyworth MA, Basu AC, Takagi S, et al. Multiple risk pathways for schizophrenia converge in serine racemase knockout mice, a mouse model of NMDA receptor hypofunction. Proc Natl Acad Sci U S A. 2013; 110(26):E2400–2409. [PubMed: 23729812]
65. Cheng HY, Papp JW, Varlamova O, Dziema H, Russell B, Curfman JP, et al. microRNA modulation of circadian-clock period and entrainment. Neuron. 2007; 54(5):813–829. [PubMed: 17553428]
66. Mohawk JA, Green CB, Takahashi JS. Central and peripheral circadian clocks in mammals. Annu Rev Neurosci. 2012; 35:445–462. [PubMed: 22483041]
67. Asarnow LD, Soehner AM, Harvey AG. Circadian rhythms and psychiatric illness. Curr Opin Psychiatry. 2013; 26(6):566–571. [PubMed: 24060916]

68. Shende VR, Neuendorff N, Earnest DJ. Role of miR-142-3p in the post-transcriptional regulation of the clock gene Bmal1 in the mouse SCN. PLoS One. 2013; 8(6):e65300. [PubMed: 23755214]
69. Lee KH, Kim SH, Lee HR, Kim W, Kim DY, Shin JC, et al. MicroRNA-185 oscillation controls circadian amplitude of mouse Cryptochrome 1 via translational regulation. Mol Biol Cell. 2013; 24(14):2248–2255. [PubMed: 23699394]
70. Davis CJ, Clinton JM, Krueger JM. MicroRNA 138, let-7b, and 125a inhibitors differentially alter sleep and EEG delta-wave activity in rats. J Appl Physiol (1985). 2012; 113(11):1756–1762. [PubMed: 23104698]
71. Zhou W, Li Y, Wang X, Wu L, Wang Y. MiR-206-mediated dynamic mechanism of the mammalian circadian clock. BMC Syst Biol. 2011; 5:141. [PubMed: 21902842]
72. Davis CJ, Clinton JM, Taishi P, Bohnet SG, Honn KA, Krueger JM. MicroRNA 132 alters sleep and varies with time in brain. J Appl Physiol (1985). 2011; 111(3):665–672. [PubMed: 21719725]
73. Alvarez-Saavedra M, Antoun G, Yanagiya A, Oliva-Hernandez R, Cornejo-Palma D, Perez-Iratxeta C, et al. miRNA-132 orchestrates chromatin remodeling and translational control of the circadian clock. Hum Mol Genet. 2011; 20(4):731–751. [PubMed: 21118894]
74. Saus E, Soria V, Escaramis G, Vivarelli F, Crespo JM, Kagerbauer B, et al. Genetic variants and abnormal processing of pre-miR-182, a circadian clock modulator, in major depression patients with late insomnia. Hum Mol Genet. 2010; 19(20):4017–4025. [PubMed: 20656788]
75. Luo W, Sehgal A. Regulation of circadian behavioral output via a MicroRNA-JAK/STAT circuit. Cell. 2012; 148(4):765–779. [PubMed: 22305007]
76. Kadener S, Menet JS, Sugino K, Horwich MD, Weissbein U, Nawathean P, et al. A role for microRNAs in the Drosophila circadian clock. Genes Dev. 2009; 23(18):2179–2191. [PubMed: 19696147]
77. Cardno AG, Owen MJ. Genetic relationships between schizophrenia, bipolar disorder, and schizoaffective disorder. Schizophr Bull. 2014; 40(3):504–515. [PubMed: 24567502]
78. Zhou R, Yuan P, Wang Y, Hunsberger JG, Elkahloun A, Wei Y, et al. Evidence for selective microRNAs and their effectors as common long-term targets for the actions of mood stabilizers. Neuropsychopharmacology. 2009; 34(6):1395–1405. [PubMed: 18704095]
79. Rong H, Liu TB, Yang KJ, Yang HC, Wu DH, Liao CP, et al. MicroRNA-134 plasma levels before and after treatment for bipolar mania. J Psychiatr Res. 2011; 45(1):92–95. [PubMed: 20546789]
80. Croce N, Mathe AA, Gelfo F, Caltagirone C, Bernardini S, Angelucci F. Effects of lithium and valproic acid on BDNF protein and gene expression in an in vitro human neuron-like model of degeneration. J Psychopharmacol. 2014
81. Yasuda S, Liang MH, Marinova Z, Yahyavi A, Chuang DM. The mood stabilizers lithium and valproate selectively activate the promoter IV of brain-derived neurotrophic factor in neurons. Mol Psychiatry. 2009; 14(1):51–59. [PubMed: 17925795]
82. Modarresi F, Faghihi MA, Lopez-Toledano MA, Fatemi RP, Magistri M, Brothers SP, et al. Inhibition of natural antisense transcripts in vivo results in gene-specific transcriptional upregulation. Nat Biotechnol. 2012; 30(5):453–459. [PubMed: 22446693]
83. Bahi A, Chandrasekar V, Dreyer JL. Selective lentiviral-mediated suppression of microRNA124a in the hippocampus evokes antidepressants-like effects in rats. Psychoneuroendocrinology. 2014; 46:78–87. [PubMed: 24882160]
84. Li YJ, Xu M, Gao ZH, Wang YQ, Yue Z, Zhang YX, et al. Alterations of serum levels of BDNF-related miRNAs in patients with depression. PLoS One. 2013; 8(5):e63648. [PubMed: 23704927]
85. Smalheiser NR, Lugli G, Rizavi HS, Torvik VI, Turecki G, Dwivedi Y. MicroRNA expression is down-regulated and reorganized in prefrontal cortex of depressed suicide subjects. PloS one. 2012; 7(3):e33201. [PubMed: 22427989]
86. He Y, Zhou Y, Xi Q, Cui H, Luo T, Song H, et al. Genetic variations in microRNA processing genes are associated with susceptibility in depression. DNA and cell biology. 2012; 31(9):1499–1506. [PubMed: 22694265]
87. Araragi N, Lesch KP. Serotonin (5-HT) in the regulation of depression-related emotionality: insight from 5-HT transporter and tryptophan hydroxylase-2 knockout mouse models. Curr Drug Targets. 2013; 14(5):549–570. [PubMed: 23547810]

