Spring 5-16-2020

EXOSOMAL SECRETION OF A PSYCHOSIS-ALTERED MICRORNA REGULATES GLUTAMATE RECEPTOR EXPRESSION; EFFECTS OF ANTIPSYCHOTICS AND MATERNAL IMMUNE ACTIVATION

Stephen Amoah

Stephen Amoah

Candidate

Biomedical Sciences Graduate Program: Neuroscience

Department

This dissertation is approved, and it is acceptable in quality and form for publication:

Approved by the Dissertation Committee:

Nikolaos Mellios, MD, PhD, Chairperson

Nora Perrone-Bizzozero, PhD

Juan Bustillo, MD

Erin Milligan, PhD

Lauren Jantzie, PhD

EXOSOMAL SECRETION OF A PSYCHOSIS-ALTERED MICRORNA REGULATES GLUTAMATE RECEPTOR EXPRESSION; EFFECTS OF ANTIPSYCHOTICS AND MATERNAL IMMUNE ACTIVATION

by

STEPHEN KWAKU AMOAH

B.Sc. Botany, University of Ghana, 2004

M.Phil., Human Anatomy, University of Ghana, 2008.

DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy

Biomedical Sciences

The University of New Mexico
Albuquerque, New Mexico

May, 2020.

DEDICATION

To my wife, you putting your life on hold while your husband pursued his terminal degree is a decision I will perpetually treasure. To my parents, your constant support and encouragement to pursue my dreams but to be the best I can be in any career I choose, has wonderfully paid off.

ACKNOWLEDGEMENTS

I am grateful to my mentor Dr. Nikolaos Mellios for his unstinted support and versatile guidance throughout these years of training to become a neuroscientist. I am equally grateful to my committee members: Drs. Nora Peronne-Bizzozero, Juan Bustillo, Erin Milligan, and Lauren Jantzie, you asked the tough questions, provided strategic directions and refreshing encouragement in the tumultuous times. You have ignited my unquenchable passion for neuroscience research.

I am thankful to the Department of Neurosciences for administrative support and broad exposure to the diversity and integration of nervous system biology via multiple collaborations and seminars, beautifully portraying team science.

I am immensely grateful to the Biomedical Sciences Graduate Program (BSGP), for the overarching support in creating the enabling environment especially, Dr. David Peabody, Dr. Nancy Kanagy, Mary Fenton, and Alec Reber, for the impactful support during various challenging times preceding and during my program of study. To the Global Education Office (GEO) especially Linda Melville, your support to international students and their families sustained me in the program despite the various adversities that kept cropping up.

To my 2015 BSPG cohort, your first year beneficial ‘unstructured group therapy’ were indispensable. I thank my lab members Brian Rodriguez, Evelyn Lozano and Alex Hafez, for the “bench support” and a great working environment.

To my wife and rest of my wider family, your support and understanding has made all the difference in both good and difficult times.

To the Almighty, faith in You brings out the impossible.

We gratefully acknowledge the support of a mentored PI grant as part of a P20 grant from the NIGMS (1P20GM121176-01) and Dedicated Health Research Funds from the University of New Mexico School of Medicine. We would like to thank the SMRI brainbank for providing us with postmortem brain specimen, Colleen Ramsower and Crystal Richt at the University of Arizona Genetics Core for assistance in miRNA profiling, Dr. Mathew Campen, and Tamara Young for help with NanoSight, and Tamara Howard for EM assistance.

EXOSOMAL SECRETION OF A PSYCHOSIS-ALTERED MICRORNA REGULATES GLUTAMATE RECEPTOR EXPRESSION; EFFECTS OF ANTIPSYCHOTICS AND MATERNAL IMMUNE ACTIVATION

By

Stephen Kwaku Amoah

B.Sc. Botany, University of Ghana, 2004

M.Phil. Human Anatomy, University of Ghana, 2008.

Ph.D. Biomedical Sciences, 2020.

ABSTRACT

MicroRNAs are a subcategory of evolutionarily conserved small non-coding RNAs that are altered in psychiatric conditions. The ability of small secretory microvesicles known as exosomes to influence neuronal and glial function via their microRNA (miRNA) cargo has positioned them as a novel and effective method of cell-to-cell communication. Inflammation, which is evident in schizophrenia (SCZ) and bipolar disorder (BD), and antipsychotics usage may alter miRNA expression in the brain. However, little is known about the role of exosome-secreted miRNAs in the regulation of neuronal gene expression and their relevance for SCZ and BD. Here, we used miRNA profiling and qRT-PCR (quantitative real-time PCR) in the orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC) of SCZ, BD, and unaffected control subjects, rodent brains and cell culture to measure miRNA and related mRNA expression. We uncovered that miR-223, an inflammation-related and exosome-secreted miRNA that targets glutamate receptors, was increased at the mature miRNA level in the OFC of patients with SCZ as well as BD patients with positive history of psychosis at the time of death and was inversely associated with deficits in the expression of its targets glutamate ionotropic receptor NMDA-type subunit 2B (*GRIN2B*) and glutamate ionotropic receptor AMPA-type subunit

2 (*GRIA2*). Additionally, changes in miR-223 levels in the OFC were positively and negatively correlated with inflammatory and GABAergic gene expression, respectively. Intriguingly, no changes in miR-223 mature miRNA levels and miR-223-related mRNAs was observed in the DLPFC of patients with SCZ and BD, despite increases in inflammatory gene expression. Interestingly, miR-223 levels were higher and further increased by maternal immune activation in the prenatal than in adult rat brain. Moreover, miR-223 was found to be enriched in astrocytes and secreted via exosomes, and antipsychotics were shown to control its cellular and exosomal localization in a cell-specific manner. Furthermore, addition of astrocytic exosomes in neuronal cultures resulted in a significant increase in miR-223 expression and a notable reduction in *Grin2b* and *Gria2* mRNA levels, which was strongly inversely associated with miR-223 expression. Remarkably, inhibition of astrocytic miR-223 abrogated the exosomal-mediated reduction in neuronal *Grin2b* levels. Lastly, antipsychotic treatment in astrocytes exacerbated the exosomal miR-223-mediated downregulation of neuronal *Grin2b* expression. Taken together, our results demonstrate that the exosomal secretion of a psychosis-altered and glial-enriched miRNA that controls neuronal gene expression is regulated by antipsychotics.

TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER 1: INTRODUCTION

1a. Schizophrenia and bipolar disorder

Schizophrenia (SCZ) is a heterogeneous neuropsychiatric disorder with prevalence of approximately 1% of the adult population (McGrath et al. 2008; Kessler et al. 2005). Patients with SCZ manifest a triad of symptoms namely, positive, negative, and cognitive impairments ("NIMH » Schizophrenia" 2016). Positive symptoms are those that are "acquired" in schizophrenia, principally delusions and hallucinations ("NIMH » Schizophrenia" 2016). The negative symptoms are those are "lost" by SCZ patients; these essentially alter the affect (emotions) such as anhedonia (inability to express or experience pleasure) and inability to process and express emotions in the SCZ subject or understand same in others (Lawrence, First, and Lieberman 2015). Cognitive deficits in SCZ subjects affect various aspects of memory such as working memory and is linked to unemployment and homelessness in SCZ subjects (Kurtz et al. 2001; Tan 2009; Cirillo and Seidman 2003; Pomarol-Clotet et al. 2008; Goldberg et al. 2010; van Os and Kapur 2009). There is a higher prevalence of SCZ in males who also exhibit an approximately eight year earlier age of onset than females (Ochoa et al. 2012; van Os and Kapur 2009; Addington et al. 2007).

Bipolar disorder is a multifactorial neuropsychiatric disorder that affects 2.5% of the adult population (Merikangas et al. 2007). Patients with bipolar disorder cycle between two sets of contrasting symptoms namely a manic phase (Beentjes, Goossens, and Poslawsky 2012) and a depressive phase (Muneer 2013; Swann et al. 2013) with a subset of subjects under the depressive phase

exhibiting suicidal ideation with up to 15% completion rate (Novick, Swartz, and Frank 2010). In episodes of mania, BD subjects exhibit high surge of energy, impulsivity, risky behavior and seem oblivious to the consequences, and may experience circadian rhythm disruptions (Anderson, Haddad, and Scott 2012). During the depressive phase, patients exhibit prolong periods of sadness including crying, sense of hopeless, lethargy, and loss of interest in activity that previously brought them pleasure (Beentjes, Goossens, and Poslawsky 2012; "NIMH » Bipolar Disorder" 2020). There is a higher prevalence of BD in females with estrogen fluctuations attributed to the etiology (Meinhard, Kessing, and Vinberg 2014).

Despite the elusiveness of the etiology of SCZ and BD, pharmacological, genetic, postmortem, and animal studies have linked N-methyl-D-aspartate receptor (NMDA) hypofunction (Coyle 2006; Egan and Weinberger 1997), impairments in dopamine (Egan and Weinberger 1997; Andreazza and Young 2014; Davis et al. 1991), wingless-related integration site (WNT) (Muneer 2017; Singh 2013), calcium signaling (Berridge 2014), and GABAergic gene expression deficits (Bullock et al. 2009; Akbarian et al. 1995; Fatemi et al. 2005; Guidotti et al. 2000; Hashimoto et al. 2003; Mellios et al. 2009; Volk et al. 2000). Additionally, genome-wide association studies (GWAS) have linked various single nucleotide polymorphisms (Lin et al. 2016; Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011) to SCZ and BD. Moreover, an increasing number of studies have reported an upregulation in non-neuronal gene expression related to inflammation in the brain of subjects with SCZ (Fillman et al. 2013; Horváth and

Mirnics 2014; Hwang et al. 2013; Saetre et al. 2007; Trépanier et al. 2016; Zhang et al. 2016; Arion et al. 2007) and less in BD (Fillman et al. 2014), such as the acute-phase inflammation marker serpin family A member 3 (*SERPINA3*—also known as alpha 1-antichymotrypsin) (Fillman et al. 2013; Saetre et al. 2007; Zhang et al. 2016).

Multiple brain regions, neuronal genes, and neurotransmitters are altered in SCZ and/or BD. The affected brain regions and circuits include dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), thalamus, amygdala, and hippocampus (Xu et al. 2015; DeLisi et al. 2006; Harrison 1999; Fornito et al. 2009; Javadapour et al. 2007; Chai et al. 2011; Frey et al. 2007; Clark and Sahakian 2008; Jackowski et al. 2012).

1b. MicroRNAs

MicroRNAs (miRNAs) are a subcategory of small evolutionarily conserved noncoding RNAs (ncRNAs) approximately 18–22 nucleotides in length (Krol, Loedige, and Filipowicz 2010; Ha and Kim 2014). They are transcribed independently as large precursor RNA molecules (pri-miRNAs) from intergenic regions or spliced from introns of protein-coding genes to form hairpin structure precursors (pre-miRNAs), which are exported into the cytoplasm (Fig. 1), where they are cleaved by the RNase III enzyme Dicer to yield the mature miRNA transcript that is loaded into the RNA induced silencing complex (RISC) (Krol, Loedige, and Filipowicz 2010; Ha and Kim 2014; Ruby, Jan, and Bartel 2007). Numerous studies have suggested that miRNAs post-transcriptionally control gene

expression by binding to complementary sequences in the 3′ untranslated region (UTR) of mRNAs, thereby inhibiting mRNA translation and leading to subsequent mRNA decay (Krol, Loedige, and Filipowicz 2010; Siomi and Siomi 2010).

