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## Diagnostic and therapeutic potential of microRNAs in neuropsychiatric disorders: Past, present, and future

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### Abstract

Neuropsychiatry disorders are common health problems affecting approximately 1% of the population. Twin, adoption, and family studies have displayed a strong genetic component for many of these disorders; however, the underlying pathophysiological mechanisms and neural substrates remain largely unknown. Given the critical need for new diagnostic markers and disease-modifying treatments, expanding the focus of genomic studies of neuropsychiatric disorders to include the role of non-coding RNAs (ncRNAs) is of growing interest. Of known types of ncRNAs, microRNAs (miRNAs) are 20–25-nucleotide, single-stranded, molecules that regulate gene expression through post-transcriptional mechanisms and have the potential to coordinately regulate complex regulatory networks. In this review, we summarize the current knowledge on miRNA alteration/dysregulation in neuropsychiatric disorders, with a special emphasis on schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD). With an eye toward the future, we also discuss the diagnostic and prognostic potential of miRNAs for neuropsychiatric disorders in the context of personalized treatments and network medicine.

### Keywords

Non-coding RNA; MiRNA; Schizophrenia; Bipolar disorder; Neuroplasticity

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## 1. Introduction

Neuropsychiatric disorders are chronic and severe medical conditions characterized by a complex range of symptoms including psychosis, depression, mania, and cognitive deficits. The underlying pathogenic mechanisms of these disorders remain largely elusive; however it is considered that both genetic factors and environmental exposures play important roles. In particular, as discussed below in more detail, recent genome-wide association studies (GWAS) and next-generation sequencing of common neuropsychiatric disorders such as schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD), have identified multiple genetic variants associated with risk, indicating that variation in a single gene is insufficient to cause the underlying disorder (McCarroll and Hyman, 2013). This etiology contrasts to rare neuropsychiatric disorders, such as Fragile X syndrome (*FMR1*) (Fu et al., 1991), Rett syndrome (*MECP2*) (Amir et al., 1999), and Pitt-Hopkins syndrome (*TCF4*) (Amiel et al., 2007), where highly penetrant, most often de novo mutations in a single gene are sufficient to cause characteristic neurodevelopmental, cognitive, and behavioral symptoms of each disorder.

MiRNAs play a role in almost all biological processes, such as cell proliferation, development, differentiation, and apoptosis (Krol et al., 2010). Compared to other organs, the brain has a particularly high percentage of tissue-specific and tissue-enriched miRNAs, implying possible roles in neuronal differentiation, synaptic plasticity, and neurite outgrowth (Sun and Shi, 2015). On the other hand, deregulation of miRNA expression and function is associated with the pathogenesis of neuropsychiatric disorders.

Considering emerging evidence for the involvement and important roles of miRNAs in the pathogenesis of neuropsychiatric disorder, as well as accumulating evidence for single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) in miRNAs and their target genes, we aim here to summarize recent studies and discuss the possible biomarker value of miRNAs for diagnostic assessment improvement and personalized medicine.

## 2. Pathogenesis of neuropsychiatric disorders

### 2.1. Alterations in neurodevelopment

Neural development starts during early stages of embryogenesis, and involves proliferation and differentiation of neurons, migration of immature neurons to their ultimate brain region, outgrowth of axons and dendrites, and generation, as well as proper maintenance, of synapses (Stiles and Jernigan, 2010). The neurodevelopmental hypothesis of SCZ has been linked to adverse conditions, such as genetic or environmental factors leading to abnormal or altered brain development and inappropriate connections of neurons during the perinatal period (Rapoport et al., 2012). The damage of the brain from the altered early development causes reduced cortical volume, altered gray matter loss, and ventricular enlargement at the onset of SCZ (Kochunov and Hong, 2014). In addition to SCZ, altered brain development has been implicated in BD. Neuroimaging studies showed that BD patients lose gray matter volume of emotion related brain areas including the insula and orbitofrontal, rostral, and dorsolateral prefrontal cortical (DLPFC) areas (Najt et al., 2015).

Recent genetic and molecular findings further support a role for altered neurodevelopment in neuropsychiatric disorders. For example, GWAS have shown that the *ANKK3* gene encoding the protein Ankyrin-G, which has many roles in cellular processes including neural development, is associated with risk for BD (Chen et al., 2013; Ferreira et al., 2008; Muhleisen et al., 2014). As evidence of this, Ankyrin-G has been shown to play a key role in organizing the axon initial segment in polarized neurons, to mediate AMPA-receptor mediated synaptic transmission, and to maintain proper dendritic spine morphology in glutamatergic neurons (Smith et al., 2014), and Durak et al. have recently reported that loss of *ANKK3* elevated the number of newborn neurons in the embryonic “ mouse brain (Durak et al., 2015). Furthermore, recent studies using BD-patient derived induced pluripotent stem cell (iPSC) models have provided a new line of evidence for altered neurodevelopmental processes in BD (Chen et al., 2014; Madison et al., 2015), including alterations of miRNAs such as miR-34a that targets *ANKK3* as discussed below in more detail (Bavarian et al., 2015).

## 2.2. Disrupted synaptic plasticity

Synaptic plasticity is a term that describes the changes in the synapse strength that occur over time. Synaptic plasticity plays a major role in establishing and maintaining the correct connections between neurons. All brain activities, including higher cortical functions involved in cognition, depend on the presence of the correct synaptic connections (Cowan et al., 1984; Tau and Peterson, 2010).

Historically, SCZ is associated with abnormal connections or disconnections between brain regions. Electroencephalography (EEG) and magnetoencephalography/ electroencephalogram (MEG/EEG) studies supported the disconnection hypothesis (Uhlhaas and Singer, 2010). Additionally, functional neuroimaging studies have found reduced frontotemporal connectivity by functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) (Stephan et al., 2009). These anatomical changes may be mediated by abnormal synaptic plasticity that leads to changes in size and numbers of dendritic spines and postsynaptic receptor density and thereby affects connectivity patterns in the brain.

Post-mortem studies have also revealed several abnormalities in synaptic formation and plasticity in BD. These abnormalities include lower number of neurons in specific brain regions, and decreased glial cell density in frontal cortical regions (Harrison, 2002; Vawter et al., 2000). Apart from these morphological changes, protein marker of synaptic numbers (such as Growth Associated Protein 43) is lower in depression, and increases with antidepressant treatment (Schloesser et al., 2008). Region-specific alterations in the expression of synaptic vesicular proteins, including synaptosomal-associated protein 25 (SNAP-25), syntaxin, synaptobrevin and synaptophysin, have been reported in brain samples of patients with BD (Gray et al., 2010).

## 2.3. Large-scale human genetic studies

Adoption and twin studies have confirmed that heritable genetic risk factors in psychiatric disorders (including SCZ and BD) play a major role in disease etiology. In two Swedish

population studies, heritability for SCZ and BD was reported as 64% and 58%, respectively (Lichtenstein et al., 2009, J. Song et al., 2015). Linkage and association studies have identified several chromosomal regions that are linked to psychiatric disorders. For SCZ, these studies have recently led to the association of over 108 loci, including multiple components of glutamatergic synapses and chromatin modifications (Network & Pathway Analysis Subgroup of Psychiatric Genomics, 2015; Schizophrenia Working Group of the Psychiatric Genomics, 2014), although further studies are required to unambiguously elucidate causal genetic factors in each locus [reviewed in (Sullivan et al., 2012; Kotlar et al., 2015)]. Additional genetic findings on rare variants, as identified by CNV and exome sequencing studies in SCZ, have also pointed to a key role for synaptic proteins as well as for the actin cytoskeleton (Fromer et al., 2014; Kirov et al., 2012; Need et al., 2012; Purcell et al., 2014; Timms et al., 2013). Furthermore, emerging functional studies on these rare variants in SCZ provide support for dysregulation of synaptic signaling pathways including G1T1-PAK3 involved in actin cytoskeleton dynamics (Kim et al., manuscript under review).

The results of GWAS point out to several chromosomal regions, which are associated with BD risk (Chen et al., 2013; Ferreira et al., 2008; Muhleisen et al., 2014), although the total sample size analyzed to date is smaller than that of SCZ. This includes genetic variation within the loci encoding the axonal initial segment protein Ankyrin-G encoded by the *ANKK3* gene (Chen et al., 2013; Ferreira et al., 2008; Hughes et al., 2015; Muhleisen et al., 2014; Rueckert et al., 2013) as well as the *CACNA1C* gene encoding a subunit of the L-type calcium channel, both of which play key roles in diverse aspects of neuronal development and function (Berger and Bartsch, 2014; Sinnegger-Brauns et al., 2009).

Several CNVs are associated with increased risk for psychiatric disorders. More than 15 genomic regions are associated with increased risk for SCZ; however, these variants are less common in BD (Kotlar et al., 2015). A deletion in 2p16.3 region, which contains synaptic protein gene neurexin-1 (*NRXN1*), increases the risk of SCZ 8.9 fold (Vinas-Jornet et al., 2014). Another locus (3q29 region) that contains 22 genes has also been implicated as a risk for SCZ: a recent meta-analysis of 25,904 SCZ patients and 62,871 healthy controls indicate that the 3q29 deletion confers a 41.1-fold increased risk for SCZ (Mulle, 2015). Various candidate genes are located in this region, including Disks large homolog 1 (*DLG1*), p21 activated kinase (*PAK2*), and F-box only protein 5 (*FBXO45*) (Mulle, 2015). Further studies for understanding of biological results of these CNVs will help us clarify the mechanism of psychiatric diseases.

In sum, on-going large-scale, genetic studies on SCZ, BD, and MDD populations are likely to yield more accurate and replicable findings that will facilitate the discovery of the true causal variants within the multiple loci implicated. Gaining insight into how these genetic risk factors collectively impact the biological mechanisms underlying the pathophysiology of any one individual will require a deeper understanding of the molecular mechanisms that coordinately regulate neurodevelopment and neuroplasticity. For this, consideration of how non-genetic mechanisms, i.e. epigenetic mechanisms and post-transcriptional forms of gene regulation, involving non-coding RNAs and other regulatory molecules that operate at the level of specific cells within defined neurocircuits is likely to be informative.