88. 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(5998):1537–1541. [PubMed: 20847275]

89. Launay JM, Mouillet-Richard S, Baudry A, Pietri M, Kellermann O. Raphe-mediated signals control the hippocampal response to SRI antidepressants via miR-16. Transl Psychiatry. 2011; 1:e56. [PubMed: 22833211]

90. Asan E, Steinke M, Lesch KP. Serotonergic innervation of the amygdala: targets, receptors, and implications for stress and anxiety. Histochem Cell Biol. 2013; 139(6):785–813. [PubMed: 23494464]

91. Issler O, Haramati S, Paul ED, Maeno H, Navon I, Zwang R, et al. MicroRNA 135 Is Essential for Chronic Stress Resiliency, Antidepressant Efficacy, and Intact Serotonergic Activity. Neuron. 2014

92. Thounaojam MC, Kaushik DK, Basu A. MicroRNAs in the brain: it's regulatory role in neuroinflammation. Mol Neurobiol. 2013; 47(3):1034–1044. [PubMed: 23315269]

93. Rotheneichner P, Lange S, O'Sullivan A, Marschallinger J, Zaunmair P, Geretsegger C, et al. Hippocampal Neurogenesis and Antidepressive Therapy: Shocking Relations. Neural Plast. 2014; 2014:723915. [PubMed: 24967107]

94. Anacker C. Adult Hippocampal Neurogenesis in Depression: Behavioral Implications and Regulation by the Stress System. Curr Top Behav Neurosci. 2014

95. Scott KA, Hoban AE, Clarke G, Moloney GM, Dinan TG, Cryan JF. Thinking small: towards microRNA-based therapeutics for anxiety disorders. Expert opinion on investigational drugs. 2015:1–14.