In the brain, miRNAs display a developmental-, laminar-, and cell-specific expression and can modulate molecular functions ranging from neurogenesis, neuronal differentiation, and circuitry establishment, to plasticity (Follert, Cremer, and Beclin 2014; Rajman and Schratt 2017; McNeill and Van Vactor 2012; Shi et al. 2010). Literature abounds with dysregulation of miRNAs in the brain, blood and cells derived from SCZ and BD subjects (Beveridge and Cairns 2012; Mellios and Sur 2012; He et al. 2017; Hauberg et al. 2016; Fries, Carvalho, and Quevedo 2018). Moreover, elevated in blood miRNAs such as miR-193a and miR-330 may function as biomarkers for SCZ and BP, respectively (Wei et al. 2015; Maffioletti et al. 2016).

Maternal immune activation (MIA) as a result of viral and bacterial infections during pregnancy has been identified as a significant risk factor for psychiatric disorders (Sørensen et al. 2009; Canetta and Brown 2012; Feigenson, Kusnecov, and Silverstein 2014). It has been proposed that the increases in inflammatory markers observed in the brain of subjects with SCZ could be related to neuro-immune disturbances conferred by prenatal inflammation especially during the second and third trimester of gestation (Canetta and Brown 2012; Feigenson, Kusnecov, and Silverstein 2014). Moreover, animals subjected to maternal immune activation (MIA) using polyinosinic–polycytidilic acid (Poly(I:C)) and lipopolysaccharide (LPS) to mimic viral infection (Reisinger et al. 2015) and

bacterial infection (Wischhof et al. 2015), respectively, display behavioral abnormalities reminiscent of psychosis. Molecular alterations in synaptic gene expression, and neuroinflammatory markers are similar to those seen in postmortem brains of subjects with SCZ (Reisinger et al. 2015; Wischhof et al. 2015). Thus, mechanisms that regulate neuroinflammation may also be stimulated in MIA and can be of relevance for psychiatric disorders.

An inflammation elicited miRNA (inflammiR) that can regulate both inflammation and neuronal function is miR-223. miR-223 was initially considered to be a 'fine-tuner' in shifting hematopoietic progenitors into granulocyte differentiation (Johnnidis et al. 2008; Fazi et al. 2007). However during inflammation most of the peripheral blood mononuclear cells (PBMC) upregulate miR-223 levels to limit excessive inflammation (Neudecker et al. 2017; Haneklaus et al. 2013; Gilicze et al. 2014). Additionally, in conditions such as stroke and epilepsy, miR-223 is elevated in the blood (Chen et al. 2017; Khoshnam et al. 2017) and its overexpression in the brain conferred neuroprotection in model systems of stroke (Khoshnam et al. 2017), epilepsy (Cava et al. 2018), multiple sclerosis (Morquette et al. 2018), and glioblastoma multiforme (Glasgow et al. 2013) probably by targeting glutamate receptor expression (Harraz et al. 2012) so as to limit excitotoxicity. Despite these interesting outcomes, the endogenous and cellular sources of miR-223 within the brain parenchyma remains to be elucidated. Of the cells within the brain parenchyma, miR-223 is not detected in microglia (Ponomarev et al. 2011), and its endogenous expression in neurons, astrocytes and oligodendrocytes are yet to be determined. However, miR-223 downstream

mRNA targets are expressed in astrocytes and neurons suggesting that it is either synthesized in these cells or can be trafficked into them via exosomes since miR-223 has been observed to be efficiently packaged and secreted through exosomes (Shurtleff et al. 2016). Thus identifying the cellular expression of miR-223 within the brain parenchyma may elucidate its physiological function and possible contribution to disorders within the central nervous system (CNS).

Antipsychotics are used to treat psychosis in SCZ and BP. Despite their general efficacy for some of the symptoms of SCZ and BP, serious side effects and suboptimal efficacy in a subgroup of the patients has been associated with poor compliance (Correll, Sheridan, and DelBello 2010; Leucht et al. 2012). There are two types of antipsychotics: typical (first generation) and atypical (second generation) antipsychotics. Antipsychotics have been reported to dysregulate miRNA expression in mouse brain and i.p. olanzapine administration resulted in miR-223 downregulation (Santarelli et al. 2011). Additionally, antipsychotics appear to alter inflammiR expression by downregulating pro-inflammatory and elevating anti-inflammatory gene levels (Al-Amin, Nasir Uddin, and Mahmud Reza 2013; Gardiner et al. 2014; Swathy and Banerjee 2017; Obuchowicz et al. 2017). Thus, the effect of antipsychotics on cellular miRNA expression will further illumine the glial-neuronal crosstalk probably mediated by exosomes within the brain parenchyma.

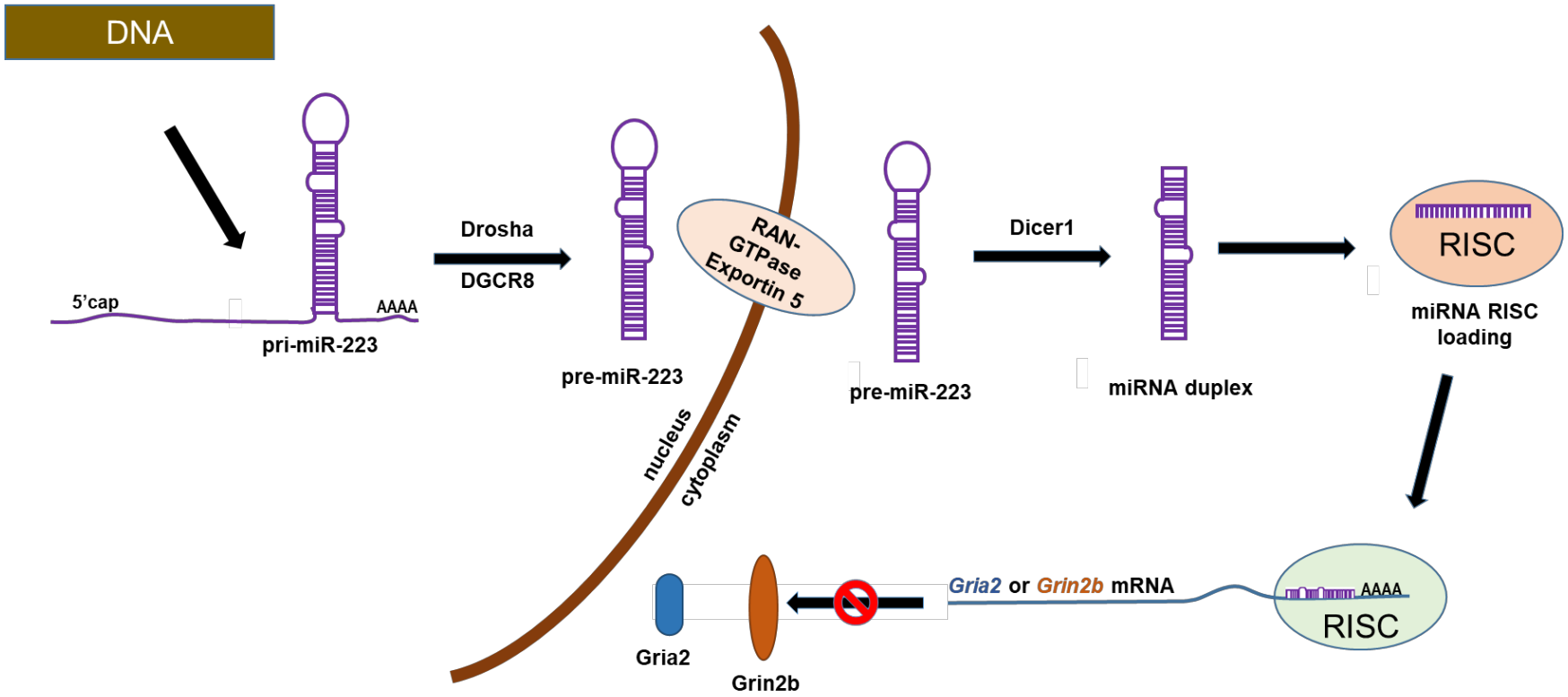

Figure 1: Overview of the miRNA biogenesis. MiRNA biogenesis through the canonical pathway (focusing on miR-223). Primary or pri-miRNA (pri-miR-223) is transcribed from the DNA and cleaved by a microprocessors Drosha and DGCR8 into hairpin structured precursor (pre-miR-223) transcript that is exported via exportin 5 by RAN-GTPase into the cytoplasm. In the cytoplasm, RNAse III Dicer cleaves the pre-miRNA into a duplex strand that is unwound of which one strand, the mature miRNA, is incorporated into the RNA-induced silencing complex (RISC). The mature miRNA serves as a template to scan mRNAs from the 3' untranslated region and repress successfully targeted mRNA from being translated into proteins. Mature miR-223 directly targets *Gria2* and *Grin2b* in neurons.

1c. Exosomes

Recent work has revealed the presence of small secretory microvesicles between 30 and 150 nm in diameter, known as “exosomes”, which are mainly produced from the multivesicular bodies of the endosomal pathway (Colombo, Raposo, and Théry 2014; Holm, Kaiser, and Schwab 2018). Exosomes contain proteins, lipids, and RNAs of the cell of origin and are particularly enriched in miRNAs (Colombo, Raposo, and Théry 2014; Holm, Kaiser, and Schwab 2018; Prada et al. 2018; Lafourcade et al. 2016). Exosomes can fuse with the cell membrane of the recipient cells and unload their miRNA cargo, which in turn facilitates the post-transcriptional inhibition of multiple protein-coding mRNAs (Prada et al. 2018; Lafourcade et al. 2016).

The secretion of large numbers of exosomes from glia and neurons and the perceived ability of exosomes to influence various aspects of neuronal and glial development and function has positioned them as an exciting and novel method of cell-to-cell communication with important implications for brain disease (Holm, Kaiser, and Schwab 2018; Prada et al. 2018; Lafourcade et al. 2016). Interestingly, immune cells utilize exosomes to coordinate inflammatory response in normal cells (Chan et al. 2019; Alexander et al. 2017), while diseased cells such as metastatic cells transport exosomes to transform other cells to assume cancer phenotypes (Maia et al. 2018; Wortzel et al. 2019). Furthermore, antipsychotics have been documented to alter exosome homeostasis (Desdín-Micó and Mittelbrunn 2016) and biogenesis (Canfrán-Duque et al. 2015) and hence modify exosomal function.

1d. Rationale of study

Multiple studies have linked miRNA dysregulation and inflammation to the development of neuropsychiatric disorders, such as SCZ and BD. Prenatal and/or postnatal biological insults (Tanaka et al. 2017; Canetta and Brown 2012) involving inflammation in genetically vulnerable subjects are hypothesized to contribute to the development of psychiatric disorders (He et al. 2017).

Despite potently shaping the landscape of brain development (McNeill and Van Vactor 2012), impacted by inflammation (Prada et al. 2018) and antipsychotics (Gardiner et al. 2014), and trafficked by exosomes (Shurtleff et al. 2016), miRNAs that mediate the neuro-immune axis have not been adequately studied in the context of psychiatric disorders. Additionally, examination of the developmental, regional, and cellular origins of miRNAs and their exosomal trafficking by neurons and glia in a coordinated setting will be essential to dissect relevant mechanisms. Consequently, a study screening for the differential expression of miRNAs in the postmortem brain of SCZ and BD is required. The neuron and glia expression and exosomal trafficking of such dysregulated miRNAs and their effect on gene control *in vitro* and *in vivo* settings may uncover posttranscriptional pathways at work.

