MicroRNAs (miRNAs) have emerged as prospective players in the pathophysiology of psychiatric disease. These small noncoding RNA molecules have the capacity to regulate the expression of many genes simultaneously and influence cellular functions at the pathway level. This capacity makes miRNAs potentially very significant in the context of complex neurodevelopmental syndromes, such as schizophrenia (SZ) and other neuropsychiatric disorders.

The miRNA genes are dispersed throughout the genome, often set apart from protein-coding genes, although many are intrinsic (1–3). After transcription, the hairpin in the primary miRNA transcript is recognized and cleaved into an ∼70-nt precursor miRNA by the microprocessor complex consisting of Drosha (an RNase III) and DGCR8 ((DiGeorge syndrome critical region 8) (Figure 1) (4,5). These are translocated to the cytoplasm where Dicer (another RNase III) removes the hairpin loop, leaving an ∼22-nt double-stranded RNA. One strand of the mature miRNA is loaded into the RNA-induced silencing complex, containing Dicer, TAR RNA binding protein, and a member of the Argonaute family (6). In many cases, either strand can become the functional mature miRNA, with the suffix “-3p” or “-5p” added to the name to distinguish between the strands derived from the precursor’s 3’ and 5’ ends, respectively (7). The miRNA–RNA-induced silencing complex binds to the 3’ untranslated region of a messenger RNA target through complementarity to nucleotides 2–8—the “seed region”—of the miRNA (8) and destabilizes the transcript, or represses its translation, often followed by degradation, making it possible to assess miRNA function via gene expression profiling (9,10).

The importance of miRNAs and their biogenesis to the developing brain has been known for almost a decade, with a study demonstrating that zebrafish depleted of functional DICER protein display severe developmental abnormalities, particularly in the brain (11). These mutants developed asymmetrically, with severely reduced ventricle size and no midbrain–hindbrain boundary. Similarly, mice with selective Dicer deletion in excitatory forebrain neurons displayed enlarged lateral ventricles associated with increased postnatal cell death, decreased dendritic branching, abnormally long dendritic spines, and loss of axonal pathfinding (12). Additionally, these relatively short-lived mutants were microcephalic and displayed ataxia. When Dicer is lost from dopamine D1 receptor neurons in the striatum, mice have a decreased life span, smaller brain size and mass, and smaller medium spiny neurons and show ataxia and astrogliosis (13). These studies demonstrate that miRNA biogenesis is extremely important for normal brain development and function.

In this review, we revisit some of the recent highlights in the neurobiology of miRNA associated with neuropsychiatric syndromes and examine the support for their involvement in psychiatric pathophysiology. We also discuss the possible clinical applications for miRNAs in psychiatric treatment and what is needed for the field to progress.
EVIDENCE FOR miRNA DYSFUNCTION IN PSYCHIATRIC DISORDERS

In view of the vital role for miRNAs in the brain, it is not surprising that they are also emerging as significant players in the pathophysiology of several neurologic conditions. There is substantial research supporting the dysregulation of miRNA in psychiatric syndromes from expression studies that use microarrays and quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) analyses and genetic association studies that identify single nucleotide polymorphisms (SNPs) and copy number variations (CNVs). Expression studies have typically used either postmortem brain or other tissue samples such as peripheral blood mononuclear cells. Although postmortem brain samples provide direct evidence of miRNA dysregulation within the brain, peripheral tissue samples can be obtained from living subjects and have the potential to yield biomarkers that could be used as diagnostic tools. Genetics studies do not assess miRNA expression levels, but they present evidence for a causative role for miRNAs in psychiatric illness; in contrast, expression studies can demonstrate only a correlation between miRNAs and disease. We review the evidence linking SZ, bipolar disorder (BD), major depressive disorder (MDD), and autism spectrum disorders (ASDs) with altered miRNA expression and genetic variations that interfere with miRNA function.