96. Domschke K. Patho-genetics of posttraumatic stress disorder. Psychiatr Danub. 2012; 24(3):267–273. [PubMed: 23013629]

97. Zhou J, Nagarkatti P, Zhong Y, Ginsberg JP, Singh NP, Zhang J, et al. Dysregulation in microRNA Expression Is Associated with Alterations in Immune Functions in Combat Veterans with Post-Traumatic Stress Disorder. PLoS One. 2014; 9(4):e94075. [PubMed: 24759737]

98. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. Immunol Res. 2014; 58(2-3):193–210. [PubMed: 24798553]

99. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014; 140(3):774–815. [PubMed: 24417575]

100. Jones KA, Thomsen C. The role of the innate immune system in psychiatric disorders. Molecular and cellular neurosciences. 2013; 53:52–62. [PubMed: 23064447]

101. Balakathiresan NS, Chandran R, Bhomia M, Jia M, Li H, Maheshwari RK. Serum and amygdala microRNA signatures of posttraumatic stress: Fear correlation and biomarker potential. Journal of psychiatric research. 2014

102. Haramati S, Navon I, Issler O, Ezra-Nevo G, Gil S, Zwang R, et al. MicroRNA as repressors of stress-induced anxiety: the case of amygdalar miR-34. J Neurosci. 2011; 31(40):14191–14203. [PubMed: 21976504]

103. Dias BG, Goodman JV, Ahluwalia R, Easton AE, Andero R, Ressler KJ. Amygdala-Dependent Fear Memory Consolidation via miR-34a and Notch Signaling. Neuron. 2014; 83(4):906–918. [PubMed: 25123309]

104. Hanin G, Shenhar-Tsarfaty S, Yayon N, Hoe YY, Bennett ER, Sklan EH, et al. Competing targets of microRNA-608 affect anxiety and hypertension. Hum Mol Genet. 2014; 23(17):4569–4580. [PubMed: 24722204]

105. Durairaj RV, Koilmani ER. Environmental enrichment modulates glucocorticoid receptor expression and reduces anxiety in Indian field male mouse Mus booduga through up-regulation of microRNA-124a. General and comparative endocrinology. 2014; 199:26–32. [PubMed: 24457250]

106. Shaltiel G, Hanan M, Wolf Y, Barbash S, Kovalev E, Shoham S, et al. Hippocampal microRNA-132 mediates stress-inducible cognitive deficits through its acetylcholinesterase target. Brain structure & function. 2013; 218(1):59–72. [PubMed: 22246100]

107. Jensen KP, Kranzler HR, Stein MB, Gelernter J. The effects of a MAP2K5 microRNA target site SNP on risk for anxiety and depressive disorders. American journal of medical genetics Part B,

Neuropsychiatric genetics: the official publication of the International Society of Psychiatric Genetics. 2014; 165B(2):175–183.