Furthermore, the established anti-inflammation role of miR-223 and its ability to directly target and downregulate glutamate receptors *GRIA2* and *GRIN2B* offers a unique opportunity to illuminate its posttranscriptional function in the glia-neuron and brain-immune crosstalk.

Antipsychotics differentially alter miRNAs and olanzapine reportedly downregulates miR-223, suggesting that miRNAs may be responsive to antipsychotic treatment. Subsequently, elucidating the sources miR-223 and its involvement in potential trafficking between neurons and glia, and the impact of antipsychotics may yield novel insights into the posttranscriptional regulation of psychosis-associated genes, which may ultimately contribute to the better understanding and treatment of psychiatric disorders. Towards that end we have formulated the following hypothesis and specific objectives.

Hypothesis

Based on the extensive background adduced above my central hypothesis is: There is a differential expression miR-223 in the postmortem brain of subjects with psychiatric disorders and miR-223 downregulates its neuronal gene targets via exosomes.

The hypothesis will be achieved through the specific aims below.

Specific aim 1: Determine whether there is a differential expression of miR-223 in the postmortem brain. This will be achieved by quantifying miR-223 and miR-223-related neuronal and inflammatory gene levels in the postmortem orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC) brain of subjects with BD, SCZ and unaffected controls. This approach will require utilizing miRNA microarray profiling and qRT-PCR and determination of correlations between miR-223 and its related genes.

Specific aim 2: Determine the miR-223 cellular sources and endogenous expression in neuron and astrocytes, and developmental levels and antipsychotic impact. This will be achieved by quantifying miR-223 localization in cells and exosomes of neurons and astrocytes. Additionally, miR-223 levels during brain development, maternal immune activation and antipsychotic usage will be analyzed. The approach here will require utilizing human induced pluripotent stem cell (iPSC)-derived neuroprogenitor cells (NPCs) differentiated over a period, antipsychotics usage in rodent neuronal and astrocytic cell culture, prenatal and adult rodent brains, and maternal immune activation elicited by lipopolysaccharide (LPS) i.p. injection of pregnant dams followed by harvesting of prenatal pub brains. miR-223 levels of these samples will be analyzed.

Specific aim 3: Determine whether exosomal miR-223 can be assimilated by neurons to downregulate their neuronal gene targets. This will be achieved by harvesting astrocytic exosomes and growing them with neurons and then quantify miR-223 levels and its downstream targets Gria2 and Grin2b, and miRNA processing gene Adar1/2 in neurons. Additionally, anti-miR-223 and antipsychotics will be cultured with astrocytes prior to harvesting the exosomes to be grown with neurons and the miR-223 levels will be analyzed. The approach will involve utilizing cell culture to harvest mouse astrocytic exosomes grown with rat neurons and determine expression of the miR-223 and its downstream targets such as Gria2 and Grin2b, as well as Adar1/2 levels. Additionally, mouse astrocytes treated with olanzapine or lock nucleic acid anti-miR-223 and non-targeted miRNA probes

prior to harvesting the exosomes that will be grown with rat and mouse neurons, and followed by analysis of relevant genes.

Note that the data for specific aims 1 and 3 have been published.

CHAPTER 2: METHODS

2a. Animal experiments

The Institutional Care and Use Committee (IACUC) at the University of New Mexico Health Sciences Center approved all experimental procedures (protocol No: 17-200657-HSC). For each experiment described, equal numbers of male and female pups were used, and data represent true *n* (individual pups).

2b. Postmortem samples

Human postmortem brain total RNA samples from the OFC of subjects with SCZ ($N = 29$), BD ($N = 26$), and unaffected controls ($N = 25$) were derived from the Stanley Medical Research Institute (Torrey et al. 2000). Samples with an RNA integrity number (RIN) higher than 6.5 were selected for RNA quantification. Summarized and detailed demographics are shown in Tables S1–2 (Appendix II).

2c. RNA extraction and mRNA/miRNA quantification

RNA extraction and mRNA/miRNA quantification was done as shown before (Mellios et al. 2018; Bavamian et al. 2015; Mellios et al. 2011; 2014). Briefly, total RNA was isolated using the miRNeasy RNA isolation kit (Qiagen, Hilden, Germany). RNA quality and concentration were assayed through Nanodrop 2000 spectrophotometer and Qubit 3 (ThermoFisher Scientific, Waltham, MA). Mature miRNA reverse transcription was performed with Taqman miRNA Reverse Transcription kit and quantitative real-time PCR (qRT-PCR) was done using Taqman miRNA assays (all from ThermoFisher Scientific). All miRNA qRT-PCR measurements were performed in triplicate for each sample and the mean of the three cycle thresholds (Cts) was calculated. Two miRNAs highly expressed in the

OFC that are not altered in SCZ and BD (miR-30d-5p and let-7e) based on our own miRNA NanoString profiling (shown further below) were used for miRNA normalization via their geometric mean (Tables S3–4). For miRNA quantification, the following formula was used: Relative value = $2\text{^}Ct^{\text{geometric mean of miR-30d and let-7e}}/2\text{^}Ct^{miRNA}$. In cases where no normalization was used, the following formula was utilized: Relative value = $2\text{^}–Ct^{miRNA}$. For mRNA quantification, 100–400 ng of total RNA was reverse transcribed using the SuperScript IV First-Strand Synthesis System (ThermoFisher Scientific). cDNA was then used together with Taqman mRNA primers (ThermoFisher Scientific) for mRNA qRT-PCR. *18S rRNA* was used as a normalizer in cDNA samples further diluted by 20-fold and showed no changes in either BD or SCZ OFC relative to controls (Fig. S1) (Appendix I). For mRNA quantification, the following formula was used: Relative value = $E\text{^}Ct^{normalizer}/E\text{^}Ct^{mRNA}$, where $E = 10\text{^}(-1/\text{primer slope})$. Detailed information about the Taqman mRNA, miRNA, and pri-miRNA primers used in our study is included in Table S5 (Appendix II).

2d. Primary cultures

Mouse cortical astrocyte and neuronal cultures were derived from the cortices of P0-P1 C57BL/6 male and female pups (The Jackson Laboratory, Bar Harbor, ME), respectively and were established according to previously published method (Schildge et al. 2013; Weick et al. 2003). Rat primary cortical neurons were derived from Sprague Dawley E18 male and female rats (Gibco/ThermoFisher Scientific, Waltham, MA). Both mouse and rat cortical neuronal cultures were cultured as described previously (Weick et al. 2003). Brain dissection in P0-P1 C57BL/6 pups

was performed in ice-cold Hanks' balanced salt solution (HBSS) (Sigma Aldrich, St. Louis, MO) supplemented with the following: 20% FBS and NaHCO3 (4.2mM), HEPES (1 Mm; Sigma); pH 7.4. Dissected cortex, excluding hippocampus, cerebellum and brain stem was digested for 10 min with 0.25% trypsin (ThermoFisher Scientific). Tissue was washed and dissociated with flame-polished Pasteur pipettes of decreasing diameter in ice cold HBSS containing DNase (1500 U; Sigma). The cells were pelleted, resuspended in plating media and plated at a density of 4-5 x 10^4 cells/12-mm coverslip coated with poly-Ornithine (0.1 mg/ml; Sigma, catalog #4638) and laminin (5ug/ml; ThermoFisher Scientific). Cells were allowed to adhere in 20 min before addition of 500µl plating media containing Neurobasal supplemented with 1x B27 plus, 2mM Glutamax 0.5 mg/ml Penicillin/Streptomycin/Neomycin (PSN) (all from ThermoFisher Scientific). In parallel, embryonic day 18 rat cortical neurons (ThermoFisher Scientific) of 2x10^4 density were plated recapitulating the steps used for the primary mouse neurons. Serum was eliminated from the media after 24 h and again replaced after 48 h supplemented with 4 µM cytosine 1-β-D-arabinofuranoside (Ara-C; Sigma). Neurons were fed by replacing half the volume of spent media with fresh media without serum or Ara-C every 5 days. Primary mouse neurons and rat cortical neurons were grown for 18 and 12 days, respectively. For primary astrocytic cultures, cells were pelleted, resuspended in DMEM supplemented with 10% FBS and 10% 1x PSN plated at a density of 1 x 10^6 cells/tissue Culture plate (ThermoFisher Scientific). The cells were plated in a tissue culture plate and grown for 5-7 days until 90% confluent, then passaged using 0.25% trypsin

(ThermoFisher Scientific). The passaged astrocytes were split into 4 tissue culture plates and grown for 10-14 days until 90% confluent; exosomes were generated from the conditioned media. The astrocyte-conditioned media (ACM) was changed every 5 days and stored in -80^{0}C and the astrocytes were split between 5-15 days following seeding when the cells achieved 90% confluence.

2e. Exosome generation and utilization

Primary astrocytes were seeded into 24-well plates and after 1 day were subjected to the following therapeutic treatments: olanzapine (100nM), haloperidol (100nM) (Sigma-Aldrich) (Faour-Nmarne and Azab 2016; Tanahashi et al. 2012a), or equivalent volume of vehicle (0.08 % ethanol) and were cultured for an additional 2 days. The same treatments and duration of treatment were performed in day 18 mouse primary cortical neuronal cultures. The stored astrocyte conditioned media (ACM) and neuron-conditioned media (NCM) were thawed and centrifuged at 2000g for 30 minutes to remove cells and debris, then Total Exosome Isolation buffer (ThermoFisher Scientific) corresponding to one half of the volume of the media were added i.e. 1.5mL ACM and NCM had 0.75mL, while 30mL ACM had 15mL of the buffer added. The media and buffer mixture was briefly vortexed and kept in 4^{0}C overnight. The next day, the media and exosome isolation buffer was spun (without vortexing) at 10,000g at 4^{0}C for 1 hr. Exosomes generated from 24mL of astrocytic media were measured with NanoSight NS300 (Malvern Panalytical, Malvern, UK) and assessment using zeta potential nanoparticle tracking analysis (NTA) software was performed to determine the quantity and sizes of the exosomes defined within a range of 30-150 nm. To treat rat neuronal

cultures with mouse astrocytic exosomes, exosomes were derived from 0.8-6.4mL mouse ACM and diluted in 50 µl neuronal media were added to $2x10^4$ rat or mouse cortical neurons in each well of the 24 well plates. Exosomes were serially diluted in 50 µl neuronal media and added to neurons, and incubated for 1-2 days - in exosome-depleted FBS and 10% penicillin, streptomycin and neomycin (PSN) (ThermoFisher Scientific). Vehicle-treated neuronal cultures received 50ul neuronal media without any exosomes. Following either 1 or 2 days of incubation the media was removed and the neurons were carefully washed and neuronal pellets were harvested tor RNA extraction and analysis.

2f. Electron microscopy of exosomes

Grids with carbon films were glow-discharged for 30 seconds. Grids were floated face-down for 35 minutes on 10 µl drops of sample 0.1x sample diluted in PBS, then washed in 3 drops of ultrapure water. Excess liquid was wicked off onto filter paper, then the grids were stained for 1.5 minutes on 10 µl droplets of 2% uranyl acetate (aq.). Stain was cleaned and the grids air-dried.