SZ

The association between miRNA dysfunction and SZ has been reported in several studies (Table S1 in Supplement 1). One of the earliest expression studies investigated postmortem brain tissue from the dorsolateral prefrontal cortex (DLPFC) Brodmann area (BA) 9 (14). Using a custom microarray, the authors identified 16 significantly differently expressed miRNAs in subjects with SZ compared with control subjects including miR-26b, miR-30a-5p, miR-30b/d/e, miR-29a/b/c, miR-195, miR-92, miR-20b, miR-212, miR-7, miR-24, miR-9-3p, and miR-106b. Only miR-106b was upregulated leaving the remaining 15 miRNAs downregulated, 7 of which were also confirmed by qRT-PCR in a small subcohort. Using a similar approach, we investigated postmortem miRNA levels in the DLPFC (BA9) and the superior temporal gyrus (BA22) (15,16). Among numerous miRNA species showing elevated expression was miR-107 and members of the miR-15 family (miR-15a/b, miR-16, and miR-195), which all share similar seed regions and common target genes and roles in neuronal function, including neuronal proliferation and differentiation, making them important with regard to the neurodevelopmental aspect of SZ (Supplement 1) (17,18). Members of this family have been identified in other psychiatric disorders (Table 1). Additionally, the miRNA biogenesis gene DGCR8 was found to be upregulated, suggesting that miRNA biogenesis was increased and responsible for the global elevation of miRNA.
miRNA Dysregulation in Psychiatry

This finding was significant given that DGCR8 is also affected by the hemizygous deletion of 22q11.2 deletion syndrome, which predisposes individuals to DiGeorge syndrome and a high risk of developing SZ (19,20). We also observed an upregulation of miRNAs in SZ, including miR-107 again, alongside an upregulation of the miRNA biosynthesis gene Dicer in the DLPFC (BA46) (21). Although these analyses suggest that miRNAs are important in the etiology of SZ, there is significant heterogeneity and some direct conflicts among studies. For example, in contrast to the study by Perkins et al. (14), we observed miR-26b, miR-29c, and miR-195 to be upregulated in BA9 (15). Kim et al. (22) also analyzed postmortem tissue from the DLPFC (BA46) using a TaqMan Low Density Array (TLDA; Applied Biosystems Waltham, Massachusetts) and observed a discrepancy among individuals concerning the direction of dysregulation. On average, however, they discovered seven miRNAs were significantly upregulated (miR-34a, miR-132, miR-132*, miR-212, miR-544, miR-7, and miR-154*). In contrast, miR-212 was observed to be downregulated by Perkins et al. (14). The dysregulation of miR-312 and miR-212 is also particularly significant because these miRNAs are part of a cluster that has been identified in other psychiatric disorders. These miRNAs also have known functions in the brain, including regulating synaptic transmission and plasticity in the hippocampus and neocortex (23) and regulating memory formation (24). These miRNAs have been the focus of many studies and have particular relevance to SZ and MDD (Supplement 1). Other miRNAs species have also been associated with SZ and other psychiatric disorders on multiple occasions (Table 1), and despite conflicting findings, patterns are emerging with significance to SZ.

Analysis of mRNA expression in peripheral tissues has also revealed associations with SZ. We explored mRNA expression in peripheral blood mononuclear cells using a microarray and qRT-PCR and observed 83 downregulated miRNAs in SZ with a false discovery rate <5% (25). Of these, 17 came from the imprinted DLK1-DIO3 region at the 14q32 locus and are part of many maternally expressed miRNA clusters in the region (26). Transcription of the larger miR-379/410 cluster is induced by neuronal activity, suggesting their importance in neuronal function (27). In a similar study, Lai et al. (28) observed six upregulated miRNAs by TLDA and qRT-PCR, including miR-449a, miR-564, miR-432, miR-548, miR-572, and miR-652, and one downregulated miRNA (miR-34a). In an analysis of serum mRNA expression by qRT-PCR, Shi et al. (29) found miR-195 downregulated, whereas miR-181b, miR-219-2-3p, miR-1308, and let-7g were upregulated. These studies demonstrate the potential of peripheral biomarkers for psychiatric disease.