## 2.4. Alterations in epigenetic mechanisms

While genetic factors play important roles in the etiology of neuropsychiatric disorders, the results of twin studies indicate that additional factors, such as epigenetic mechanisms, are essential for disease onset. Epigenetic mechanisms include histone and DNA modifications such as acetylation, ubiquitination, SUMOylation, methylation, phosphorylation of noncoding RNAs (Nestler et al., 2015). Epigenetic mechanisms contribute to brain development and physiological function of the brain. Disruption of epigenetic regulatory mechanisms could be associated with psychiatric disorders (Nestler et al., 2015).

Postmortem human brain and blood studies in patients with SCZ have shown that promoter regions of several genes including *REELIN*, SRY-box 10 (*SOX10*), major histocompatibility complex (*HLA*), glutamate decarboxylase 1 (*GAD1*), catechol-O-methyltransferase (*COMT*) and *BDNF* (Abdolmaleky et al., 2005; Carrard et al., 2011; Ikegame et al., 2013; Kundakovic et al., 2015; Walton et al., 2014) are methylated. Target genes of abnormal DNA methylation are common SCZ and BD. *HLA9* and *GAD1* gene methylation changes were observed in the brain tissue of patients with BD (Kaminsky et al., 2012; Ruzicka et al., 2015). Dynamic changes in histone acetylation and methylation have also been shown to contribute to rodent stress models and antidepressants affect these same histone-modifying mechanisms (Nestler et al., 2015), although the full relevance of these observations to human disease is unknown given challenges inherent to modeling complex behaviors in rodent models. Understanding if changes in miRNA expression occur in neuropsychiatric disorders due to epigenetic regulatory mechanism, such as DNA methylation in miRNA genes, represents an important avenue for future studies.

## 3. MiRNAs

MiRNAs are short, single stranded, endogenous, and noncoding RNAs that regulate gene expression by binding to complementary sequences principally in their target mRNAs' 3'-untranslated region (UTR), and also to a lesser extent to the 5'-UTR and coding regions (Hamzeiy et al., 2014). A region of about 2–8 to nucleotides within the structure of the miRNA is called the “seed sequence/region”. Target recognition is primarily determined by this seed sequence, leading to the regulation of gene expression (Lewis et al., 2003). Here the definition of a miRNA target refers to a specific pairing of a miRNA and a mRNA sequence, with the recognition that formal proof of a target of a miRNA requires extensive experimental validation beyond what can be simply predicted based upon sequence homology. In many cases the manipulation of a miRNA may lead to alterations of the expression of a gene through secondary indirect effects of a miRNA on other regulatory mechanisms or genes, which is an important caveat when considering list of reported target genes in many studies.

The canonical miRNA biogenesis applies to the maturation of most miRNA families, except unique miRNA families that have been described before (Hammond, 2015). In the canonical pathway, a primary transcript (pri-miRNA) is transcribed in the nucleus by RNA polymerase II; next, Drosha and ‘DiGeorge syndrome critical region gene 8’ (DGCR8) process the pri-miRNA to generate precursor miRNA (pre-miRNA). Pre-miRNAs are then exported to the cytoplasm via exportin 5, a double-stranded RNA-binding protein, where Dicer cleaves the

pre-miRNA hairpin loop to form ~22 base pair mature miRNAs. Finally, mature miRNAs are loaded into the RNA-induced silencing complex (RISC) to regulate translation process (Fig. 1) (Ha and Kim, 2014). Depending on the complementarity between the miRNA and its target(s), miRNAs either repress translation, or cause degradation of target mRNAs (Dalmay, 2013).

Conventional methods used to measure miRNA expression include microarrays, real-time PCR, in situ hybridization. In addition, various methods are currently being developed, such as nanoparticle-derived probes, isothermal amplification, electrochemical methods, and next-generation sequencing (Tian et al., 2014). Considering that i) single base differences can significantly affect miRNA binding to target genes, and ii) different miRNA family members share closely-related sequences, sequencing is a highly valuable approach to detect and quantify specific miRNAs.

Approximately 75% of annotated miRNAs are expressed in the brain and contribute both physiological brain development and neural function including neurogenesis, neuronal differentiation, and synaptogenesis (Ji et al., 2013). Moreover, miRNAs play critical roles in cell fate determination of neurons and glia, by suppressing specific target genes. For example, miR-124 is one of the best-studied miRNAs, which is richly expressed in the brain and is related to brain development and neuronal differentiation (Sun et al., 2015). Another brain-specific miRNA is miR-9, which is expressed in both neurons and glia. miR-9 plays an essential role in various aspects of neurogenesis (Smirnova et al., 2005).

MiRNAs appear to be differentially distributed between distinct brain areas (Hommers et al., 2015). In addition to brain region or neuron type specific expression differences, neurons display differential intraneuronal miRNA compartmentalization. The contributor mechanisms of specific enrichment of miRNAs within synapses, dendrites, and axons remain unknown, but involvement of some RNA-binding proteins for delivering or anchoring miRNAs to particular neuron areas is possible (O'Carroll and Schaefer, 2013). For example, Fragile X mental retardation protein (FMRP), a component of the RISC that interacts with Ago1 (Jin et al., 2004), is expressed in many tissues. FMRP expression is especially high in dendrites and spines of neurons (Li and Jin, 2009). Indeed, several brain-enriched miRNAs, including miR-125b, miR-128, and miR-132, are associated with FMRP (Edbauer et al., 2010). Mutations in protein activator of interferon induced protein kinase (*PRKRA*), which encodes PACT one of the RISC loading complex (RLC) proteins, cause young-onset dystonia-parkinsonism disorder (Camargos et al., 2008). *TRIM32* positively regulates miRNA activity, and shows strong expression in differentiating neurons in the ventricular zone (VZ) (Kawahara et al., 2012). Collectively, these reports suggest that miRNA biogenesis is closely related to the pathogenesis of nervous system disorders.

#### 4. Genetic variants in miRNA-related genes

In the past few years accumulating evidence have supported that changes in miRNA regulation or function are associated with psychiatric disorders, including major depressive disorder (MDD), BD and SCZ. Alterations in miRNA activity can occur as a result of different variations (Fig. 2): (1) in the machinery genes related to miRNA biogenesis; (2) in



the miRNA promoter sequences; (3) in the sequences responsible for pre-miRNA cleavage; (4) the miRNA binding sites in target genes; or (5) in the seed sequences (Hogg and Harries, 2014).

In this review, we focus on three categories of polymorphisms in the miRNA regulatory pathway: (1) SNPs or CNVs in miRNA genes; (2) SNPs or CNVs in miRNA binding sites in target genes and (3) SNPs or CNVs in genes involved in miRNA biogenesis and processing with the major findings summarized in Table 1.

#### 4.1. Variants in miRNA genes in neuropsychiatric disorders

Variations in pri- and pre-miRNAs can affect miRNA processing, and variations in mature miRNAs can influence miRNA-binding to its target transcripts. In addition, SNPs in promoters of miRNA genes or miRNA host genes may have impact on miRNA expression.

SNPs in miRNA genes have been most extensively studied in SCZ among various neuropsychiatric disorders. Hansen et al. have carried out the first study in this field, and showed that SNPs in miR-198 (rs1700) and miR-206 (rs17578796) are associated with SCZ (Hansen et al., 2007). SNPs in other miRNAs, including miR-498, pre-miR-30e, and miR-130b, have also associated with SCZ in different ethnic groups (Begemann et al., 2010; Green et al., 2013; Whalley et al., 2012; Xu et al., 2010). Additionally, different SNPs (rs1625579; rs1198588, rs1702294) in the upstream region of the host gene for miR-137 have been strongly associated with SCZ (Cummings et al., 2013; Green et al., 2013; Psychosis Endophenotypes International et al., 2014; Ripke et al., 2013; Schizophrenia Psychiatric Genome-Wide Association Study, 2011; Whalley et al., 2012). Besides SNPs, variable number tandem repeats (VNTRs) and rare variants have been also reported within the same *MIR137* locus (Duan et al., 2014; Strazisar et al., 2015; Warburton et al., 2015). Recently, Warnica et al. reported CNVs at eight loci (1q21.1, 2q13, 12q21.31, 14q32.33, 15q11-15q13, 16p11.2, 16p13.11, and 19q13.42), which overlap with a total of 25 miRNAs (Warnica et al., 2015), providing abundant evidence for the potential contribution of disrupted miRNA levels to the underlying pathophysiology.

To date, less evidence is available for a role of genetic variation in miRNAs in BD and MDD. Whalley et al. performed the first study in individuals with higher genetic risk of developing BD, and found a SNP in miR-137 (rs1625579) gene (Whalley et al., 2012). A recent comprehensive analysis of 609 autosomal miRNAs was performed in the context of a large bipolar disorder genome-wide association study (9747 patients and 14,278 controls). This study provided evidence for the nominally significant association of 98 unique miRNA loci that was reduced to 9 loci after correction for multiple testing, including miR-499, miR-708 and miR-1908 (Forstner et al., 2015).

Finally, 2 SNPs in pre-mir-182 (rs76481776) and pre-miR-30e (ss178077483) are associated with MDD (Saus et al., 2010a,b; Xu et al., 2010). With larger GWAS of MDD underway, it is likely that additional miRNAs will be implicated by genetic variation associated with MDD.

## 42. Variants in miRNA target genes in neuropsychiatric disorders

Since there is a strict recognition requirement between the miRNA seed region and its target, a naturally occurring SNP in a gene may have significant functional implications for miRNA binding and post-transcriptional regulation of gene expression.