2g. NanoString miRNA profiling

For mature miRNA profiling the NanoString nCounter system miRNA Expression Assay Kit (NanoString, Seattle, Washington, USA) was utilized at the University of Arizona Genetics Core per vendor's instruction and as shown before (Sellgren et al. 2017). Normalization (utilizing the geometric mean of all miRNAs) and data analysis were performed using nSolver software (NanoString).

2h. miRNA expression in human microglia and monocytes/macrophages

We pooled NanoString nCounter miRNA data related to human miR-223-3p expression in purified human adult brain microglia, immortalized microglia, and human monocytes and macrophages from a previously published report (Mellios et al. 2018; Lafourcade et al. 2016).

2i. Locked nucleic acid (LNA)-mediated miRNA Inhibition

To inhibit miR-223 in mouse cortical astrocytes we added miRCURY® power LNA® miRNA inhibitors for mouse miR-223 (Qiagen, Hilden, Germany) without transfection reagents and at a concentration of 25 pmol per the manufacturer's instructions.

2j. Immunohistochemistry

Immunocytochemistry was performed as previously described (Weick et al. 2013). Primary antibodies consisted of polyclonal anti-Grin2b antibody (#ab65783, Abcam, Cambridge, UK, 1:200) and polyclonal anti-MAP2 (#822501, BioLegend, San Diego, CA, 1:2000). Secondary antibodies DyLight 488 (1:1000; Thermo Fisher Scientific) and 680 (1:1000; Li-Cor, Lincoln, NE), were used. Image acquisition was performed with a spectral Leica TCS SP* confocal microscope and ImageJ was used for image analysis and quantification of Grin2b staining intensity in MAP2+ neurons (3-4 replicates per coverslip were used for each biological replicate).

2k. Statistical Analysis

For postmortem measurements, a Univariate General Linear Model which corrects for RIN, Brain pH, PMI, and Refrigeration Interval was chosen (IBM SPSS

Statistics 24 – IBM, Armonk, New York), given the normal distribution of values as assayed by D'Agostino-Pearson (omnibus K2) test (GraphPad Software, La Jolla, CA). Normalized values were divided to the mean of each control group and the relative to control miRNA/mRNA ratios were plotted as means ± SE using GraphPad Prism after removing up to 2 outliers using iterative ROUT test (GraphPad Software). In all other comparisons between two groups a two-tailed one sample *t*-test was used. For correlations Spearman's correlation coefficients and two-tailed p-values were calculated. Correlations were considered strong when they resulted in statistical power of more than 0.80.

CHAPTER 3: RESULTS

3a. Postmortem results

Significant associations between changes in miR-223 and glutamate receptor, GABAergic, and inflammatory gene expression in the OFC of subjects with psychiatric disorders.

We utilized postmortem brain samples from the OFC of subjects with SCZ ($N = 29$), BD ($N = 26$), and unaffected controls ($N = 25$) derived from the Stanley Medical Research Institute (Torrey et al. 2000); only samples with an RNA integrity number (RIN) higher than 6.5 were included (Tables S1–2) (Appendix II). To selectively and accurately detect mature miRNA transcripts we utilized NanoString nCounter miRNA profiling (Tables S3–4) (Appendix II). Focusing on the top 200 most highly expressed miRNAs in the OFC, we uncovered a subset of dysregulated SCZ and/or BD miRNAs (Fig. 2a, b and Tables S3–4). Using mature miRNA qRT-PCR, with the geometric mean of two highly expressed miRNAs that are not altered in SCZ and BD OFC as a normalizer (miR-30d-5p and let-7e, based on both the miRNA NanoString and qRT-PCR—Fig. 2c and Tables S3–4 (Appendix II)), and further correcting all results for RIN, brain pH, postmortem interval, and refrigeration interval using a univariate general linear model (see also “Materials and methods” section), we first validated increases in the majority of cases with SCZ but not in BD in miR-223-3p (mentioned henceforth as miR-223), a miRNA shown to target NMDA and AMPA receptor subunits, and thus, regulate rodent and human neuronal function (Harraz et al. 2012; 2014) (Fig. 2d). On the other hand, miR-132, a neuronal-enriched miRNA involved in synaptic plasticity (Mellios

et al. 2011) was reduced in SCZ (Fig. 2e), in accordance with previous reports (Miller et al. 2012). Moreover, miRNA-specific qRT-PCR confirmed moderate increases in the expression of both miR-330-3p and miR-1260 in BD (Fig. 2f, g). Lastly, we validated an increase in miR-193b-3p and miR-28a-3p in both SCZ and BD (Fig. 2h, i). Although a subset of these altered miRNAs have been reported to be secreted by exosomes, only miR-223 is a bona fide exosome-enriched miRNA shown in numerous reports to control glial and immune cell gene expression in response to ischemia and neuroinflammation (Shurtleff et al. 2016; Chen et al. 2017; Harraz et al. 2014; Cantoni et al. 2017; Shin et al. 2014). Furthermore, a previous study reported that olanzapine treatment can significantly reduce cortical levels of miR-223 in adult mice (Santarelli et al. 2013), thus suggesting that it could also be responsive to antipsychotics.

Focusing on miR-223, we then examined the expression of proven miR-223 targets, *GRIA2* and *GRIN2B* (Harraz et al. 2012), which are of relevance to psychiatric disorders, in our cohort using qRT-PCR with normalization to the unaltered and reliable for postmortem studies *18S rRNA* (Mellios et al. 2009; Bavamian et al. 2015; Durrenberger et al. 2010) (Fig. S1) (Appendix II). Our results, which were again further corrected for multiple postmortem demographics using a univariate general linear model, showed a significant reduction in *GRIA2* mRNA and a trend for reduction in *GRIN2B* mRNA in the OFC of subjects with SCZ, with *GRIN2B* also being downregulated in BD (Fig. 3a, b). Moreover, changes in miR-223 levels in the OFC of subjects with SCZ/BD were significantly inversely correlated with *GRIA2* and *GRIN2B* mRNA expression

(Fig. 3c, d). These correlations were specific, since other significantly decreased SCZ/BD mRNAs produced by neurons, such as neuronal pentraxin 2 (*NPTX2*) (Kimoto et al. 2015) (a gene that is not upstream or downstream of miR-223), did not show any association with miR-223 (Fig. 3e, f). Moreover, changes in astrocyte-enriched inflammation-related mRNA *SERPINA3* were positively associated with miR-223 expression (Fig. 3g, h). Again, this positive correlation with increased *SERPINA3* in SCZ appeared to be specific, and no association was found with the expression of other inflammation-related genes known to be increased in psychiatric disorder postmortem brains, such as Complement 4 (*C4*) (Sekar et al. 2016) (Fig. 3i, j). Of note, we did observe a modest negative correlation between miR-223 and changes in *GAD1* mRNA, which is not a target of miR-223, suggesting a potential indirect association with GABAergic gene expression (Fig. 3k, l). We therefore conclude that alterations in exosome-enriched miR-223 in the OFC of subjects with psychiatric disorders are strongly associated with changes in miR-223 targets related to glutamate receptor gene expression.

Analyzing the primary miR-223 precursor transcript, pri-miR-223, we observed that there was no significant difference, rendering transcriptional alterations as an unlikely source of the upregulation in mature miR-223 transcript levels seen in SCZ (Fig. S2a). In contrast, pri-miR-132 appeared to be reduced in SCZ, suggesting a transcriptional mechanism for the observed deficits in mature miR-132 expression (Fig. S2b). We then assessed the levels of genes involved in miRNA processing. We found no changes in our cohort in *DICER1*, and DiGeorge

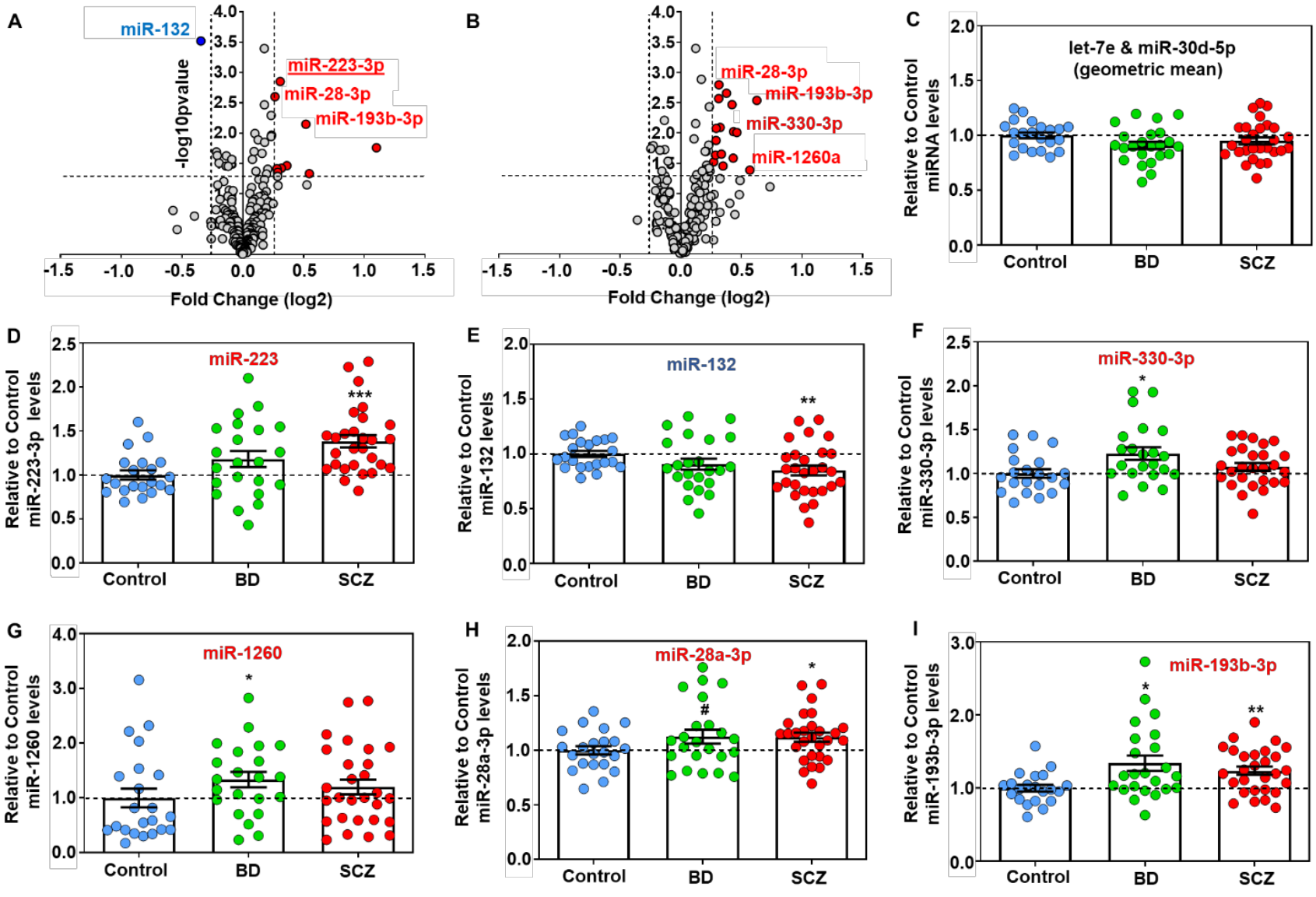
A
miR-132
miR-223-3p
miR-28-3p
miR-193b-3p
-log10pvalue
Fold Change (log2)
B
miR-28-3p
miR-193b-3p
miR-330-3p
miR-1260a
Fold Change (log2)
C
let-7e & miR-30d-5p
(geometric mean)
Relative to Control
miRNA levels
Control
BD
SCZ
D
miR-223
Relative to Control
miR-223-3p levels
E
miR-132
Relative to Control
miR-132 levels
F
miR-330-3p
Relative to Control
miR-330-3p levels
G
miR-1260
Relative to Control
miR-1260 levels
H
miR-28a-3p
Relative to Control
miR-28a-3p levels
I
miR-193b-3p
Relative to Control
miR-193b-3p levels