Numerous SNPs in miRNA genes have been associated with SZ. In one of the largest genome-wide association studies of SZ undertaken by the Psychiatric Genome Consortium, with 17,836 cases and 33,859 controls, the SNP rs1625579 within the intron for a putative primary transcript of miR-137 was the strongest new association with SZ (30). Four other loci associated with SZ in the same study were also predicted targets of miR-137, supporting the functional significance of this regulatory network in SZ. More recently, the Psychiatric Genome Consortium confirmed the association within the MIR548AJ2 gene in 36,989 cases and 113,075 controls (31). Further research into miR-137 revealed numerous functional implications relevant to the etiology of SZ, including a role in proliferation and differentiation of neuronal stem cells in the developing brain (32) and roles in glutamatergic and GABAergic signaling and long-term potentiation (33). The risk allele rs1625579 has been observed to correspond with reduced miR-137 expression in the DLPFC and hyperactivation of this region (Supplement 1) (34,35). Another SZ-associated SNP, rs3822674, has been identified and found to affect a binding site of miR-498 in the 3’ untranslated region of complex 2 (CPLX2) (36). Using a luciferase assay, the T allele at this SNP was found to induce translational repression in the presence of miR-498, whereas the C allele prevented repression. This C allele, in combination with the C and T alleles of SNPs rs1366116 and rs3892909 (also within CPLX2), was associated with the poorest cognitive performance within the study. This effect on cognitive function in mice was observed only after minor brain lesions were applied during puberty, supporting a developmental two-hit hypothesis of SZ (37).

Environmental factors can also influence miRNA levels and have implications for SZ. For example, maternal immune activation (MIA) in animals using polyclinobiosinose-polyribocytidic acid (poly-I:C) is an important tool for studying the role of maternal infections in pathophysiology of SZ and causes phenotypic abnormalities in the offspring that mimic SZ. We identified 21 miRNA species that were differentially expressed after MIA treatment in rats (38). In the same study, we treated poly-I:C control adolescent rats with the cannabinoid receptor (CB1) agonist HU210 as a model for human adolescent cannabis exposure and observed dysregulation of seven miRNA species, most of which were also observed to be dysregulated in the MIA group. Finally, a two-hit model in which poly-I:C-affected rats were exposed to HU210 during adolescence produced 18 differentially expressed miRNA species. Target prediction of these 18 miRNAs revealed potential roles in mitogen-activated protein kinase signaling, important for neuronal development and cognition (39), and the Wnt signaling pathway, also important in neuronal development and SZ (40). This study highlights the ability of environmental factors to influence miRNA expression, which may have a role to play in the etiology of SZ.

BD
Emerging research links miRNAs to BD with several studies showing significant alterations in miRNA expression levels in postmortem cortical brain tissue from affected individuals (Table S1 in Supplement 1). A few of these studies were run in parallel alongside SZ studies discussed in the preceding section. Kim et al. (22) used another TLDA array to analyze postmortem DLPPFC tissue samples of individuals with BD and healthy control subjects (BA46) and identified seven miRNAs (miR-504, miR-145, miR-145*, miR-22*, miR-133b, miR-154*, and miR-889) to be upregulated, with a further eight miRNAs (miR-454*, miR-29a, miR-520c-3p, miR-140-3p, miR-767-5p, miR-874, miR-32, and miR-573) downregulated in individuals with BD compared with control subjects. Moreau et al. (41) also analyzed miRNA expression in BD with multiplexed qRT-PCR alongside their SZ study and found a slight trend toward downregulation of miRNA expression, with 24 miRNAs

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This text is a natural reading of the provided document, ensuring all relevant information is included and presented clearly.
Table 1. Psychiatric Disease-Associated miRNAs Identified by Multiple Studies

<table>
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<th>miRNA</th>
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<th>miRNA</th>
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</table>

These miRNAs have been associated with schizophrenia, bipolar disorder, major depressive disorder, or autism spectrum disorders by more than one study.

miRNA, microRNA.