One of the earliest studies on psychiatric diseases was carried out on SCZ patients. Begemann et al. found a SNP in rs3822674 in the complexin 2 gene (*CPLX2*) that affects binding of miR-498 to its target site (Begemann et al., 2010). Previous studies found common variants in the *CPLX2* gene to be highly associated with cognitive dysfunction in SCZ patients (Eastwood and Harrison, 2005; Ripke et al., 2013). Other SNP findings associated with SCZ are located in predicted binding site of miR-625 and miR-1302 in purinergic receptor P2X (*P2RX7*) gene, in the miR-124 binding site of regulator of G protein signaling 4 (*RGS4*) gene (rs10759); and 3 other SNPs (rs17110432, rs11178988 and rs11178989) in the 3'-UTR of TBC1 domain family member 15 (*TBC1D15*) gene (Gong et al., 2013; Liu et al., 2012; Rahman et al., 2010). P2RX is a ligand gated ion channel that is activated by adenosine triphosphate (ATP), and mediates GABA release (Hansen et al., 2008). Altered GABA neurotransmission has been seen in prefrontal cortex (PFC) of schizophrenic patients (Lewis et al., 1999). Deletion of 22q11.2 is a well-known SCZ-associated CNV (Bassett and Chow, 1999; Chow et al., 1999). Notably, miR-185 is located on this locus, and the role of this miRNA and its downstream pathways has also been implicated in SCZ (Brzustowicz and Bassett, 2012; Forstner et al., 2013; Gardiner et al., 2012).

So far, only three studies have investigated the role of SNPs in miRNA target genes in mood disorders. The first study was conducted on patients with BD or MDD, which showed a significant association between the SNP in *P2RX7* gene (rs1653625) and disease conditions (Rahman et al., 2010). Purinergic signaling in the peripheral and central nervous systems was discovered in the 1970s (Burnstock, 2006) and suggesting as a susceptibility gene for both MDD and BD (Halmai et al., 2013). The over activity of P2 receptors has been seen in MDD and P2X receptor antagonism leads anti-depressant and anti-anxiety effects in mice (Ortiz et al., 2015). Additionally, a SNP was detected in the metabotropic glutamate receptor 7 (*GRM7*) gene, which was predicted to cause alterations in the miRNA binding sites for the mutated base of rs56173829 (Kandaswamy et al., 2014). In another study, a SNP in the mitogen-activated protein kinase kinase 5 (*MAP2K5*) gene (which contains a predicted binding site of miR-330-3p), is associated with MDD in African American subjects, but not in European American subjects (Jensen et al., 2014).

A full understanding of the functional consequence of these SNPs in miRNA target genes awaits further biological investigations.

## 4.3. Variants in miRNA biogenesis genes in neuropsychiatric disorders

SNPs, chromosomal deletions, insertions, duplications or CNVs in regions related to miRNA biogenesis are associated with susceptibility to neuropsychiatric disorders (Table 1). For instance, there is a strong and specific connection between 22q11.2 microdeletion and SCZ. One gene disrupted by the 22q11.2 microdeletion is DGCR8 (Fenelon et al., 2011;



Merico et al., 2014; Zhao et al., 2015). In addition, DGCR8 expression is upregulated in the DLPFC (BA9) of SCZ patients (Beveridge et al., 2010). In a subsequent study on SCZ, Santarelli et al. found an increase in the levels of miR-15 family miRNAs, such as miR-15a, miR-15b, miR-195 and DGCR8 mRNA expression in the superior temporal gyrus and DLPFC (Santarelli et al., 2011). Despite the lack of studies on deregulated miRNA biogenesis in BD, 2 SNPs located in DGCR8 (rs3757) and AGO1 (RISC component) (rs636832) are associated with MDD (He et al., 2012). In contrast, no association was observed between the mRNA levels of Dicer, Drosha and DGCR8; but this finding is based on data from small subset of MDD patients and control subjects (Smalheiser et al., 2012).

## 5. MiRNA expression studies in neuropsychiatric disorders

Besides mutations in miRNA-related genes, altered miRNA expression levels have been identified in multiple studies. Expression studies have generally used postmortem brain tissue samples, cerebral spinal fluid (CSF) or peripheral blood; thus, they can demonstrate the correlation between miRNAs and disease. Here, we summarized the studies that demonstrate altered miRNA expression in SCZ, BD, and MDD (Tables 2–4). It is important to note that despite the high number of disease-associated miRNAs, only a small number of miRNAs are common between different studies. This is not completely surprising, given the polygenic and complex nature of these disorders. However, the limitations of these studies (including limited sample size, cellular heterogeneity of brain regions, and cell-specific miRNA expression) must be considered when interpreting the results. Thus, more detailed, large-scale, association studies are needed to further clarify the involvement of miRNAs in these diseases.

### 5.1. Schizophrenia

The changes in miRNA expression profiles in SCZ have been investigated in several studies. In most of the miRNA profiling studies, postmortem brain tissues from SCZ patients are used, and a vast number of differentially expressed miRNAs have been identified (Banigan et al., 2013; Beveridge et al., 2008, 2010; A. H. Kim et al., 2010; Levinson et al., 2014; Perkins et al., 2007; Santarelli et al., 2013; Wong et al., 2013; Zhu et al., 2009).

Although the studies vary in their findings, some of these miRNA alterations are consistent. For example, upregulation of miR-181a and miR-181b is detected in the superior temporal gyrus (BA22) (Beveridge et al., 2008), and DLPFC from SCZ patients (Beveridge et al., 2008, 2010), and in blood (Shi et al., 2012). miR-181a is strongly enriched in the synaptodendritic compartment of the nucleus accumbens. It can regulate the glutamate receptor 2 subunit (GluA2) of AMPA receptors, which are vitally involved in synaptic plasticity, at the post-transcriptional level (Saba et al., 2012). On the other hand, alteration of some miRNAs, like miR-132 (A. H. Kim et al., 2010; Miller et al., 2012; Yu et al., 2015) and miR-134 (Gardiner et al., 2012; Santarelli et al., 2011; Yu et al., 2015) were inconsistent between different studies.

Studies of miRNA expression in peripheral tissues have also revealed associations with SCZ. Lai et al. found 6 upregulated miRNAs and 1 downregulated miRNA in the white blood cells of SCZ patients compared to healthy controls (Lai et al., 2011). Gardiner et al. identified 7

downregulated miRNAs in peripheral blood mononuclear cells of SCZ patients (Gardiner et al., 2012). Shi et al. also analyzed miRNA expression in the serum of SCZ patients, and observed 4 upregulated miRNAs whereas one miRNA was downregulated (Shi et al., 2012). In a recent study, global plasma miRNAs were profiled in an initial discovery cohort of 164 SCZ patients and 187 controls followed by replication in a cohort of 400 SCZ patients, 213 controls, and 162 non-SCZ psychiatric patients, and miR-130b and miR-193a-3p levels are upregulated in SCZ but not controls or other psychiatric disorders (Wei et al., 2015). The functional targets of these miRNAs include a number of genes, such as BDNF, the dopamine receptor (*DRD1*), the synaptic protein neuregulin 1 (*NRG1*) (Stefansson et al., 2002), neurotrophic tyrosine kinase receptor (TrkB-T1) and early growth response gene 3 (*EGR3*) (S. H. Kim et al., 2010; Yamada et al., 2007), that have been linked with schizophrenia in previous studies.

Whole transcriptome sequencing is an important analytical technique that uses massively parallel RNA-seq to carry out transcriptome analyses at a far higher resolution (Nagalakshmi et al., 2010). Pietersen et al. used laser capture microdissection (LCM)-isolated neurons from the superior temporal gyrus of postmortem schizophrenia and normal control brain. Using whole transcriptome sequencing, the authors identified 15 miRNAs that were differentially expressed in SCZ (Pietersen et al., 2014b). The same group also profiled the miRNA expression of LCM-isolated pyramidal neurons from the superior temporal gyrus of postmortem brains from SCZ and normal control subjects, and identified 10 miRNAs that were differentially expressed in neurons using the same methods (Pietersen et al., 2014a). A number of the differentially expressed miRNAs are in concordance with previous studies on postmortem SCZ samples. These miRNAs include miR-150 (Miller et al., 2009; Santarelli et al., 2011), miR-328 (Santarelli et al., 2011), and miR-30b (Mellios et al., 2012; Perkins et al., 2007). Additionally, Kohen et al. used RNA-seq of dentate gyrus granule cells LCM-isolated from hippocampus of postmortem SCZ, BD MDD patients and control brain. Their results showed evidence of disrupted miR-182 signaling in subjects with SCZ and MDD (Kohen et al., 2014).

## 5.2. Bipolar disorder

Studies of miRNA expression in BD have also showed significant alterations in postmortem brain tissue from affected subjects. These studies have usually focused on two brain areas; PFC (BA9/BA10) and DLPFC (BA46) and detected several upregulated and downregulated miRNAs (Banigan et al., 2013; A. H. Kim et al., 2010; Miller et al., 2012; Moreau et al., 2011; Smalheiser et al., 2012). On the other hand, Zhu et al. analyzed miR-346 levels in DLPFC (BA 46) tissues from SCZ and BD, but did not found significant alteration in BD patients (Zhu et al., 2009). Despite substantial heterogeneity of miRNA identified in association with BD, a few miRNAs have appeared in multiple studies (see Table 3 for complete and detailed list of studies).

In addition to studies in peripheral blood, CSF, and post-mortem tissues, Bavamian et al. demonstrated a new avenue of investigation to connect dysregulation of miRNAs to BD. In this study, the authors analyzed induced neurons (iNs), neurons induced pluripotent stem cells (iPSCs) from a family with BD and post-mortem brain tissue from BD subjects and

controls and demonstrated the elevation of miR-34a expression in the context of BD (Bavamian et al., 2015; Madison et al., 2015). Moreover, miR-34a was shown to directly target the expression of the BD risk factors *ANK3* and the voltage-dependent L-type calcium channel subunit beta-3 (*CACNB3*), with an extended network of BD risk genes and dendritic morphology affected upon its overexpression. This leads to the conclusion that through the regulation of a molecular network essential for neurodevelopment and synaptogenesis, miR-34a may provide a critical link between multiple genetic risk factors for BD and its underlying pathogenesis. Given the opportunity to investigate early stages of neurodevelopment and the response to diverse pharmacological agents, such studies with iN and iPSC models of BD and other neuropsychiatric disorders hold tremendous promise for dissecting the regulation and function of miRNAs in the future (Haggarty et al., 2016).