Figure 2: Dysregulation of miRNA expression in SCZ and BD OFC. a, b Results from NanoString nCounter miRNA profiling from the 200 most highly expressed miRNAs in the OFC presented as a volcano plot. The *x* axis represents log2 fold changes and the *y* axis represents the *p*-value with 1.2-fold and $p < 0.05$ cutoff, respectively. Significantly more than 1.2-fold increased miRNAs are shown as red circles and significantly more than 1.2-fold downregulated as blue circles. Notice the significant elevation of several miRNAs in SCZ (**a**) and BD (**b**) with one miRNA reduced in SCZ. Altered miRNAs chosen to be validated with qRT-PCR are named in the graph. c–i Graphs showing mean ± SEM relative to the mean of unaffected controls let-7e and miR-30d-5p geometric mean (**c**), miR-223-3p (**d**), miR-132 (**e**), miR-330-3p (**f**), miR-1260 (**g**), miR-28-3p (**h**), and miR-193b-3p (**i**) levels in SCZ, BD, and controls based on mature miRNA qRT-PCR. Graphs in (**d–i**) are normalized to the geometric mean of unaltered in BD and SCZ miRNAs let-7e and miR-30d-5p (see also (**c**) and Materials and methods). Data from each case are also depicted in the graph as blue circles (control), green circles (BD), and red circles (SCZ). $^{\#}0.05 < p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, based on a univariate general linear model that corrects for RIN, brain pH, PMI, and refrigeration interval.

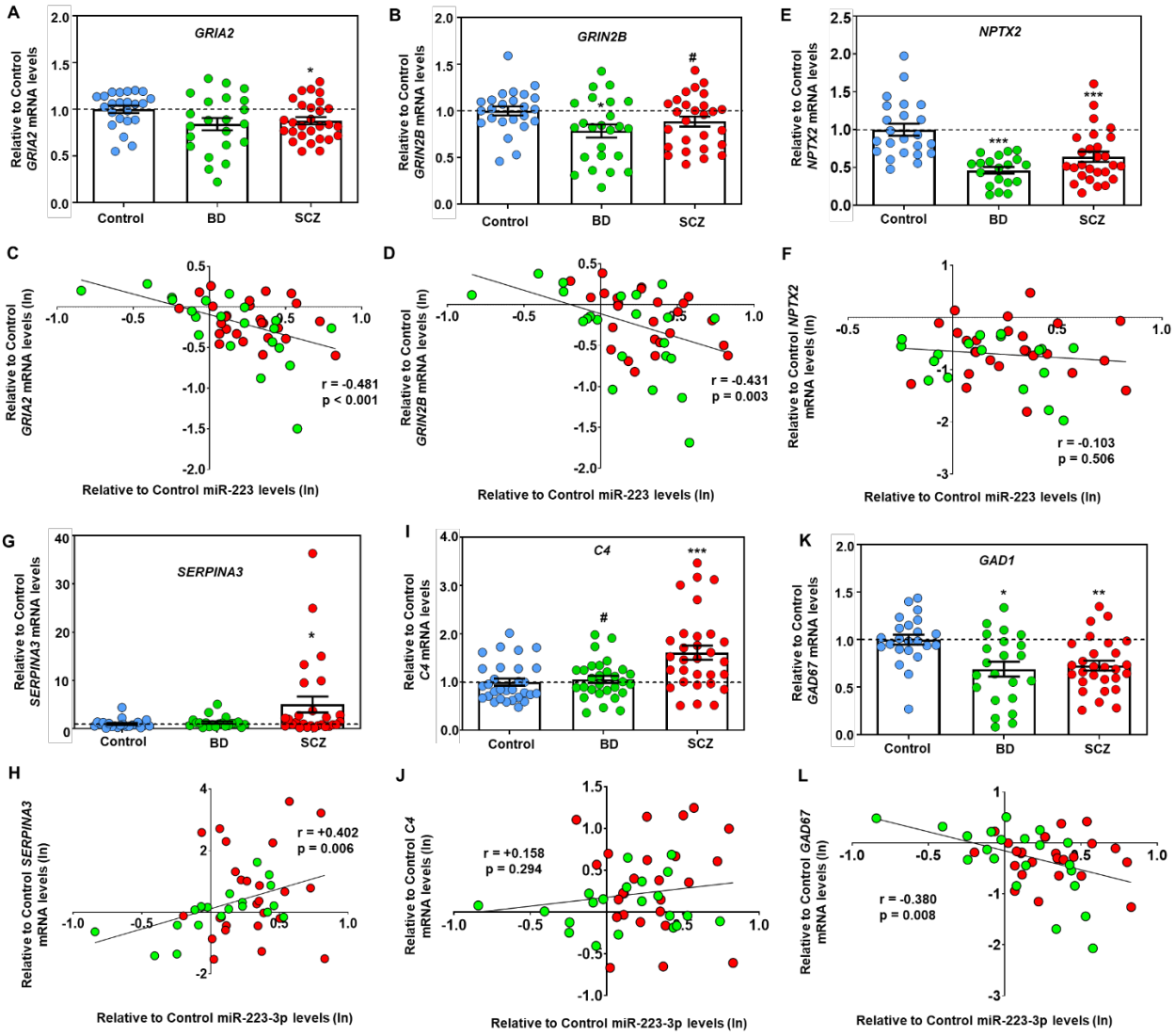

Figure 3: Alterations in glutamate receptor subunit, GABAergic, and inflammatory gene expression in the OFC are significantly associated with miR-223 changes in SCZ and BD. a, b, e Graphs showing mean ± SEM relative to the mean of unaffected controls mRNA levels in SCZ, BD, and control OFC for GRIA2 (**a**), GRIN2B (**b**), and NPTX2 (**e**) mRNAs, based on qRT-PCR and normalized to the unaltered in SCZ and BD 18S rRNA (see also Fig. S1 and Materials and methods). **c–d**, **f** Correlations between changes in miR-223 and GRIA2 (**c**), GRIN2B (**d**), and NPTX2 (**f**) mRNA expression in the OFC of subjects with SCZ and BD. Spearman's correlation coefficients and two-tailed p-values are shown in the graphs. **g, i, j** Graph showing mean ± SEM relative to the mean of unaffected controls mRNA levels in SCZ, BD, and control OFC for SERPINA3 (**g**), C4 (**i**), and GAD1 (**k**) based on qRT-PCR and normalized to 18S rRNA. **h, j, l** Correlations between changes in miR-223 and SERPINA3 (**h**), C4 (**j**), and GAD1 (**l**) expression in the OFC of subjects with SCZ and BD. Data from each case are also depicted in the graph as blue circles (control), green circles (BD), and red

circles (SCZ). Spearman's correlation coefficients and two-tailed p-values are shown in the graphs. For (**a–c**, **g–i**) #0.05 < p < 0.10, *p < 0.05, **p < 0.01, ***p < 0.001, based on a univariate general linear model that corrects for RIN, brain pH, PMI, and refrigeration Interval. Data from each case are also depicted in the graph as blue circles (control), green circles (BD), and red circles (SCZ).

syndrome chromosomal region 8 (*DGCR8*) (Fig. S2c–d) (Appendix I), in contrast to what has been observed in other brain regions in SCZ (Beveridge et al. 2010; Santarelli et al. 2011). We did observe, though, that both adenosine deaminases acting on RNA transcript types 1 and 2 (*ADAR1*, *ADAR2*) were significantly downregulated in SCZ, with *ADAR2* also showing a modest reduction in BD (Fig. S2e–f). ADARs are deaminases that convert adenosine to inosine, resulting in reduced pri-miRNA processing and/or degradation of intermediate precursor (pre-miRNA) transcripts, both of which ultimately result in reduced mature miRNA levels (Slezak-Prochazka et al. 2010; W. Yang et al. 2006). We analyzed the relationship between miR-223, and *ADAR1* and *ADAR2*, and observed that there was a significant inverse correlation between miR-223 and *ADAR1* and *ADAR2*, with the association with *ADAR2* being the strongest (Fig. S2g–h) (Appendix II). Taken together, our results indicate that reduced *ADAR1/2* levels are associated with increased expression of mature miR-223 in SCZ. These data suggest that dysregulation of mature miR-223 expression in the OFC of subjects with SCZ is unlikely to be a result of altered pri-miRNA transcription or canonical miRNA processing, but instead appears to be associated with reduced ADAR-mediated inhibition of miRNA processing.

Specific upregulation of miR-223 in the OFC of BD subjects with psychosis

To determine whether postmortem demographics could be influencing miR-223 expression in the OFC, we examined the effects of 18 separate demographics on the relative-to-control changes of miR-223 in BD and SCZ OFC (Table S6) (Appendix II). We detected no interactions with most of the postmortem

demographics, including duration of overall antipsychotic treatment (shown as fluphenazine equivalents in mg) (Table S6 (Appendix II) and Fig. 4a). However, we observed a negative correlation between changes in miR-223 and lifetime of alcohol use (which could not account for the observed increases in miR-223 expression given the higher alcohol use in patients vs. controls) and a significant positive association with psychosis at the time of death (Table S6 (Appendix II) and Fig. 4b). Although all SCZ patients are positive for psychosis, only a subset of subjects with BD in our cohort were diagnosed with psychosis close to the time of death (Table S2) (Appendix II). We therefore separated the BD group into BD with and without psychosis at the time of death. We found that miR-223 expression was significantly increased in BD patients with psychosis, whereas BD subjects without psychosis showed similar-to-control values (Fig. 4c). Given the observed significant correlations between miR-223 and *SERPINA3*, *GRIN2B*, *GRIA2*, and *ADAR2* mRNAs in the OFC, we plotted their expression into each of the two BD groups (Fig. 4d–g). Our results showed that BD patients with psychosis but not BD patients without psychosis displayed significant increases in *SERPINA3*, and reductions in *GRIN2B*, *GRIA2*, and *ADAR2* mRNAs, similar to those seen in SCZ (Fig. 4d–g). Of note, *NPTX2* mRNA, which is not associated with miR-223, was seen to be equally reduced in both BD patients with psychosis and without psychosis at the time of death (Fig. 4h). We conclude that changes in OFC miR-223 and miR-223-associated gene expression are observed in BD patients with psychosis similar to what is seen in SCZ.