*miRNA has been identified multiple times in more than one of these conditions.
miRNA Dysregulation in Psychiatry

downregulated in the prefrontal cortex (BA9). By contrast, Miller et al. (42) observed the opposite in their microarray analysis of BA46, with 10 miRNAs upregulated. More recently, Smalheiser et al. (43) reported a fairly balanced distribution using a TLDA array, with four miRNAs upregulated and five miRNAs downregulated. Banigan et al. (44) analyzed the miRNA content of exosomes from DLPFC (BA9) with a Luminex Multiplex Assay (Luminex Corporation, Austin, Texas) and qRT-PCR validation and discovered just one miRNA, miR-29c, to be upregulated. The SNP rs1625579, which affects miR-137 in SZ, was also found to be functionally associated with individuals at risk of BD (45).

Although there is no direct evidence of dysregulated miRNA biogenesis in BD, valproic acid has been shown to induce proteasomal degradation of Dicer, which causes a general downregulation of miRNA expression (46). These observations suggest that this mood stabilizer used for treatment of BD may have some influence on psychopathology through the modification of miRNA biogenesis.

Despite substantial heterogeneity of miRNA identified in association with BD, a few miRNAs have appeared in multiple studies (Table 1). Several of these miRNAs, including miR-29c, miR-132, and miR-106b, have also been associated with SZ suggesting there may be common pathways that are affected by small RNA molecules in these psychotic syndromes. In particular, miR-132, mentioned earlier, has been implicated in the circadian clock machinery, which is associated with BD and depression (Supplement 1) (47). 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 and new drug targets.

MDD

The dysregulation of miRNAs has also been linked to MDD in recent years (Table S1 in Supplement 1). One of the earliest pieces of evidence for this link was the association between depression and a SNP in the P2RX7 (purinergic receptor P2x, ligand-gated ion channel 7) gene (48), which is reportedly involved in modulating synaptic neurotransmission (49). This SNP, rs1653625, occurs in the putative miRNA target site of miR-1302 and miR-625 within the P2RX7 3′ untranslated region. Other SNPs associated with MDD by genotyping include rs178077483, which is within the pre–miR-30e gene and is associated with a longer P300 waveform latency, a correlate of slower cognitive functioning (50), and two others in the miRNA pathway genes AGO1 (Argonaute 1) (rs636832) and DGC8 (rs3757) (51). This link between miRNA pathway gene polymorphisms and depression is particularly interesting because a postmortem TLDA array study found a global downregulation of miRNA species within BA9 of the DLPFC (52). Although this global downregulation hints at the possibility for alterations in miRNA processing in the pathophysiology of depression, no changes in miRNA processing or DGC8, DROSHA, or DICER messenger RNA expression were observed.

A mouse model established in the same laboratory assessed the difference in miRNA expression profiles between mice that showed learned helplessness—an analogue for depressive symptoms—and mice that did not show learned helplessness compared with controls after repeated, inescapable shock using another TLDA array approach (53). The authors found that the mice that did not show learned helplessness demonstrated a significant global downregulation of miRNA expression as an adaptive response, whereas mice that did show learned helplessness did not demonstrate downregulation. The miRNAs included miR-96, miR-141, miR-182, miR-183, miR-298, miR-200a/b/c, miR-322, and miR-429. Three of these molecules, miR-96, miR-182, and miR-183, are part of a polycistronic miRNA cluster that may be involved in regulating genes in step with the circadian clock (54); this is significant because disruption of the circadian rhythms is thought to be a factor in many disorders, including depression (55). Taken together, these studies may suggest that depressive symptoms brought about by excessive stress are a result of a disrupted circadian clock via the perturbation of its regulation by miRNAs.

As mentioned earlier, miR-132 has been associated with many psychiatric illnesses. In one study, qRT-PCR analysis found increased serum levels of miR-132 and miR-182 in patients with depression (56). In addition, both miRNAs are capable of downregulating brain-derived neurotrophic factor, which was found at lower serum levels in the patients with depression by enzyme-linked immunosorbent assay. The interaction of miR-132 with brain-derived neurotrophic factor as well as with cyclic adenosine monophosphate response element binding protein and glucocorticoids has been proposed to have a significant role in the development of some cases of depression as well as the comorbidity of cardiovascular diseases with depression (57). Also, miR-132 has been implicated in regulating the circadian clock (58), which is thought to be important in MDD.