### 5.3. Major depressive disorder

To date, five studies have focused on miRNA expression profiles in MDD by using postmortem brain tissue samples. Similar to BD, these studies used PFC (BA9 or BA10) as the starting material. Additional studies have focused on changes of miRNA expression in peripheral blood or CSF (Belzeaux et al., 2012; Camkurt et al., 2015; Li et al., 2015; Li et al., 2013; Wan et al., 2015). Interestingly, targets of altered miRNAs in MDD play significant roles in several pathways associated with nervous system and brain functions, such as serotonin transporter (*SERT*) and metabotropic glutamate receptor 4 (*GRM4*).

Further investigation of these more robust miRNAs and their target genes should provide insight into the development these disorders, and these miRNAs could potentially serve as biomarkers (please refer to Table 4 for complete and detailed list of studies).

## 6. Effect of drugs on miRNA expression

### 6.1. Antipsychotics

The effects of different antipsychotic drugs (haloperidol, clozapine, risperidone, etc.), on miRNA expression are summarized in Table 5. In the first study, upregulation in the levels of miR-199a, miR-128a, and miR-128b were observed in rats treated with haloperidol (Perkins et al., 2007). In another animal study, Kocerha et al. found that haloperidol and clozapine decrease miR-219 level in C57BL/6 mice, and this miRNA negatively regulates the function of NMDA receptor (Kocerha et al., 2009). Santarelli et al. investigated the changes in miRNA expression associated with haloperidol, clozapine and olanzapine treatment in the mouse brain. The results of this study showed that olanzapine treatment leads to a decrease in miR-193 level, whereas haloperidol treatment leads to a decrease in miR-434-5p and miR-22 levels. Yet, the results of clozapine treatment were excluded due to incompatible results of real time-PCR validation (Santarelli et al., 2013). According to previous observations, these miRNAs are elevated in the DLPFC brain tissue of SCZ patients (Moreau et al., 2011).

In another study, peripheral samples obtained from SCZ patients (before and after treatment) were used and the expression levels of 9 SCZ-associated miRNAs were investigated. Before treatment, the expression levels of miRNA-181b, miRNA-30e, miRNA-34a and miRNA-7

were significantly upregulated in the SCZ-group. After 6-week antipsychotic treatment, expression level of miR-181b was significantly down-regulated (H. T. Song et al., 2014). Finally, a recent study showed that increased levels of miR-130b and miR-193a-3p in the plasma of SCZ patients could be suppressed after 1 year of treatment with 2 antipsychotic drugs (aripiprazole and risperidone) (Wei et al., 2015).

## 6.2. Mood stabilizers

Changes in miRNA expression in response to mood stabilizers, such as lithium and valproic acid (VPA), have been investigated in several studies (Table 5). One study in rats showed an alteration in hippocampal miRNA levels following chronic treatment with lithium or VPA (Zhou et al., 2009). In vitro studies on cell lines derived from BD patients have shown that 4 miRNAs (hsa-miR-34a-5p, hsa-miR-152-3p, miR-155-5p, hsa-miR-221-3p) were dysregulated after 16 days of treatment (Chen et al., 2009). Expression changes after drug treatment have also been investigated in cell lines. For example, rat cerebellar granule cells were treated with lithium/VPA combination and 7 miRNAs (let-7b, let-7c, miR-128a, miR-24a, miR-30c, miR-34a, and miR-221) were downregulated, whereas only miR-144 was upregulated after treatment (Hunsberger et al., 2013). Combination of lithium and VPA has been also tested in vitro, which leads to a decrease in miR-30a-5p in SH-SY5Y human neuron-like cells (Croce et al., 2014). Recently, our group investigated the role of miR-34a in neuroprotective effects of lithium, and found that lithium decreases miR-34a expression and increases expression of its target genes (*BCL2*, *NRF2* and *BDNF*) in SH-SY5Y cells (Alural et al., 2015). Given that i) miR-34a levels are elevated in patients with BD, miR-34a represents a potentially important link between pharmacological treatment options for BD and molecular mechanisms underlying disease pathophysiology (Bavamian et al., 2015).

## 6.3. Antidepressants

Regarding a possible involvement of miRNAs in the action of antidepressant drugs, effects of different drugs on miRNA expression have been investigated (Table 5). Baudry et al. found that infusion of fluoxetine in mouse brain increases miR-16 levels in serotonergic raphe nuclei, and the authors proposed that miR-16 functions as a regulator between serotonin reuptake inhibitor (SRI) treatment and hippocampal neurogenesis (Baudry et al., 2010). The same laboratory used mouse hippocampus tissue and patient-derived CSF to analyze miR-16 expression. Stereotaxic injection of fluoxetine into raphe nuclei resulted in a decrease in the endogenous level of miR-16 in the hippocampus and corresponding increase in serotonin transporter (SERT), the target of SRIs (Launay et al., 2011). Fluoxetine treatment was also found to increase secretion of BDNF, Wnt2 and 15-deoxy-delta12,14-prosta-glandin J2 from serotonergic neurons that coordinately regulated miR-16 levels in the hippocampus (Launay et al., 2011). Elevated levels of these same factors were observed in the CSF of depressed patients upon fluoxetine treatment suggesting an important role for miR-16 in SRI response (Launay et al., 2011). Another anti-depressant drug, escitalopram, also alters peripheral miRNA expression in MDD patients. Bocchio-Chiavetto et al. reported that 28 miRNAs are upregulated, and 2 miRNAs are downregulated after 12 weeks of escitalopram treatment (Bocchio-Chiavetto et al., 2013). Taken together, these results suggest that miRNA regulation may play a key role in shaping neuroplasticity involved in depressive behavior and the response to clinically effective therapeutics.

## 7. Biomarker discovery studies on miRNAs

### 7.1. Diagnostic potential of miRNA alteration in blood and CSF

Biomarkers are valuable tools to diagnose individuals at the early stages of disease, to develop therapeutic strategies, and to provide prognostic information. Currently, diagnosis of neuropsychiatric disorders relies on behavioral and clinical symptoms, which appear after several years of disease progression. Therefore, establishment of biomarkers that allows early detection is of utmost importance for the management of these disorders. In this regard, miRNAs can also be isolated from circulating blood cells or CSF, and they are promising non-invasive biomarkers for a wide variety of diseases (Stoicea et al., 2016).

Lai et al. reported the first study on miRNAs as possible biomarkers for SCZ. In this study, the authors identified a 7-miRNA signature in peripheral blood mononuclear cells (PBMCs), which is able to distinguish SCZ patients from control subjects with 93% accuracy (Lai et al., 2011). In another study, 10 SCZ-linked miRNAs were analyzed, and 5 of these miRNAs (miR-30e, miR-181b, miR-34a, miR-346 and miR-7) were shown to discriminate SCZ patients from healthy controls with 71% accuracy, a specificity of 95% and a sensitivity of 92% (Sun and Shi, 2015). Fan et al. investigated miRNA changes in PBMC samples obtained from young SCZ patients and control subjects and receiver operating characteristics (ROC) analysis of 9 miRNAs showed very high sensitivity and specificity for diagnosis of SCZ (AUC = 0.973, 95% confidence interval (CI): 0.945–1.000) (Fan et al., 2015). Fan et al. suggested that alterations in peripheral levels of miRNA-26b, miRNA-1972, miRNA-4485, miRNA-4498, and miRNA-4743 are associated with MDD (AUC = 0.636, 95% confidence interval (CI): 0.58–0.90) (Fan et al., 2014). Recently, Wan et al. analyzed differentially expressed miRNAs in both CSF and serum samples from MDD patients. The authors observed three upregulated miRNAs and one downregulated miRNA, and ROC analysis of these miRNAs showed very high sensitivity and specificity for diagnosis of MDD (AUC for each miRNA > 0.9; sensitivity > 90%; specificity > 84%) (Wan et al., 2015). Concerning plasma-based miRNA expression profiling studies in MDD, the combined use of miR-101-3p and miR-93-5p has been suggested as an optimal normalization method to contribute to more reliable and accurate results for biomarker discovery for MDD (Liu et al., 2014).

An important caveat of these studies seeking to use miRNAs as diagnostics (and below for predicting drug response) is the fact that patients are almost always on various medications, sometimes combinations, making it difficult to control for a suite of factors. Future studies will benefit from more explicit and careful study of this confounding factor.

### 7.2. Altered miRNAs as biomarkers to predict drug response

MiRNAs not only can be utilized for monitoring treatment but also promising predictive biomarkers for predicting drug response. The discovery of the role of miRNAs in drug resistance and drug response can potentially improve diagnosis, treatment and prognosis in patients. Furthermore, real-time analysis of miRNA expression can be used to adjust drug treatment to achieve optimal response in patients.

**7.2.1. Schizophrenia**—In the context of SCZ treatment, Wei et al. identified two upregulated miRNAs (miR-130b and miR-193a-3p) in the plasma of SCZ patients, which were suppressed in remitted patients after one year of treatment with antipsychotic drugs (aripiprazole and risperidone). The baseline levels of these two miRNAs were lower in patients in remission, compared to patients who were not in remission. Thus, their findings suggest that miR-130b and miR-193a-3p levels can be used as potential biomarkers to predict drug response in SCZ patients (Wei et al., 2015).

**7.2.2. Bipolar disorder**—Lithium and valproic acid are commonly used mood stabilizers for treatment of BD. Different studies have suggested that changes in miRNA expression can be used to monitor response to mood stabilizers. For instance, Hunsberger et al. showed that lithium treatment down-regulates let-7 miRNA family expression in lymphoblastoid cells in BD lithium responders (Hunsberger et al., 2015). In another example, Rong et al. reported that plasma miRNA-134 levels in drug-free patients with BD mania are significantly lower compared to control subjects. The authors also reported that plasma miRNA-134 levels increase significantly after four weeks of treatment (Rong et al., 2011). Overall, these findings suggest that monitoring let-7 family and miRNA-134 expression in BD may serve as a potential marker to predict efficacy of treatment.

**7.2.3. Major depressive disorder**—Alternation in miRNA expression in patients with MDD has been evaluated as a SSR1 response biomarker. For example, citalopram-responding patients were found to have reduced serum miR-1202 levels at baseline, compared to non-responders, and expression of miR-1202 increased during the course of treatment in antidepressant-responsive MDD patients (Lopez et al., 2014a,b). Additionally, miR-151-3p expression in LCLs has been shown to be a marker of paroxetine sensitivity (Oved et al., 2012). Overall, while miR-1202 and miR-151-3p have potential for use as biomarkers to predict response to antidepressants, further work is required to more comprehensively elucidate the potential roles of miRNAs in the variability of drug response and to provide mechanistic insight into the basis for such differential response.