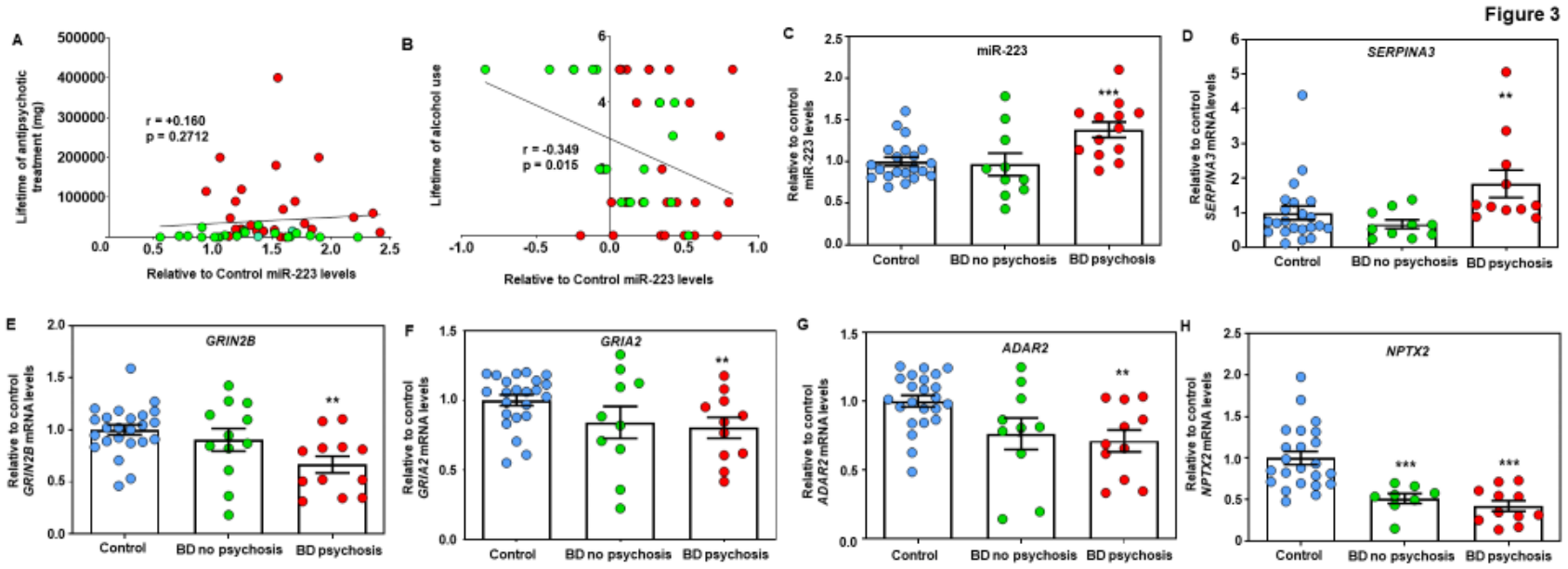

Figure 4: BD patients with psychosis display altered OFC miR-223 and miR-223-associated gene expression similar to that seen in SCZ. a, **b** Correlation between relative-to-control changes in miR-223 and lifetime of antipsychotic treatment (**a**; shown as mg of fluphenazine equivalents) and alcohol use (**b**) in the OFC of subjects with SCZ and BD. Spearman's correlation coefficients and two-tailed *p*-values are shown in the graph. Relative-to-control individual data are also shown in the graphs: SCZ = red circles, BD = green circles. **c**–**h** Graphs showing mean ± SEM relative to the mean of unaffected controls mRNA levels in BD with no psychosis, BD with psychosis, and control OFC for miR-223 (**c**), *SERPINA3* (**d**), *GRIN2B* (**e**), *GRIA2* (**f**), *ADAR2* (**g**), and *NPTX2* (**h**) expression based on qRT-PCR (mRNA expression normalized to *18S rRNA* and miRNA expression to the geometric mean of let-7e and miR-30d). Data from each case are also depicted in the graph as blue circles (control), green circles (BD with no psychosis), and red circles (BD with psychosis). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, based on a univariate general linear model that corrects for RIN, brain pH, PMI, and refrigeration interval.

No changes in miR-223 and miR-223-related gene expression in the dorsolateral prefrontal cortex of SCZ and BD patients despite increase inflammatory gene expression.

Earlier studies have observed miRNA dysregulation in the dorsolateral prefrontal cortex (DLPFC) SCZ and BD (Beveridge and Cairns 2012; Altshuler et al. 2008). We utilized postmortem brain samples from the DLPFC of subjects with SCZ (N = 25), BD (N = 26), and unaffected controls (N = 23) derived from the Stanley Medical Research Institute (Torrey et al. 2000); only samples with an RNA integrity number (RIN) higher than 6.5 were included. Utilizing qRT-PCR we analyzed the various miRNAs and observed that let 7e and miR-223 were not changing in our DLPFC cohort (Fig. 5a, b). Analyzing *18S rRNA* revealed that it did not change across the DLPFC cohort and hence could be used as the normalizer (Fig. 5c). We next analyzed the inflammation mRNA expression and observed that the inflammation gene SERPINA3 mRNA was elevated by approximately four- and twelve-fold in bipolar disorder and schizophrenia, respectively (Fig. 5d), suggesting intense involvement of inflammation with SCZ and BD in our DLPFC cohort. Additionally, analysis of the neuronal genes indicated that GRIA2 mRNA did not change in our DLPFC cohort (Fig. 5e) while NPTX2 mRNA was moderately reduced in both SCZ and BD disorder subjects (Fig. 5g) in the DLPFC. Furthermore, the posttranscriptional gene modifier adenosine deaminase acting on RNA 2 (ADAR2) expression did not change across our DLPFC cohort (Fig. 5f).

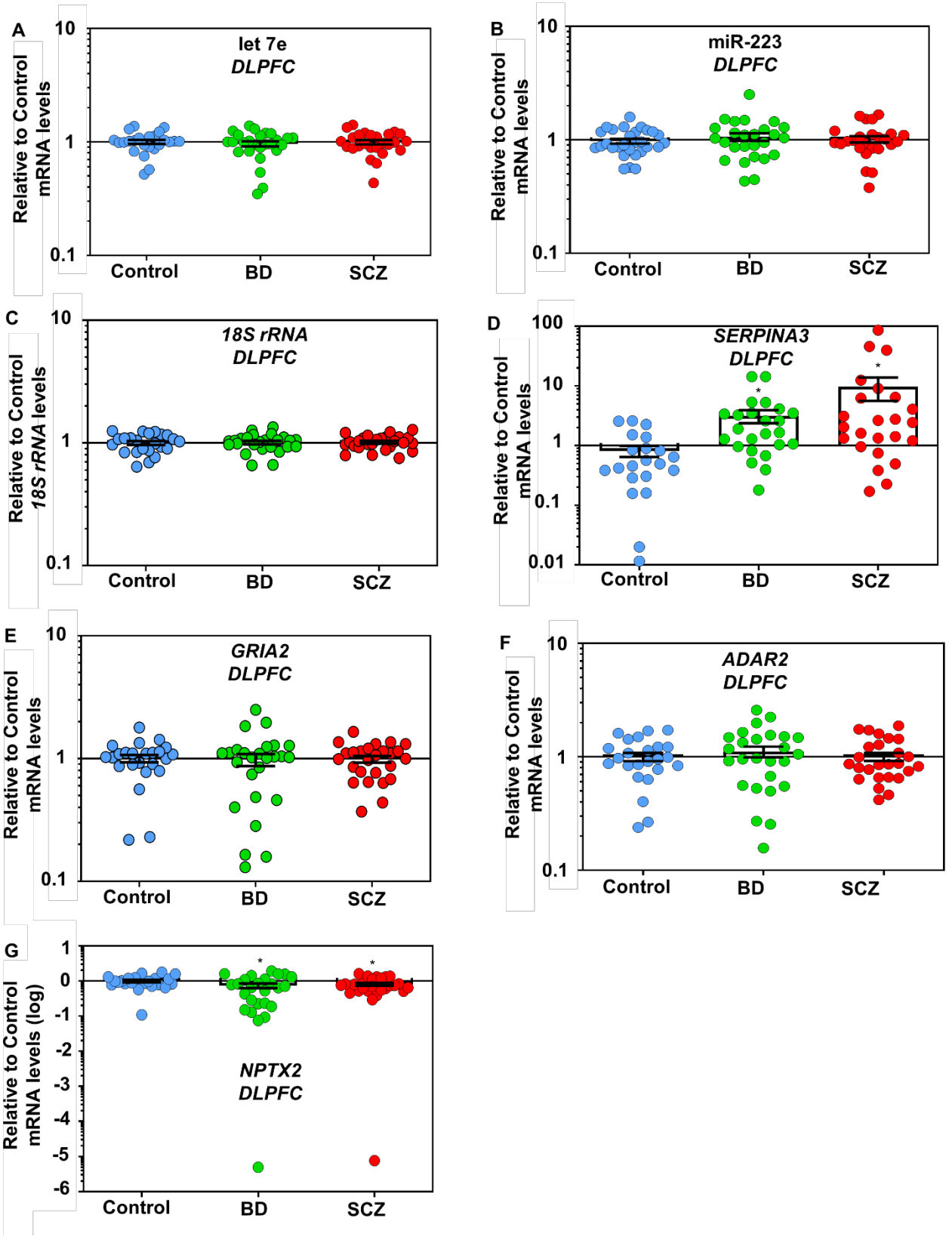
A
let 7e
DLPFC
Relative to Control mRNA levels
10
1
0.1
Control
BD
SCZ
B
miR-223
DLPFC
Relative to Control mRNA levels
10
1
0.1
Control
BD
SCZ
C
18S rRNA
DLPFC
Relative to Control 18S rRNA levels
10
1
0.1
Control
BD
SCZ
D
SERPINA3
DLPFC
Relative to Control mRNA levels
100
10
1
0.1
0.01
Control
BD
SCZ
E
GRIA2
DLPFC
Relative to Control mRNA levels
10
1
0.1
Control
BD
SCZ
F
ADAR2
DLPFC
Relative to Control mRNA levels
10
1
0.1
Control
BD
SCZ
G
NPTX2
DLPFC
Relative to Control mRNA levels (log)
1
0
-1
-2
-3
-4
-5
-6
Control
BD
SCZ

Figure 5: miRNA and mRNA expression profile in DLPFC with elevated inflammation and reduced NPTX2 expression. a, **b** Graphs showing mean ± SEM relative to the mean of unaffected controls miRNA levels in SCZ, BD, and control DLPFC for let 7e and miR-223. **c-g** Graphs showing mean ± SEM relative to the mean of unaffected controls mRNA levels in SCZ, BD, and control DLPFC for (**c**), 18S rRNA, (**d**) SERPINA3 (**e**), GRIA2 (f), ADAR2 and (**g**), NPTX2 (h) expression based on qRT-PCR (mRNA expression normalized to 18S rRNA and miRNA expression normalized to the geometric mean of let-7e).

3b. Cell culture, iPSC and animal results

miR-223 and miR-132 exhibit differential developmental, cellular- and brain region-specificity.