ASDs

Direct evidence for miRNA involvement in ASDs is currently very sparse; only a few studies have associated altered miRNA expression levels in biological tissues with the incidence of autistic traits (Table S1 in Supplement 1). One study identified 28 miRNA species that were dysregulated in postmortem cerebellar cortex tissue in at least 1 of 13 subjects (59). Among these miRNAs were miR-15a/b, miR-132, miR-212, and miR-106b, which were mentioned previously in relation to SZ and mood disorders. However, there has been some contention over the validity of these data (60). Three other studies investigated miRNA expression levels in lymphoblastoid cells by microarray analysis and found differentially expressed miRNA species associated with autism (61–63). The findings reported by Sarachana et al. (62) included the dysregulation of miR-107, miR-195, and miR-106b, which were also observed to be dysregulated in SZ. These studies not only present a case for miRNA involvement in ASDs, but they also further highlight the importance of a few miRNAs that may be common to a range of psychiatric disorders.

In addition to these findings, a few studies have linked CNVs of miRNA genes to ASDs and autistic traits. Two of these studies identified the microduplication of the miR-17-92 cluster on chromosome 13q31.3—containing miR-17, miR-18a, miR-19a, miR-19b-1, miR-20a, and miR-92a-1—in patients with autistic traits (64,65). Autistic traits also have been associated with miR-211 deletions and duplications at...
chromosome 15q13.2-q13.3 (66). Finally, two groups of investigators used CNV database searches and reported a large number of miRNAs, including miR-211, that overlap with known autism-associated CNVs (67,68). Again, miR-132 has been associated with autism disorders several times, suggesting it could be a particularly important miRNA (Supplement 1).

DISCUSSION
This review has highlighted the current evidence for aberrant miRNA expression or function in four major neuropsychiatric syndromes. Many of the miRNA species identified in these studies have been characterized with regard to their functional roles within neurons and their contribution to brain function. Several miRNA species associated with these conditions are involved in proliferation, differentiation, and maturation of neurons, and their dysfunction may contribute to the neurodevelopmental deficits seen in disorders such as SZ and ASDs. Other miRNA species have roles in synaptic function and may contribute to deficits in glutamate and GABAergic signaling seen in SZ, whereas still others, including miR-132, are involved in the circadian clock pathways and have implications for mood disorders. In addition, miR-132 and a few other miRNA species have been associated with multiple conditions on several occasions, making them particularly interesting focal points for future research and possibly making them useful in a clinical context.

Clinical Implications
There are two potential clinical applications of miRNAs: as a diagnostic tool and as novel treatments. As discussed earlier, numerous studies have already associated miRNA expression in peripheral tissues with psychiatric disease. These miRNAs have the potential to be biomarkers for these conditions. Multiple studies of various psychiatric disorders have identified miRNAs such as miR-132/212 and miR-15 family members (Table 1), suggesting that these miRNAs may be particularly useful in identifying individuals at risk of psychiatric disease. However, given the wide range of miRNA species associated with these conditions and the apparent heterogeneity, the use of miRNAs as biomarkers remains a difficult proposition.

The use of miRNAs or miRNA antagonist in the treatment of psychiatric disorders is an appealing concept, particularly as understanding about their function and roles in these conditions increases. At the present time, these approaches are limited by our capacity to deliver these molecules effectively. Some progress has been made more recently in clinical trials comprising patients with cancer receiving small interfering RNA nanoparticles, which are chemically identical to synthetic miRNAs, intravenously. These formulations successfully downregulated the target messenger RNA and protein (69). Inhibition of miRNAs in vivo has also been successful; cardiac miR-15b expression was reduced in mice injected with anti-miR-15b oligonucleotides (70). Manipulating miRNA in the brain may not be as effective, as Krutzfeldt et al. (71) discovered, with intravenous administration of anti-miR-16 unable to affect miRNA levels in the brain, whereas direct injection into the cerebral cortex was effective. Intracerebroventricular infusion of anti-miRNAs has been found to be an effective delivery route, suggesting intrathecal delivery may be an option (72,73). These studies demonstrate that miRNA or their antagonists have the potential to be used as therapeutic tools for the treatment of brain conditions, although the feasibility of their delivery in the clinic needs to be addressed.