## 8. Conclusion & perspective

Although still in its infancy, the studies summarized above reflect the growing recognition of the importance of ncRNAs in the form of miRNAs in the potential etiological mechanisms of multiple neuropsychiatric disorder, diagnostics, and the response to pharmacological treatments. In terms of the significance of many of the findings reported to date, it will be critical for the field to rigorously test the reproducibility and generalizability of the observations made in independent samples and larger cohorts. Here, the ability to systematically study the expression of miRNAs in patient-derived samples from peripheral blood, CSF, patient-derived iNs and iPSCs, and post-mortem tissue holds promise for the elucidation of the role specific miRNAs in different cell types, stages of neurodevelopment, and in response to pharmacological agents (Haggarty et al., 2016).

With growing recognition of the polygenic nature of neuropsychiatric disorders like SCZ, BD and MDD, the ability of a single miRNA to simultaneously control the expression of multiple genetic factors linked to the etiology of each disease or to a pathway of interest



makes understanding the impact of disease-associated genetic variation on miRNA expression and function of paramount importance. In this context, through the systematic investigation of the network of genes affected by dysregulated miRNAs in different neuropsychiatric disorders, either due to genetic variation itself in the miRNAs or their target genes, it may be possible to provide insight into the unique, as well as overlapping, complex mechanisms underlying disease pathophysiology (Barabasi et al., 2011). As the ability of ncRNAs to be used as potential therapeutic agents themselves improves through advances in delivery of nucleic acids (Kumar et al., 2015), along with the creation of RNA-targeted therapeutics (Bernat and Disney, 2015), this network-based approach may in turn help facilitate the discovery of novel therapeutics for treating and ideally preventing neuropsychiatric disorders.

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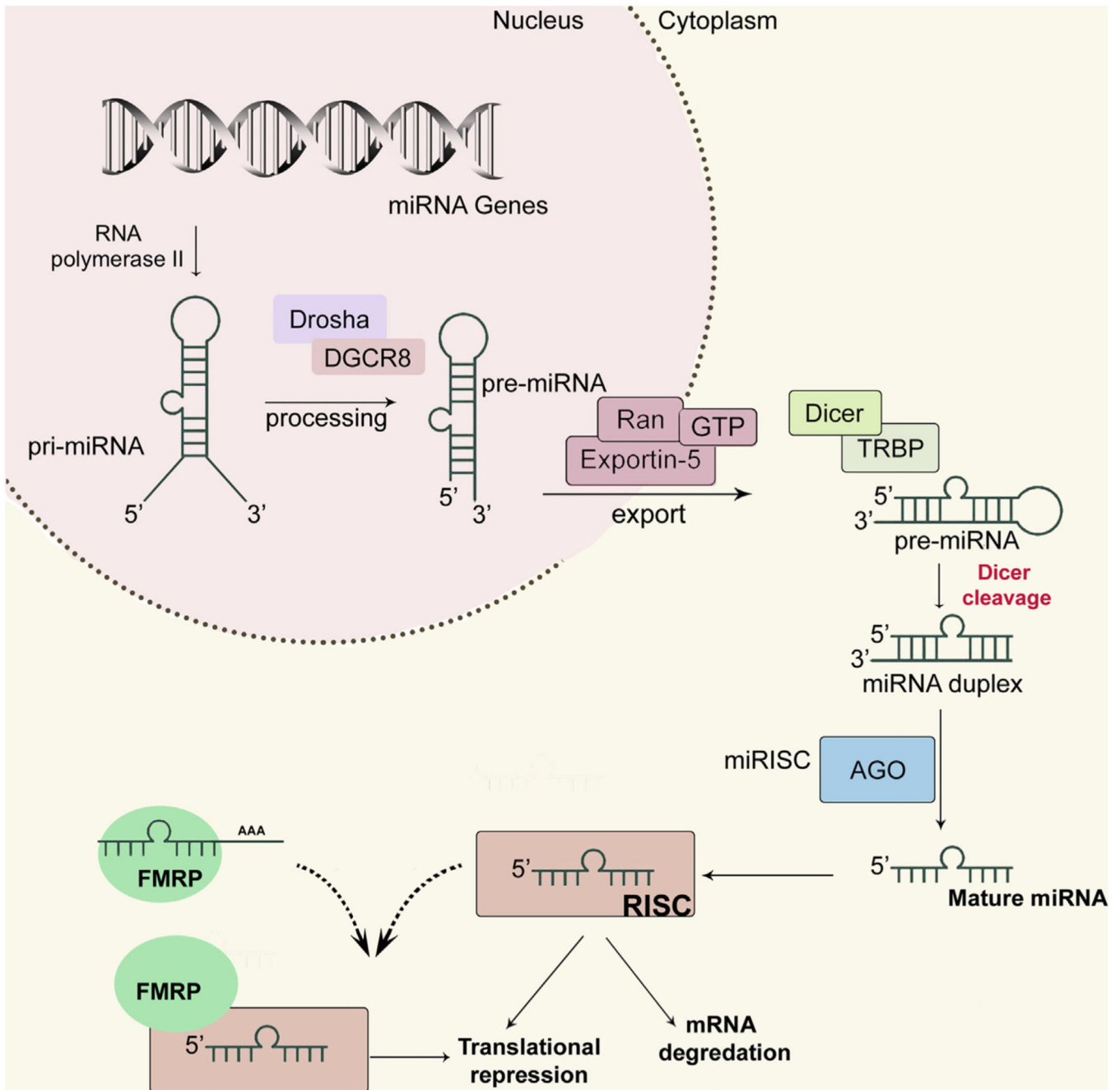
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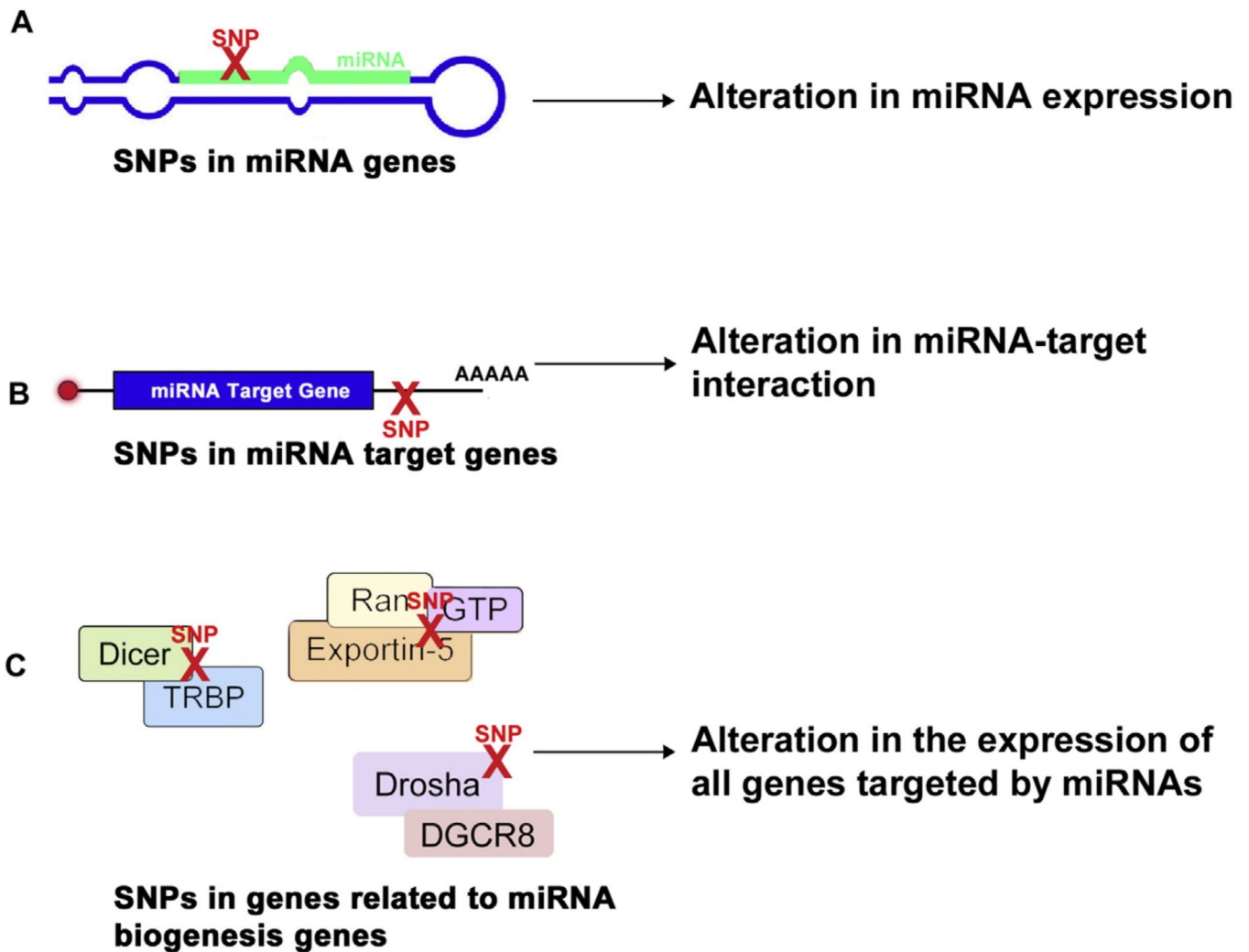




**Fig. 1.**

Overview of miRNA biogenesis and its interaction with FMRP. RNA polymerase transcribes the miRNA genes, and Drosha processes the resulting pri-miRNAs. Then, pre-miRNAs are exported into the cytoplasm and are further processed by Dicer. Mature miRNAs are loaded into the RISC, which in turns binds to complementary sequences on 3' UTRs of target mRNAs. According to an alternative hypothesis, FMRP binds to some mRNAs, and miRNA-RISC can interact with FMRP-mRNA complex, thereby leading to translational inhibition.