108. Yoon Y, McKenna MC, Rollins DA, Song M, Nuriel T, Gross SS, et al. Anxiety-associated alternative polyadenylation of the serotonin transporter mRNA confers translational regulation by hnRNPK. Proc Natl Acad Sci U S A. 2013; 110(28):11624–11629. [PubMed: 23798440]
109. Honda M, Kuwano Y, Katsuura-Kamano S, Kamezaki Y, Fujita K, Akaike Y, et al. Chronic academic stress increases a group of microRNAs in peripheral blood. PLoS One. 2013; 8(10):e75960. [PubMed: 24130753]
110. Mannironi C, Camon J, De Vito F, Biundo A, De Stefano ME, Persiconi I, et al. Acute stress alters amygdala microRNA miR-135a and miR-124 expression: inferences for corticosteroid dependent stress response. PLoS One. 2013; 8(9):e73385. [PubMed: 24023867]
111. Cuellar TL, Davis TH, Nelson PT, Loeb GB, Harfe BD, Ullian E, et al. Dicer loss in striatal neurons produces behavioral and neuroanatomical phenotypes in the absence of neurodegeneration. Proc Natl Acad Sci U S A. 2008; 105(14):5614–5619. [PubMed: 18385371]
112. Muinos-Gimeno M, Espinosa-Parrilla Y, Guidi M, Kagerbauer B, Sipila T, Maron E, et al. Human microRNAs miR-22, miR-138-2, miR-148a, and miR-488 are associated with panic disorder and regulate several anxiety candidate genes and related pathways. Biol Psychiatry. 2011; 69(6):526–533. [PubMed: 21168126]
113. Lin Q, Wei W, Coelho CM, Li X, Baker-Andresen D, Dudley K, et al. The brain-specific microRNA miR-128b regulates the formation of fear-extinction memory. Nat Neurosci. 2011; 14(9):1115–1117. [PubMed: 21841775]
114. Smalheiser NR, Lugli G, Rizavi HS, Zhang H, Torvik VI, Pandey GN, et al. MicroRNA expression in rat brain exposed to repeated inescapable shock: differential alterations in learned helplessness vs. non-learned helplessness. Int J Neuropsychopharmacol. 2011; 14(10):1315–1325. [PubMed: 21275079]
115. Wu J, Xie X. Comparative sequence analysis reveals an intricate network among REST, CREB and miRNA in mediating neuronal gene expression. Genome Biol. 2006; 7(9):R85. [PubMed: 17002790]
116. Clark BS, Blackshaw S. Long non-coding RNA-dependent transcriptional regulation in neuronal development and disease. Frontiers in genetics. 2014; 5:164. [PubMed: 24936207]
117. Ng SY, Lin L, Soh BS, Stanton LW. Long noncoding RNAs in development and disease of the central nervous system. Trends Genet. 2013; 29(8):461–468. [PubMed: 23562612]
118. Bian S, Sun T. Functions of noncoding RNAs in neural development and neurological diseases. Mol Neurobiol. 2011; 44(3):359–373. [PubMed: 21969146]
119. Chung DW, Rudnicki DD, Yu L, Margolis RL. A natural antisense transcript at the Huntington's disease repeat locus regulates HTT expression. Hum Mol Genet. 2011; 20(17):3467–3477. [PubMed: 21672921]
120. Chubb JE, Bradshaw NJ, Soares DC, Porteous DJ, Millar JK. The DISC locus in psychiatric illness. Mol Psychiatry. 2008; 13(1):36–64. [PubMed: 17912248]
121. Devon RS, Anderson S, Teague PW, Burgess P, Kipari TM, Semple CA, et al. Identification of polymorphisms within Disrupted in Schizophrenia 1 and Disrupted in Schizophrenia 2, and an investigation of their association with schizophrenia and bipolar affective disorder. Psychiatr Genet. 2001; 11(2):71–78. [PubMed: 11525420]
122. Millar JK, James R, Brandon NJ, Thomson PA. DISC1 and DISC2: discovering and dissecting molecular mechanisms underlying psychiatric illness. Ann Med. 2004; 36(5):367–378. [PubMed: 15478311]
123. Zhong J, Chuang SC, Bianchi R, Zhao W, Lee H, Fenton AA, et al. BC1 regulation of metabotropic glutamate receptor-mediated neuronal excitability. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2009; 29(32):9977–9986. [PubMed: 19675232]
124. Maccarrone M, Rossi S, Bari M, De Chiara V, Rapino C, Musella A, et al. Abnormal mGlu 5 receptor/endocannabinoid coupling in mice lacking FMRP and BC1 RNA. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2010; 35(7):1500–1509. [PubMed: 20393458]

125. Tay Y, Rinn J, Pandolfi PP. The multilayered complexity of ceRNA crosstalk and competition. Nature. 2014; 505(7483):344–352. [PubMed: 24429633]

126. Faghihi MA, Zhang M, Huang J, Modarresi F, Van der Brug MP, Nalls MA, et al. Evidence for natural antisense transcript-mediated inhibition of microRNA function. Genome Biol. 2010; 11(5):R56. [PubMed: 20507594]