Future Studies
Understanding of the role miRNAs play in brain function and psychiatric disorders is still a growing field. What is clear is that the relationship between miRNA expression and these conditions is complex; the dysregulation of numerous miRNA species appears to correlate with these disorders. Some miRNAs, such as miR-137, miR-132/212, and the miR-15 family, have been identified on multiple occasions, making them particularly interesting targets for further research.

A better understanding of how miRNAs are differentially expressed spatially and temporally throughout development would aid in determining which miRNAs are the most important for psychiatric disorders as well as at what stages during development they contribute to disease. Some progress has been made in this regard; a recent study identified changes to the miRNA profile across brain regions and through development in samples from 18 normal individuals 4 months to 19 years old (74). A few of the miRNAs discussed here were identified; miR-212 was downregulated from infancy to early childhood in the DLPFC, and miR-137 was downregulated in the same time frame in the cerebellar cortex. We also investigated developmental changes in genome-wide miRNA expression in the human DLPFC and found an interesting inflection of miRNA expression during adolescence (75). More recently, we explored the relationship between gene and miRNA expression in the developing midbrain and hindbrain of rat embryos and found significant differences in the timing of miRNA expression, particularly miR-132 and miR-137, which accorded with the cortical maturity in the two regions (76). Further research in normal healthy brain tissue in this way will be invaluable for understanding how miRNAs contribute to disease. Another important question is how miRNAs associated with psychiatric disorders are localized in individual neurons. For example, localization to dendritic spines or axon terminals may suggest a role in synaptic activity or neurite growth and development. In this regard, miR-212 has been observed enriched in axons, whereas miR-137 and miR-15 family members miR-195 and miR-16 were enriched in the cell body (77). Dicer has been observed to localize in the cell body and dendrites and at the Golgi complex and endoplasmic reticulum of cerebellar granule neurons in vitro (78). The combination of these high-resolution studies with the collection of data from large cohorts of postmortem samples and genetic associations will greatly enhance understanding of the role miRNAs play in neurobiology and psychiatric disorders.

CONCLUSIONS
Research in the past decade suggests that miRNAs have a significant role to play in the function of the brain, and their dysregulation and dysfunction may be part of the pathophysiology of psychiatric disorders, including SZ, mood disorders, and ASDs. Numerous studies have shown genetic associations of miRNA genes and targets as well as altered expression levels in
these syndromes. The association of DGCR8 dysregulation with SZ and the association of SNPs in DGCR8 and AGO1 with MDD add further weight to this hypothesis of miRNA involvement in psychiatric disease, suggesting that, at least in some cases, miRNA dysregulation on a global scale via abnormal biogenesis may be involved in these conditions. The study of this relationship between miRNA function and psychiatric disease is a growing field, and much of the information to date is preliminary, with much still to be understood about the mechanisms by which these small RNA molecules may influence the development of psychiatric disease. However, these miRNAs are clearly important in posttranscriptional organization of gene network structures that are perturbed in complex disorders of the mind and may prove to be useful tools for diagnosis and treatment of these disorders.

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ARTICLE INFORMATION
From the School of Biomedical Sciences (MG, MJC), Faculty of Health and Medicine, University of Newcastle, Callaghan; Schizophrenia Research Institute (MJC), Sydney; and Centre for Translational Neuroscience and Mental Health (MG, MJC), Hunter Medical Research Institute, Newcastle, New South Wales, Australia.

Address correspondence to Murray J. Cairns, Ph.D., School of Biomedical Sciences and Pharmacy, The University of Newcastle, Australia, University Drive, Callaghan, NSW 2308, Australia; E-mail: Murray.Cairns@newcastle.edu.au.

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