Neuronal and brain development is shaped by multiple differentially expressed miRNAs of which miR-132 is associated with the neuronal fate (McNeill and Van Vactor 2012; Cho et al. 2019). Although, miR-223 is observed in both the adult central nervous system and peripheral sources, and is associated with aspects of neurogenesis such as inhibiting dendrite outgrowth (Morquette et al. 2019; Ji et al. 2016; Ponomarev et al. 2011, Harraz et al. 2014), its endogenous neuronal expression is yet to be determined. Thus, we decided to quantify the expression of these two miRNAs during neurogenesis and in prenatal and adult mouse brains. Utilizing qRT-PCR in human induced pluripotent stem cell (iPSC)-derived neuronal cultures, we found that miR-223 was barely detected but miR-132 was significantly expressed in neuronal progenitors (NPCs) and increased over the six-week period of NPC differentiation (Fig. 6a, b). Our interest in the whole brain expression of these miRNAs led us to analyze their levels in the prenatal and adult mouse brain and in multiple adult brain regions. Interestingly, we observed that miR-223 expression was approximately four-fold higher in the embryonic day 19 (E19) mouse brain than in the total adult mouse brain, and that miR-223 expression in the adult brain was comparable in most brain regions such as the frontal (FC) and parietal cortices (PC), cerebellum (CB) and brain stem (BS), but lower in hippocampus (HIP) and hypothalamus (HYP) (Fig. 6c). Conversely, miR-132 expression in the E19 mouse brain was 47-fold lower than in the total adult mouse

brain, and the regional miR-132 expression in adult brain was characterized by higher levels in the FC and PC but lower in HIP, CB and BS (Fig. 6d).

Maternal immune activation eliciting prenatal inflammation has been linked to the development of neuropsychiatric disorders such as SCZ and BD. Rodent models recapitulate schizophrenia-like features such as impaired novel object recognition, spatial learning, memory, reduced parvalbumin cells in various brain regions altered in psychosis (Batinić et al. 2016). Although, inflammatory gene expression such as TNF-α and IL-6 has been shown to be elevated in this model, inflammation-related miRNAs have not been specifically analyzed. We decided to determine the expression of miR-223 in the E18 brains 1–2 days after i.p. LPS injection in the pregnant dam and observed a robust 1.5-fold increase (Fig. 6e). These results indicate that miR-223 could potentially contribute to the molecular mechanisms that alter neurodevelopment originating from MIA.

miR-223 is enriched in astrocytes and exosomes and is regulated by antipsychotics in a cell-specific manner

Although the enrichment of miR-223 in peripheral exosomes has been previously studied (Shurtleff et al. 2016; Chen et al. 2017; Harraz et al. 2012; Cantoni et al. 2017), little is known about its expression in the brain. To that end, we compared its cellular and exosomal expression in primary mouse cortical and astrocytic cultures (Fig. 7a). We utilized various techniques to detect and quantify exosomes. Exosomal quantity was determined using nanoparticle-tracking analysis via

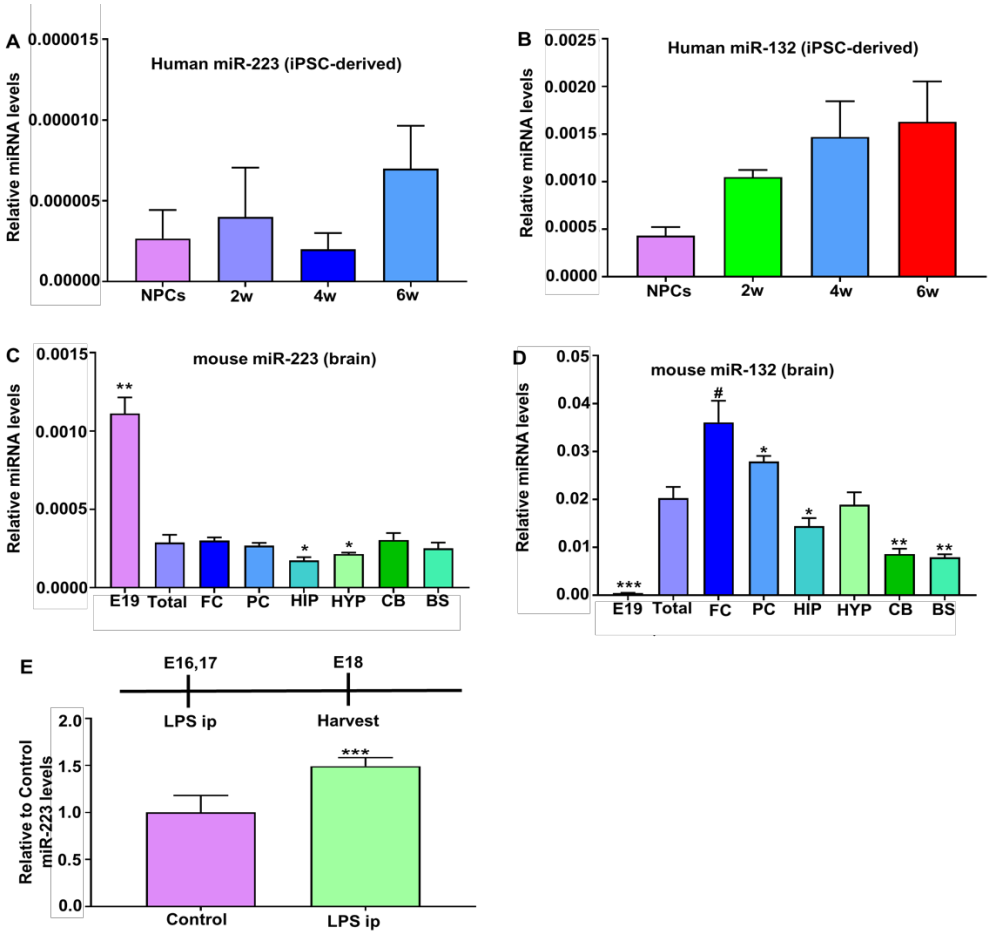

Figure 6: Enrichment of miR-223 in the prenatal brain, and effects of MIA. a-b miR-223 and miR-132 gene expression relative expression (based on mature miRNA qRT-PCR, without normalization) in human iPSC-derived neuronal progenitors (NPCs), and 2w, 4w, and 6w neuronal cultures (N=2, in each group) from unaffected controls. Notice modest miR-223 expression approximately 100-fold lower than miR-132. **c-d** mean ± SEM mature miR-223 (**c**) and (**d**) miR-132 relative expression (based on mature miRNA qRT-PCR, without normalization) in E19 (N=5) and adult whole brains (Total, N=4), as well in adult frontal cortex (FC, N=3), hippocampus (HIP, N=4), hypothalamus (HYP, N=3), cerebellum (CB, N=3), and Brainstem (BS, N=3). *p < .05, **p < .01, based on two-tailed one sample *t*-test compared to the mean of miR-223 expression in adult whole brain. Notice higher in prenatal than adult mouse brain miR-223 expression, and conversely, a robust miR-132 relative expression in adult brains than prenatal brain with highest regional expressions in FC. **e** Upper: Schematic of LPS i.p. administration in rat dams (E16 and E17) and whole brain tissue harvesting in E18 embryos. Lower: Mean ± SEM mature miR-223 relative expression (based on mature miRNA qRT-PCR and normalized to the geometric mean of let-7e and miR-30d) in a rat LPS model of MIA (Control: N=10, LPS i.p: N=11). ***p < .001, based on two-tailed one sample *t*-test compared to vehicle. *p < .05, based on two-tailed one sample *t*-test compared to vehicle.

NanoSight (NS300) (Fig. 7b), electron microscopy was used to visualize the size and shape of the exosomes (Fig. 7c), and ELISA via CD63 immunoreactivity to quantity serial dilutions of exosomes, which indicated a robust linear correlation (Fig. 7d). We next analyzed the expression of miR-223 in the cellular pellets and exosomal fractions of mouse cortical neurons and astrocytes. We found that the cellular expression of miR-223 was significantly higher in astrocytes than in neurons, whereas exosomes from both neurons and astrocytes expressed equal amounts of miR-223 (Fig. 7e). Conversely, analysis of let-7e expression in mouse cortical neurons and astrocytes showed an enrichment in neuronal pellets with lower levels in the exosomal fractions (Fig. S3a) (Appendix II).

Given that olanzapine is associated with reduction of miR-223 expression in the mouse brain (Santarelli et al. 2013), we were interested in the effect of the antipsychotics on cellular and exosomal miR-223 levels in cortical neurons and astrocytes. Using a subacute (2-day) treatment of olanzapine and haloperidol doses, we found that antipsychotics significantly reduce miR-223 expression in both neuronal pellets and neuronal exosomal fractions (Fig. 7f), suggesting a reduction in miR-223 synthesis within neurons. On the other hand, subacute treatment of the same antipsychotics reduced miR-223 expression in astrocytic pellets but increased miR-223 levels in the exosomal fraction, suggesting that antipsychotics could increase the secretion of miR-223 in astrocytes (Fig. 7g). Previous work has shown that miR-223 is not expressed in adult mouse microglia yet is abundant in mouse macrophages or monocytes (Ponomarev et al. 2011). To determine miR-223 expression in human microglia and monocytes/macrophages,