**Fig. 2.**

The effect of SNPs on miRNA-mediated regulation of gene expression. SNPs in different steps of miRNA biogenesis exert diverse effects on the regulation of gene expression. (A) SNPs in miRNA genes can alter miRNA expression. (B) SNPs in target mRNAs also affect miRNA function by altering miRNA-target interaction. (C) SNPs in miRNA machinery genes affect the entire transcriptome that is subject to miRNA-mediated regulation.

Table 1

Variants in miRNA genes in neuropsychiatric disorders.

	MiRNA	Population	Number of samples	Functional result
Hansen et al. (2007)	SNP in miR-198 (rs1700) and miR-206 (rs17578796)	Scandinavian	Danish subjects: 420 SCZ patients, 1006 control subjects Norwegian subjects: 257 SCZ patients, 293 control subjects Swedish subjects: 163 SCZ patients, 177 control subjects	One pathway was identified with 8 common targets to both miRNAs (PTPN, CCND2, CREB5, MET, N-PAC, MEIS1, PUM2.APIG1)
Burmistrova et al. (2007)	SNP in miR-130b (rs861843)	Russian	300 SCZ patients, 316 control subjects	Not assessed
Feng et al. (2009)	SNP in miR-188, miR-18b/18b*, miR-502, miR-505, miR-510, miR-660, miR-325, miR-509-3, let-7f-2	Caucasian	193 SCZ patients, 191 control subjects	CLCN5, HMGA2, NRXN3, DISC1, NRG1, MECP2, RGS4, GRM3, ERBB4, MAGI2, DLG2
Xu et al. (2010) Schizophrenia Psychiatric Genome-Wide Association Study (2011)	SNP in pre-miR-30e (ss178077483) SNP in miR-137 (rs1625579)	Chinese Genome-Wide Association Study	456 SCZ patients, 453 control subjects 17,836 SCZ patients, 33,859 control subjects	<i>Ubc9</i> Implicated in regulation of adult neurogenesis and neuronal maturation. Four predicted targets (TCF4, CACNA1C, CSMD and C10orf26) were found to have SNPs associated with schizophrenia
Whalley et al. (2012) Begemann et al. (2010)	SNP in miR-137 (rs1625579) SNP in miR-498 (rs3822674)	Scottish Caucasian, 95.3%; other, 1.6%; unknown, 3.1%)	44 high genetic risk of SCZ, 81 controls 792 SCZ patients, 159 patients with schizoaffective disorder, 120 suspected schizophrenic psychosis cases, 1079 control subjects	Not assessed 3' UTR of candidate schizophrenia genes, a SNP in the complexin 2 (CPLX2) 3' UTR in a predicted binding site of miR-498.
Green et al. (2013)	SNP in miR-137 (rs1625579)	Australian	526 SCZ patients, 91 patients with schizoaffective disorder, 764 control subjects	Not assessed
Cummings et al. (2013)	SNP in mir-137 (rs1625579)	Irish	821 SCZ patients, BD patients and schizoaffective disorder, 171 control subjects	Associated with a specific psychosis phenotype.
Ripke et al. (2013)	SNP in miR-137 (rs1198588)	Swedish	5001 SCZ patients, 6243 control subjects	The SNP with the strongest association to schizophrenia (rs1198588) is 39 kb upstream of <i>MIR137</i> , and might regulate the transcription of <i>MIR137</i> .
Psychosis Endophenotypes International et al. (2014)	SNP in miR-137 (rs1702294) and miR-548aj2(rs215411)	Genome-Wide Association Study	36,989 SCZ patients, 113,075 control subjects	Not assessed
Warnica et al. (2015)	CNVs at eight loci: Iq21.1, 2q13, 12q21.31, 14q32.33, 15q11-15q13, 16p11.2, 16p13.11, and 19q13.42	Canadian	420 SCZ patients, 2357 control subjects	Predicted gene targets: CAPRN1, NEDD4, NTRK2, PAK2, RHOA, and SYNGAP1

	MI RNA	Population	Number of samples	Functional result
Whalley et al. (2012)	SNP in miR-137 (rs1625579)	Scottish	90 high genetic risk of BD, 81 control subjects	Not assessed
Forstner et al. (2015)	SNPs in miR-199, miR-640, miR-708, miR-581, miR-644, miR-135a-1, miR-1908, let-7g	Genome-Wide Association Study	9747 BD patients, 14,278 controls	Target gene and pathway analyses revealed 18 significant canonical pathways, including brain development and neuron projection.
Saus et al. (2010a,b)	SNP in pre-mir-182 (rs76481776)	Spanish	359 MDD patients, 341 control subjects	Associated with late insomnia in MDD.
Xu et al. (2010)	SNP in pre-miR-30e (ss178077483)	Chinese	1088 MDD patients, 1102 control subjects	Not assessed
<i>Variants in miRNA target genes in neuropsychiatric disorders</i>				
	SNP/CNV	Population	Number of samples	Functional result
Begemann et al. (2010)	SNP in <i>CPLX2</i> gene (affecting miR-498 binding) (rs3822674)	Caucasian	1071 SCZ patients, 1079 control subjects	CPLX2 gene is associated with altered cognition in SCZ patients.
Gong et al. (2013)	SNPs in <i>GABRA6</i> (rs3219151), <i>COMT</i> (rs165599) and <i>RCS4</i> (rs10759) (affecting miR-124 binding)	Chinese	598 SCZ patients, 500 control subjects	In vitro luciferase assays demonstrated that regulator of G-protein signaling 4 (RGS4) downregulation was mediated by miR-124, and that miR-124 binding can be modified by SNP rs10759.
Liu et al. (2012)	SNPs in <i>TBCW15</i> gene (rs17110432, rs11178988, rs11178989) possibly affecting miRNA binding	Chinese	746 SCZ patients, 1599 control subjects	Not assessed
Kandaswamy et al. (2014)	SNP in <i>CRM7</i> gene (rs56173829) predicted to differential miRNA binding.	British	553 BD patients and 547 control subjects	Bioinformatic analyses predicted a change in the centroid secondary structure of RNA and alterations in the miRNA binding sites for the mutated base of rs56173829.
Rahman et al. (2010)	SNP in predicted binding site of miR-625 and miR-1302 in <i>P2RX7</i> gene (rs16536251)	Unspecified	171 MDD or BD patients, 178 control subjects	P2RX7
Jensen et al. (2014)	SNPs: Predicted binding site of miR-330-3p in <i>MAP2K5</i> gene; only significant in African Americans (rs41305272)	European Americans: 465 cases, 2010 controls African Americans: 427 cases, 2584 controls	314 MDD patients, 252 control subjects	MAP2K5. Enriched pathways include TGF, WNT and cytoskeletal remodeling, neurotrophin family signaling, roles of HDAC and CaMK in control of skeletal myogenesis, nervous system development, system development, neurogenesis, axonal guidance, FSH-beta signaling pathway, FGF-ErbB signaling. Genes involved in mental disorders, psychiatry and psychology, and

MI RNA	Population	Number of samples	Functional result	
<i>Variants in miRNA biogenesis genes in neuropsychiatric disorders</i>				
Gene	Population	Number of samples	Functional result	
Beveridge et al. (2010)	Upregulation: DGCR8 (miRNA biogenesis gene)	Caucasian	21 SCZ patients, 21 control subjects	schizophrenia. Upregulation of the microprocessor component DGCR8 mRNA; related to an increase of both mature miRNA and precursor forms of miR-181b and miR-26b
Santarelli et al. (2011)	Upregulation: Confirmed by qPCR: Dicer (miRNA biogenesis gene)	Caucasian	37 cases (SCZ or schizoaffective disorder), 37 control subjects	
Zhou et al. (2013)	Two polymorphisms in the DGCR8 and DICER genes (rs3757 and rs3742330)	Chinese	255 SCZ patients, 252 control subjects	Polymorphisms in two miRNA machinery genes, functional significance of these variants is, as yet, undetermined.
Smalheiser et al. (2012)	No significant differences were found in Dicer, Drosha and DGCR8 mRNAs (miRNA biogenesis gene).	Unspecified	18 MDD, 17 controls	Not assessed
He et al. (2012)	SNPs: DGCR8 (miRNA biogenesis gene) (rs3757), AGO1 (RISC component) (rs636832)	Chinese	314 MDD, 252 controls	Not assessed

Table 2

## Studies of miRNAs in schizophrenia.

MIRNA	Sample type	Methods	Number of samples	Affected function/pathway
Burmistrova et al. (2007)	Postmortem tissue — parietal cortex (BA7)	Microarray	12 SCZ patients, 12 control subjects	Not assessed
Perkins et al. (2007)	Postmortem tissue — PFC (BA9)	Custom microarray and real-time PCR	15 SCZ patients, 21 control subjects	Authors' pathway analysis revealed predicted enrichment of pathways involved in synaptic plasticity, including MAPK and phosphatidylinositol signaling and focal adhesion.
Beveridge et al. (2008)	Postmortem tissue — superior temporal gyrus (BA22)	Microarray	21 SCZ patients, 21 control subjects	Authors validated two of the putative target genes of miR-181b, VSNL1 and GRIA2, as miR-181b target genes by using target gene reporter assay and in vitro cell culture silencing studies.
Zhu et al. (2009)	Postmortem tissue — DLPPFC (BA46)	Real-time PCR	193 SCZ patients, 191 control subjects	Authors compared the targets of miR-346 with previous SCZ-related genetic association studies. With the exception of CSF2RA, all the genes predicted to be targeted by miR-346 do not have undisputed positive results.
Beveridge et al. (2010)	Postmortem tissue — superior temporal svrus (BA22) and DLPPFC (BA9)	Microarray real-time PCR	21 SCZ patients, 21 control subjects	Author's pathway analysis showed enrichment of neuronal pathways including axonal guidance, LTP, Wnt, ErbB and MAPK signaling; miR-15 family predicted to target neuronal genes
S. H. Kim et al. (2010), A. H. Kim et al. (2010)	Postmortem tissue — DLPPFC (BA46)	TLDA array	35 SCZ patients, 35 control subjects	Author's pathway analysis revealed some predicted pathways that are involved in nervous system function and disease, including schizophrenia. miR-132 and miR-212 both downregulate TH and PGD.
Moreau et al. (2011)	Postmortem tissue — PFC (BA9)	Real-time PCR	35 SCZ patients, 35 control subjects	Not assessed
Santarelli et al. (2011)	Postmortem tissue — DLPPFC (BA46)	Microarray real-time PCR	37 cases (SCZ or schizoaffective disorder), 37 control subjects	Authors' pathway analysis revealed several neurologically important and schizophrenia-related pathways including nervous system development, neurogenesis,