127. Mercer TR, Dinger ME, Sunkin SM, Mehler MF, Mattick JS. Specific expression of long noncoding RNAs in the mouse brain. Proc Natl Acad Sci U S A. 2008; 105(2):716–721. [PubMed: 18184812]

128. Lipovich L, Dachet F, Cai J, Bagla S, Balan K, Jia H, et al. Activity-dependent human brain coding/noncoding gene regulatory networks. Genetics. 2012; 192(3):1133–1148. [PubMed: 22960213]

129. Mercer TR, Qureshi IA, Gokhan S, Dinger ME, Li G, Mattick JS, et al. Long noncoding RNAs in neuronal-glial fate specification and oligodendrocyte lineage maturation. BMC Neurosci. 2010; 11:14. [PubMed: 20137068]

130. Bond AM, Vangompel MJ, Sametsky EA, Clark MF, Savage JC, Disterhoft JF, et al. Balanced gene regulation by an embryonic brain ncRNA is critical for adult hippocampal GABA circuitry. Nature neuroscience. 2009; 12(8):1020–1027. [PubMed: 19620975]

131. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013; 495(7441):384–388. [PubMed: 23446346]

132. Taylor MS, Devon RS, Millar JK, Porteous DJ. Evolutionary constraints on the Disrupted in Schizophrenia locus. Genomics. 2003; 81(1):67–77. [PubMed: 12573262]

133. Johnstone M, Thomson PA, Hall J, McIntosh AM, Lawrie SM, Porteous DJ. DISC1 in schizophrenia: genetic mouse models and human genomic imaging. Schizophr Bull. 2011; 37(1): 14–20. [PubMed: 21149852]

134. Barry G, Briggs JA, Vanichkina DP, Poth EM, Beveridge NJ, Ratnu VS, et al. The long non-coding RNA Gomafu is acutely regulated in response to neuronal activation and involved in schizophrenia-associated alternative splicing. Mol Psychiatry. 2014; 19(4):486–494. [PubMed: 23628989]

135. Liu Z, Li X, Sun N, Xu Y, Meng Y, Yang C, et al. Microarray profiling and co-expression network analysis of circulating lncRNAs and mRNAs associated with major depressive disorder. PLoS One. 2014; 9(3):e93388. [PubMed: 24676134]

136. Punzi G, Ursini G, Shin JH, Kleinman JE, Hyde TM, Weinberger DR. Increased expression of MARCKS in post-mortem brain of violent suicide completers is related to transcription of a long, noncoding, antisense RNA. Mol Psychiatry. 2014; 19(10):1057–1059. [PubMed: 24821221]

137. Coon SL, Munson PJ, Cherukuri PF, Sugden D, Rath MF, Moller M, et al. Circadian changes in long noncoding RNAs in the pineal gland. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109(33):13319–13324. [PubMed: 22864914]

138. Vollmers C, Schmitz RJ, Nathanson J, Yeo G, Ecker JR, Panda S. Circadian oscillations of protein-coding and regulatory RNAs in a highly dynamic mammalian liver epigenome. Cell Metab. 2012; 16(6):833–845. [PubMed: 23217262]

139. Xue Z, Ye Q, Anson SR, Yang J, Xiao G, Kowbel D, et al. Transcriptional interference by antisense RNA is required for circadian clock function. Nature. 2014

140. Staehler CF, Keller A, Leidinger P, Backes C, Chandran A, Wischhusen J, et al. Whole miRNome-wide differential co-expression of microRNAs. Genomics, proteomics & bioinformatics. 2012; 10(5):285–294.