	miRNA	Sample type	Methods	Number of samples	Affected function/pathway
Banigan et al. (2013)	miR-652 Up-regulation: miR-497	Postmortem tissue — PFC (BA9) — exosomes	Luminex miRNA expression assay, real-time PCR	8 SCZ patients, 13 control subjects	neuron differentiation and axonogenesis Not assessed
Wong et al. (2013)	Up-regulation: miR-17	Postmortem tissue — DLPFC	Microarray real-time PCR	37 SCZ patients, 37 control subjects	Authors validated NPAS3 as miR-17 target gene by using luciferase reporter assay. NPAS3 is expressed by GABAergic interneurons and developmentally important transcription factor that has been associated with psychiatric illness.
Miller et al. (2012)	Down-regulation, corrected p-value: miR-132, miR-132* Down-regulation, uncorrected p-value: miR-150, miR-133a Up-regulation, uncorrected p-value: miR-320, miR-320c, miR-628-3p, miR-874, miR-105, miR-17*, let-7b	Human and mouse Postmortem tissue — DLPFC (BA46)	Microarray	35 SCZ, 37 control subjects	Authors' pathway analysis revealed some predicted enrichments of nervous system pathways for miR-132, including protein kinase A signaling, LTP and LDP, neuronal CREB signaling and DNA methylation.
Mellios et al. (2012)	Down-regulation: (In females, not males): miR-30b	Human and mouse Postmortem tissue — PFC (BA9 and 10) and parietal cortex (BA7)	Real-time PCR	PFC: 30 SCZ, 30 control subjects Parietal cortex: 11 SCZ, 12 control subjects	According to authors' pathway analysis, miR-30b is predicted to target several schizophrenia-linked genes including metabotropic glutamate receptors GRM3 and GRM5.
Pietersen et al. (2014a,b)	Down-regulation: miR-1243, miR-150, miR-378, miR-520d-3p, miR-875-5p Up-regulation: miR-126, miR-30b, miR-328, miR-628-5p, miR-99b	Postmortem tissue — laser-captured pyramidal neurons from layer 3 of STG (Brodmann's area 42)	Megaplex miRNA TaqMan arrays	9 SCZ patients, 9 control subjects	Authors' pathway analysis revealed some predicted pathways including TGFβ signaling, extracellular matrix-receptor interaction, DNA damage, apoptosis and actin cytoskeleton regulation pathways.
Pietersen et al. 2014b)	Down-regulation: miR-106a, miR-218, miR-342 Up-regulation: miR-151, miR-338-5p, miR-197, miR-342, miR-518f, miR-1274b, miR-151-3p, miR-197, miR-34a, miR-520c-3p	Postmortem tissue — laser-captured parvalbumin-immunoreactive neurons from layer 3 of STG (Brodmann's area 42)	Megaplex miRNA TaqMan arrays	8 SCZ patients, 8 control subjects	Authors' pathway analysis revealed some predicted pathways including WNT and NOTCH signaling, DNA damage, apoptosis, cell cycle and actin cytoskeleton regulation pathways.
Yu et al. (2015)	Down-regulation: miR-132, miR-134, miR-1271, miR-664*, miR-200c and miR-432.	Blood — PBMCs	Microarray real-time PCR	105 SCZ patients and 130 control subjects	Not assessed
Gardiner et al. (2012)	Down-regulation: miR-31, miR-99b, miR-107, miR-134, miR-431, miR-433, miR-487b	Blood — PBMCs	Microarray real-time PCR	112 SCZ patients and 76 control subjects	Authors' pathway analysis revealed significantly enriched pathways including axon guidance, regulation of the actin cytoskeleton, long-term potentiation, long-term depression, neuroactive ligand-receptor interaction, focal adhesion, neurotrophin, mammalian target of rapamycin, calcium, mitogen-activated protein kinase and ErbB signaling pathways.

	MiRNA	Sample type	Methods	Number of samples	Affected function/pathway
Lai et al. (2011)	Down-regulation: miR-432 Up-regulation: miR-34a, miR-449a, miR-548d, miR-564, miR-572, miR-652	Blood — WBCs	TaqMan low density array v.1.0	30 SCZ patients, 30 control Subjects	Not assessed
Shi et al. (2012)	Down-regulation: miR-195 Up-regulation: let-7g, miR-181b, miR-219-2-3p, miR-1308	Blood — serum	Real-time PCR	115 SCZ patients, 40 control subjects	Authors selected 9 miRNA to investigate based on the data obtained from the literature, SCZ Gene database, NCBI database and tried to find the most promising miRNAs that reflect SCZ illnesses status, 7 of them found altered expression.

Table 3

Studies of miRNAs in bipolar disorder.

MIRNA	Methods	Sample type	Number of samples	Affected function/pathway
S. H. Kim et al. (2010), A. H. Kim et al. (2010)	TLDA array	Postmortem tissue - DL-PFC (BA46)	35 BD patients and 35 control subjects	Using in silico target gene prediction programs, authors reported some predicted genes like tyrosine hydroxylase (TH), phosphoglucomate dehydrogenase (PGD) and metabotropic glutamate receptor 3 (GRM3) that are involved in neurodevelopment, behavior pathways, and SZ and BP disease development.
Moreau et al. (2011)	Real-time PCR	Postmortem tissue - PFC	35 BD patients and 35 control subjects	Not assessed
Miller et al. (2012)	Microarray	Postmortem tissue - DL-PFC	31 BD patients and 34 control subjects	Not assessed
Smalheiser et al. (2014)	TLDA array	Postmortem tissue - PFC (BA10)	15 BD patients and 15 control subjects	Not assessed
Banigan et al. (2013)	Luminex miRNA expression assay, real-time PCR	Postmortem tissue - PFC (BA9) - exosomal miRNA	9 BD patients, 13 control subjects	Authors emphasized the possible relationship between miR-29c and lithium. miR-29c is induced by canonical Wnt signaling, which is antagonized by GSK-3, a known substrate of inhibition by lithium.
Zhu et al. (2009)	Real-time PCR	Postmortem tissue - DL-PFC (BA 46)	35 BD patients, 34 controls, 35 SCZ patients	Not assessed
Bavamian et al. (2015)	Real-time PCR	Postmortem tissue - cerebellar tissue and BD patient-derived neuronal cultures	29 BD patients, 34 control subjects	Authors validated two of the putative target genes of miR-34a, Ankyrin-3 (ANK3) and voltage-dependent L-type calcium channel subunit beta-3 (CACNB3), as direct miR-34a targets.
Strazisar et al. (2015)	Sanger-based sequencing	Blood	345 BD patients, 426 SCZ patients, 1376	Authors' pathway analysis revealed some pathways that involved in nervous system

	miRNA	Methods	Sample type	Number of samples	Affected function/pathway
Walker et al. (2015)	Upregulation: miR-15b, miR-132 and miR-652	TaqMan microRNA assay, real-time PCR	Blood	control subjects 34 unaffected individuals with higher genetic risk of developing a mood disorder, 46 control subjects	development and proper synaptic function. miR-132 is transcribed from a cluster of miRNAs that are known to play an important role in neuronal development and function
Rong et al. (2011)	Downregulation: miR-134	Real-time PCR	Plasma	21 BD patients, 21 control subjects	Authors emphasized the connection between BD and one of the validated miR-134 targets Limk1, that controls synaptic development, maturation and/or plasticity.

Table 4

Studies of miRNAs in major depressive disorder.

MIRNA	Sample type	Methods	Number of samples	Affected function/pathway
Smalheiser et al. (2012)	Postmortem tissue — PFC (BA9)	Real-time PCR	18 MDD patients and 17 control subjects	Authors' target analysis revealed several validated (VEGFA, BCL2, DNMBB; targeted by miR-20a/b, 34a and 34b*) and predicted (targets of 3 or more downregulated miRNAs: ESR1, AJBE2D1, UBE2W, CAMK2G, AKAP1, NOVA1, GABRA4, CACNA1C, SMAD5, MITF, BACH2, MYCN, ARID4A) targets.
Smalheiser et al. (2014)	Postmortem tissue — PFC (BA10)	TLDA array	15 MDD patients, 15 control subjects 4	Not assessed
Maussion et al. (2012)	Postmortem tissue — PFC (BA10)	Microarray	38 suicide completers (23 MDD patients; 4 SCZ patients; 1 BD patient) 17 control subjects	Authors demonstrated a significant correlation between miR-185* and TrkB-T1, a BDNF receptor lacking a tyrosine kinase domain that is highly expressed in astrocytes and regulates BDNF-evoked calcium transient. They also validated TrkB-T1 as a target for miR-185* by luciferase assay.
Lopez et al. (2014a)	Postmortem tissue — PFC (BA44)	Real-time PCR	16 suicide completers (all MDD patients) 15 control subjects	Authors demonstrated a significant correlation between altered miRNAs and the expression levels of both SAT1 and SMOX.
Lopez et al. (2014b)	Postmortem tissue — PFC (BA44)	Real-time PCR	16 suicide completers (all MDD patients) 15 control subjects	Authors quantified the expression levels of the predicted gene targets of miR-1202 and upregulation in the level of metabotropic glutamate receptor 4 (GRM4) were found.
Fan et al. (2014)	Blood - PBMCs	Microarray real-time PCR	81 MDD patients, 46 control subjects	Authors' target analysis revealed several pathways associated with nervous system and brain functions.
J. Song et al. (2015), M. F. Song et al. (2015)	Cerebrospinal fluid (CSF) and blood	Real-time PCR	36 MDD patients, 30 control subjects	Authors emphasized the relationship between miR-16 and serotonin neurotransmitter system via targeting SERT gene (SLC6A4).
Li et al. (2015)	Blood	Real-time PCR	18 MDD patients, 18 control subjects	Authors confirmed that miR-335 can directly target glutamate receptor, metabotropic 4 (GRM4), a member of the metabotropic glutamate receptor III family.
Wan et al. (2015)	CSF and blood	Real-time PCR	CSF: 6 MDD patients, 6 control subjects. Blood: 32 MDD patients, 21 control subjects	Authors' pathway analysis revealed several pathways related to PI3K-Akt signaling, axon guidance, Wnt signaling, neurotrophin signaling, Hippo signaling, mTOR signaling, ErbB signaling, cell cycle, apoptosis, long-term depression.
Belzeaux et al. (2012)	Blood - PBMCs	Microarray	16 MDD patients and 13 control subjects	Unspecified



	MIRNA	Sample type	Methods	Number of samples	Affected function/pathway
Li et al. (2013)	miR-133a, miR-194, miR-107, miR-148a, miR-652, miR-425-3p Upregulation: miR-182, miR-132	Blood - serum	Real-time PCR	40 MDD patients and 40 control subjects	Authors emphasized the relationship between the serum BDNF levels and the miR-132/miR-182 levels. They provided evidence supporting that miR-182 is a putative BDNF-regulatory miRNA.
Camkurt et al. (2015)	Downregulation: miR-320a. Upregulation: miR-451a miR-17-5p and miR-223-3p.	Blood - plasma	Real-time PCR	50 MDD patients and 41 control subjects	Authors emphasized on GRIN2A and DISC1, two of the predicted target genes of miR-320a, and also SLC17A7, one of the predicted targets of miR-451.

Table 5

Pharmacological modulation of miRNAs in neuropsychiatric disorders.

Drug	Sample	MiRNA	Main findings	Targets	Reference
<i>Antipsychotics</i>					
Haloperidol	Rat	Up-regulation: miR-199a, miR-128a, miR-128b	Three miRNAs were up-regulated in response to haloperidol treatment in rats as compared to untreated controls but None of these miRNAs was differentially expressed in their SCZ patient group	Not assessed	Perkins et al. (2007)
Haloperidol Clozapine	C57BL/6 mice	Down-regulation: miR-219	Dizocipine is a NMDA-R antagonist that can rapidly produce schizophrenia-like behavioral Pretreatment with haloperidol and clozapine prevented dizocipine-induced effects on miR-219.	It has been proposed that miR-219 negatively regulates the function of NMDA receptors	Kocerha et al. (2009)
Risperidone	SCZ patients receiving drug treatment = 40	Down-regulation: miR-365 and miR-520c-3p	Among the seven miRNAs screened, the expression levels of miR-365 and miR-520c-3p were significantly down-regulated after 1 year of risperidone treatment	Not assessed	Liu et al. (2013)
Haloperidol Olanzapine	Mouse	Confirmed with real-time PCR: Haloperidol: Down-regulation: miR-434-5p, miR-22 Olanzapine: miR-193	For the haloperidol treatment group, miR-434-5p and miR-22, and for the olanzapine group, miR-193 was down-regulated. But validation of the clozapine treatment group was conflicting (miR-329 and miR-342-5p were significant down-regulation by qPCR and up-regulated on the microarray).	Metabolic pathways were enriched in olanzapine and clozapine treatments, possibly associated with their weight gain side effects. Neurologically and metabolically relevant miRNA-gene interaction networks were identified in the olanzapine treatment group.	Santarelli et al. (2013)
Olanzapine Quetiapine Ziprasidone Risperidone	Plasma control subjects = 20 SCZ patients receiving drug treatment = 20	Down-regulation: miR-181b	Among 20 patients, each drug group has 5 patients. 9 miRNA that were reported to be associated with SCZ were selected and after six weeks of antipsychotic treatment, only the expression level of miR-181b had significantly decreased.	miR-181b might implicate several target genes associated with synaptic transmission, nervous system development disorders.	Song et al. (2014)
Aripiprazole Risperidone	Plasma SCZ patients receiving drug treatment and remitted = 79, SCZ patients receiving drug treatment but unremitted = 28	Down-regulation: miR-130b and miR-193a-3p	Among 107 SCZ patients who completed the 1-year follow-up, 79 achieved the remission criteria. The baseline levels of plasma miR-130b and miR-193a-3p between patients who remitted and those without remission were compared.	The validated downstream target genes for miR-130b include PDGFRA, RUNX3, ITGB1, PPARG, FMR1, and STAT3, and for miR-193a-3p they include ErbB4, S6K2, and MCL1. Classification of these genes: -SCZ susceptibility genes (PDGFRA, PPARG, ErbB4),	Wei et al. (2015)

Drug	Sample	miRNA	Main findings	Targets	Reference
<i>Mood stabilizers</i>					
Lithium	Human whole blood BD patients = 5 Control subjects = 21	miR-134	miR-134 down-regulation in patients Increase in miR-134 levels after lithium treatment	-neurodevelopment-related genes (RUNX3, ITGB1, FMRI, STAT3), and -neuroprotective genes (S6 K2 and MCL1).	Rong et al. (2011)
Lithium/VPA combination	Rat cerebellar granule cells	Down-regulation: miR-34a and miR-495 Up-regulation: miR-182, miR-147, and miR-222		The pathways associated with mood stabilizer-regulated miRNAs this study, are strongly associated with pathways implicated in neuropsychiatric diseases such as SCZ.	Hunsberger et al. (2013)
Lithium or VPA	Rat hippocampus	Down-regulation: let-7b, let-7c, miR-128a, miR-24a, miR-30c, miR-34a, and miR-221 Up-regulation: miR-144	Alteration in hippocampal miRNA levels following chronic treatment with lithium or valproate (VPA), and the predicted effectors of these miRNAs are also genetic risk candidates for bipolar disorder.	These miRNAs are involved in neurite outgrowth, neurogenesis, and signaling of PTEN, ERK, and Wnt/ $\beta$ -catenin pathways. The effectors of miRNAs targeted by both lithium and VPA treatments were CAPN6, DPP10, GRM7, ESRRG, FAM126A and THRB.	Zhou et al. (2009)
Lithium	Lymphoblastoid cell lines (LCLs) BD patients = 10 Unaffected siblings = 10	miR-34a, miR-152, miR-155, and miR-221	After derivation of LCLs from patients and their unaffected siblings, miR-221, miR-152, miR-155 and miR-34a up-regulated at treatment time-point days 4 and 16.		Chen et al. (2009)
Lithium/VPA combination	SH-SY5Y	Down-regulation: miR-30a-5p		Neuroprotective and anti-oxidant effects of lithium is found to related miR-34a expression.	Croce et al. (2014)
Lithium	SH-SY5Y	Down-regulation: miR-34a			Alural et al. (2015)
<i>Antidepressants</i>					
Fluoxetine	Mouse brain	miR-16	After infusion of fluoxetine in mouse brain, a 2.5-fold increase in the level of miR-16 has been observed.	miR-16 was identified as a complementarity to the 3' untranslated region of the SERT mRNA by Using in silico computational target prediction.	Baudry et al. (2010)
Fluoxetine	Human CSF MDD = 9 and Mouse hippocampus tissue	miR-16	After fluoxetine treatment, miR-16 levels decreased in mouse hippocampus. Also, after fluoxetine treatment, miR-16 targeting molecules BDNF, Wnt2, 15d-PGJ2 levels increased in human CSF samples.	They proposed miR-16 as regulator between SRI treatment and hippocampal neurogenesis. BDNF, Wnt2 and 15-deoxy-delta12, 14-prostaglandin J2 (15d-PGJ2) act synergistically on the hippocampus by decreasing miR-16 and increasing serotonin	Launay et al. (2011)

Drug	Sample	miRNA	Main findings	Targets	Reference
Escitalopram	Human whole blood MDD = 10	Up-regulation: miR-130b*, miR-505*, miR-29-b-2*, miR-26a/b, miR-22*, miR-664, miR-494, let7d/e/f/g, miR-629, miR-106b*, miR-103, miR-191, miR-128, miR-502-3p, miR-374b, miR-132, miR-30d, miR-500, miR-589, miR-183, miR-574-3p, miR-140-3p, miR-335, miR-361-5p Down-regulation: miR-34c-5p, miR-770-5p	28 miRNAs were up-regulated, and 2 miRNAs were strongly down-regulated after 12-week escitalopram treatment	transporter (SERT) and bcl-2 levels, miRNA target gene prediction and functional annotation analysis showed that there was a significant enrichment in several pathways associated with neuronal brain function (such as neuroactive ligand-receptor interaction, axon guidance, long-term potentiation and depression).	Bocchio-Chiavetto et al. (2013)
Citalopram	Human whole blood	miR-1202	A decrease in miR-1202 levels in "depressed patients and increase in miR-1202 levels after 8 weeks of treatment	miR-1202 regulates the expression of the metabotropic glutamate receptor 4 (GRM4) gene and predicts antidepressant response at baseline.	Lopez et al. (2014a,b)
Ketamine	Rat hippocampus tissue	miR-206	18 miRNAs were significantly reduced, while 22 miRNAs were significantly increased. But researchers focused on miR-206 expression due to its modulator effect on BDNF expression.	miR-206 strongly modulated the expression of BDNF. miRNA target gene analysis referred the enrichments in several pathways associated with neuronal brain function, such as the neuroactive ligand-receptor interaction (miR-132-3p, miR-206, miR-181a-5p, miR-150-5p), amphetamine addiction (miR-497-5p, miR-29a-3p, miR-132-3p, miR-181a-5p, miR-29c-3p), Wnt signaling pathway (miR-29a-3p, miR-98-5p), dopaminergic synapse (miR-132-5p, miR-181a-5p), ErbB signaling pathway (miR-221-3p), mTOR and TNF signaling pathway (miR-206, miR-132-5p)	Yang et al. (2014)
Citalopram	Human whole blood MDD = 18 Control = 18	miR-335	Down-regulation of miR-335 levels in MDD patients and up-regulated after citalopram treatment.	Regulatory loop between GRM4 and miR-335 has been observed. The expression of miR-335 was increased and GRM4 was decreased in the blood samples of MDD patients after citalopram treatment.	Li et al. (2015)