141. Xu J, Li CX, Li YS, Lv JY, Ma Y, Shao TT, et al. MiRNA-miRNA synergistic network: construction via co-regulating functional modules and disease miRNA topological features. Nucleic Acids Res. 2011; 39(3):825–836. [PubMed: 20929877]

142. Choi JK, Yu U, Yoo OJ, Kim S. Differential coexpression analysis using microarray data and its application to human cancer. Bioinformatics. 2005; 21(24):4348–4355. [PubMed: 16234317]

143. Mo WJ, Fu XP, Han XT, Yang GY, Zhang JG, Guo FH, et al. A stochastic model for identifying differential gene pair co-expression patterns in prostate cancer progression. BMC Genomics. 2009; 10:340. [PubMed: 19640296]

Table 1
miRNAs implicated in psychiatric phenotypes

miRNA	Biological finding	References	Diagnosis
	schizophrenia risk allele	44-47	
	alters neuronal connectivity, and size of brain tissues	48-49	
miR-137	direct and indirect targets of miR-137 are linked to schizophrenia	50-53	
miRs- 137, 548	associated with schizophrenia (along with miR-137) in largest study to date on common genetic variants	46	
miRs- 181b, 26b	the premature and mature transcripts were upregulated in human prefrontal cortex	54	
miR-181b, miR-30e	associated with schizophrenia through plasma analysis of human patients	55, 56	
	alters schizophrenia behaviors in mice through NMDA-R signaling; targets CaMKIIgamma	57	
	most downregulated miR in cortical synaptosomes from schizophrenia patients; upregulated in tissue (total) from cortex	20	
miR-219-5p	upregulated in cortical tissue (total) from schizophrenia patients	54	
miR-132	repressed in mice deficient for the NMDA-R coagonist D-serine	64	schizophrenia
miR-134	altered expression in plasma of bipolar patients	79	
miRs- let-7b, let-7c, 128a, 24a, 30c, 34a, 221, 144	dysregulated in hippocampus of rats by the mood stabilizers valproate and lithium	78	bipolar disorder
miRs- 219-5p, 132, 279, 142-3p, 185, 138, let-7b, 125a, 206, 182	linked to circadian rhythm behaviors	65-66; 68-76	circadian function, potential links to multiple psychiatric diagnoses
miR-124a	regulates depression-associated behaviors in rats through BDNF	83	
miR-16	mediates depression behaviors through regulation of SERT; mechanistic connection to depression through neurogenesis pathways	88-89	
miRs- 96, 141, 182, 183, 183*, 198, 200a, 200a*, 200b, 200b*, 200c, 429	different expression profiles of these miRs between rats with learned helpless (LH) versus non-learned helpless behavior (NLH); possible link to depression phenotypes	114	
miRs- 142-5p, 142-3p, 494, 376a*, 496, 369-3p, 23b, 27b, 24-1*, 34b*, 34c, 17*, 20a, 424, 20b, 142, 301a, 324-5p, 497	downregulated in MDD patients, possibly due to alterered transcription from the pri-miRNA source	85	
miRs- let-7b, mir-132, 181b, 338-3p, 486, 650	networked together in MDD patients	85	
rs76481776 polymorphism in the pre-miR-182	associated with Clock genes	74	depression

miRNA	Biological finding	References	Diagnosis
miR-135	genetic manipulation of miR-135 leads to precipitation of anxiety and depression and antidepressant response in mice	91	depression/anxiety
miRs- 19b, 223	disrupted in human and animal models of PTSD	97, 101	PTSD
miR-34c	overexpression in mice prevents anxiety-associated responses in stressed mice; may control these behaviors through CRFR1 gene	102	
miR-34a	controls fear-responses in mice through Notch signaling	103	
miRs- 608, 330-3p,	genetic variations identified for these miR binding sites in target mRNAs with association to anxiety	104, 107	
miR-124	link to anxiety through glucocorticoid signaling	105	
	link to stress through corticosteroid signaling	110	
	linked to anxiety in medical students through peripheral blood profiling	109	stress/anxiety
miR-16	binds to SERT mRNA	108	implicated via SERT-mediated pathways
miRs- 22, 138-2, 148a, 488	genetic variations identified in miR binidng sites of gene targets associated with panic disorders	112	panic disorder