Figure 4

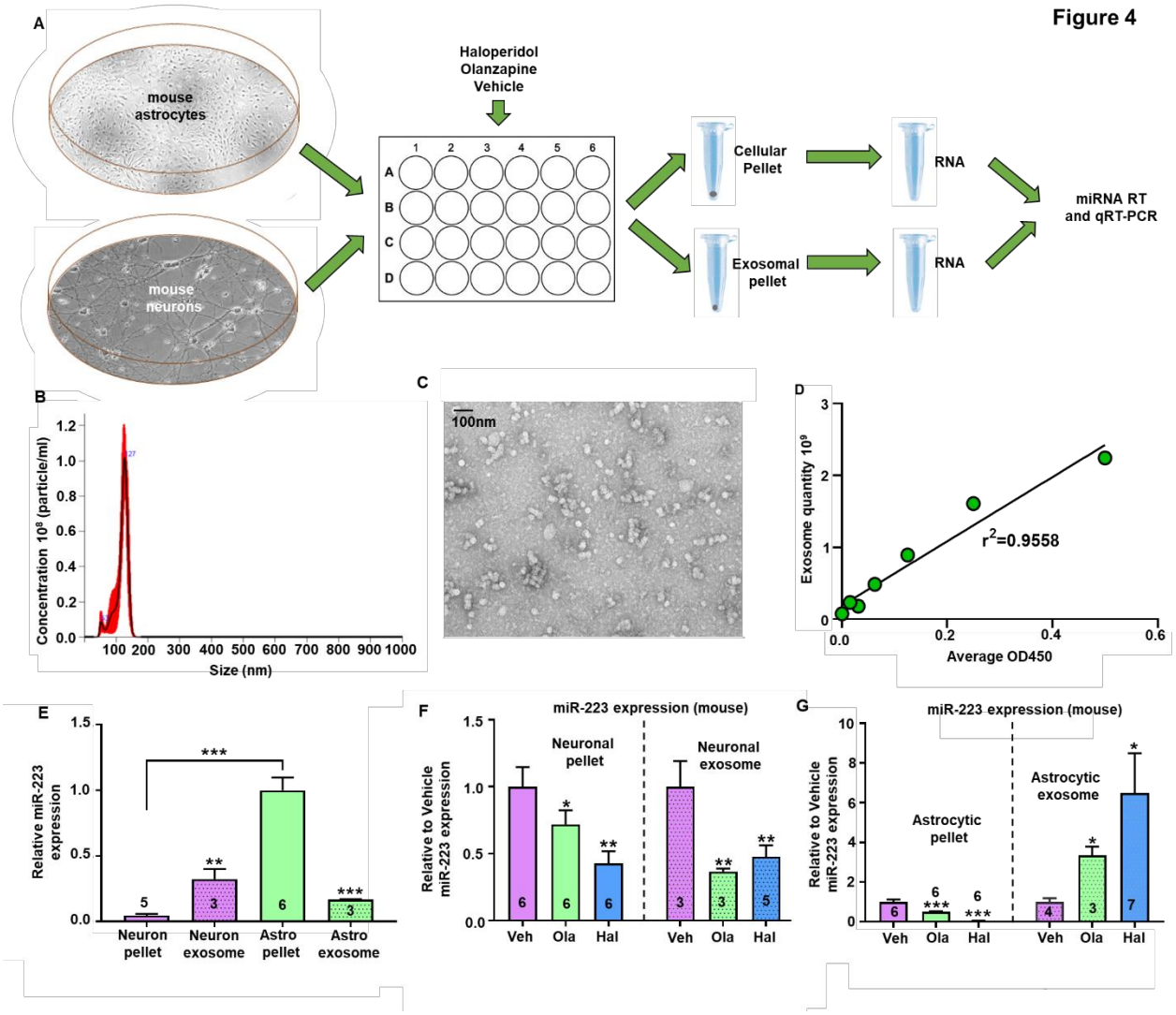

Figure 7: Enrichment of miR-223 in astrocytes and cell-specific effects of antipsychotic treatment on miR-223 expression exosomal secretion. Experimental design. **b**–**d** Exosome quantification with NanoSight (**d**), electron microscopy characterization (**c**), and dilution curve with plate reader based on ELISA CD63 exosome marker reactivity (**d**). **e** Mean ± SEM miR-223 relative expression in mouse cortical neuronal (2 weeks of differentiation) and astrocytic pellets and exosomes (based on mature miRNA qRT-PCR without normalization and shown as ratios relative to the highest expression in mouse astrocytic pellets). $^{**}p < 0.01$, $^{***}p < 0.001$, based on two-tailed one- sample *t* test compared with pellet expression of the same cell culture (stars above bars) or compared with pellet expression between different cell types (stars with connecting line). **f**, **g** Mean ± SEM miR-223 levels (based on mature miRNA qRT-PCR, without normalization, and normalized to the mean of either pellet or exosomal vehicle) in primary mouse cortical neuronal (grown in culture for 18 days) (**f**) and

astrocytic (**g**) pellets and exosomes treated for 2 days with olanzapine (Ola), haloperidol (Hal), or vehicle (Veh). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, based on two-tailed one-sample *t* test compared with the mean of miR-223 expression in vehicle-treated cultures of the same isolation (pellet or exosome). The number of biological replicates is shown in each graph.

we pulled NanoString profiling data for miR-223 from a previous study (Sellgren et al. 2017). These results showed that although miR-223 was barely detected in purified human adult brain microglia, there was robust expression of miR-223 in peripheral monocytes and macrophages (Fig. S4). We conclude that in the brain parenchyma, miR-223 is enriched in mouse astrocytes and secreted via exosomes and that antipsychotics reduce miR-223 synthesis in neurons but increase miR-223 exosomal secretion in astrocytes.

3c. Exosomal miR-223 and anti-miR-223 effects on neuronal mRNA levels

Mouse astrocytic exosomes assimilated by rat neurons increase miR-223 levels and downregulate miR-223-associated downstream targets

Given the observed enrichment of miR-223 in astrocytes and its abundance in exosomes, we decided to test whether exosomes secreted from astrocytes could regulate neuronal gene expression. Given that exosomes can also include mRNAs in addition to miRNAs, we added mouse astrocytic exosomes into rat cortical neuronal cultures so as to be certain that any changes in mRNA expression in recipient neuronal cultures are not a result of direct transport of mRNAs via exosomes. To that end, we harvested exosomes from astrocytic conditioned media and incubated the exosomes with rat cortical neurons for 1–2 days, making sure to change the media and carefully rinse the cells before harvesting the rat neuronal pellets (Fig. 8a). Using mature miRNA qRT-PCR with primers that preferentially but not exclusively detect mouse miR-223 (due to a single-nucleotide difference between mouse and rat mature miR-223 sequences, these primers are expected

to detect some small percentage of rat miR-223) as well and normalizing to let-7e expression (Fig. S5a) (Appendix I), we first observed a significant twofold increase in mature miR-223 expression in rat cortical neurons treated with mouse astrocytic exosomes as compared with untreated rat cultures (Fig. 8b). However, no changes were observed as a result of astrocytic exosome treatment in other miRNAs associated with exosomes, such as miR-132 (enriched in neuronal exosomes) and miR-155 (enriched in microglial exosomes) (Fig. 8b) (Xu et al. 2017; Udeochu et al. 2018), suggesting that enrichment of miR-223 in the astrocytic exosomal fraction could enable its assimilation into the rat neuronal culture. Interestingly, qRT-PCR analysis of rat mRNA expression with rat-specific primers and normalization to *18S rRNA* (Fig. S5b) revealed a significant reduction in *Gria2* and *Grin2b,* but not *Adar1,* levels in exosome-treated rat cortical neurons, suggesting a preferential reduction in validated miR-223 targets (Fig. 8c). In order to examine whether the reductions in rat *Grin2b* and *Gria2* mRNA levels are associated with increased mouse miR-223 expression, we compared mouse miR-223 with rat and *Grin2b* and *Gria2* mRNA expression. These comparisons revealed a strong inverse correlation between miR-223 and *Grin2b* (Fig. 8d), a significant negative correlation with *Gria2* ($r = -0.7091$, $p = 0.0182$, Spearman's correlation with two-tailed *t* test), but no significant associations between miR-223 and *Adar1* mRNA levels (data not shown). In addition, no such associations were observed between *Gria2* and *Grin2b* and miR-132 or miR-155 (Fig. S5c–f) (Appendix I), suggesting that these changes could be driven specifically by exosomal trafficking of mouse miR-223. Of note, we also observed a trend for a

negative correlation between miR-223 and reductions in rat *Gad1* mRNA (Fig. S5g–h) (Appendix I). To make sure that the effects of astrocytic exosomes on miR-223 *Grin2b* and *Gria2* expression are also observed in mouse neuronal cultures, we added astrocytic exosomes in mouse cortical neuronal cultures. We found increased levels of mouse neuronal miR-223 and reduced mouse neuronal Grin2b mRNA and protein expression (via immunostaining), as well as reduced *Gria2* mRNA expression, suggesting a conserved effect between species (Fig. 8f–g). In order to determine if the increased expression of miR-223 in astrocytic exosomes is necessary to induce reductions in neuronal *Grin2b* and *Gria2* expression, we inhibited miR-223 in astrocytes via locked nucleic acid (LNA) miRNA inhibitors and extracted exosomes. We found that inhibition of miR-223 in astrocytes was sufficient to rescue the exosomal-mediated deficits in *Grin2b* but not *Gria2* mRNA expression (Fig. 8h, i). Additionally, to determine the neuronal effect of the elevated exosomal miR-223 induced by antipsychotics, we added exosomes from olanzapine-treated astrocytes and observed a robust downregulation of Grin2b in the neurons (Fig. 8j) suggesting that antipsychotics may exacerbate neuronal function. These data suggest that exosomal-mediated reductions in *Grin2b* expression are mediated by miR-223, whereas additional exosomal miRNAs or mRNAs are needed for miR-223 to regulate *Gria2* expression in neurons. We conclude that mouse astrocytic exosomal miR-223 is assimilated by cortical neurons and is sufficient to inhibit neuronal *Grin2b* expression.

Figure 8

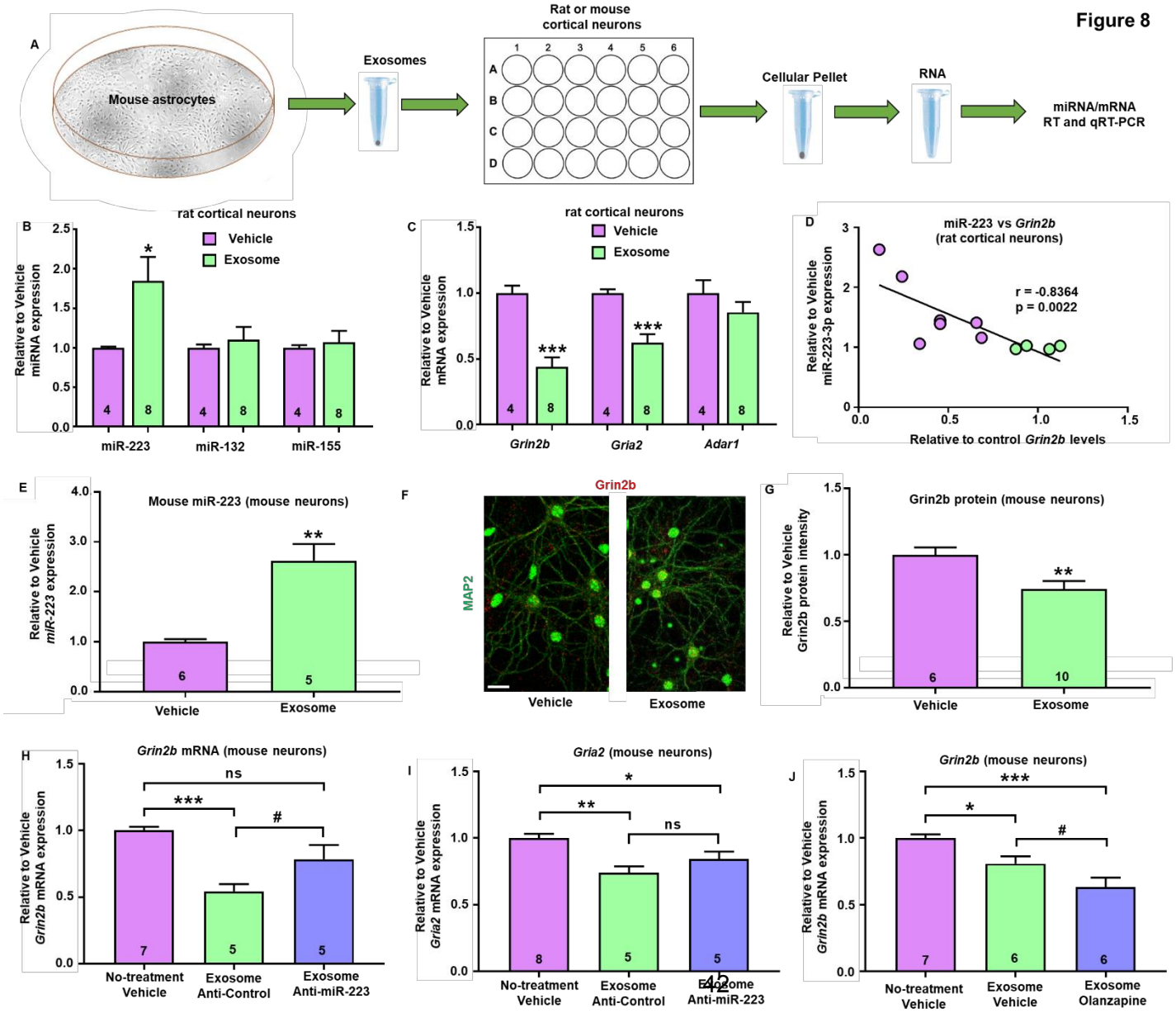
A
Mouse astrocytes
Exosomes
Rat or mouse cortical neurons
1 2 3 4 5 6
A
B
C
D
Cellular Pellet
RNA
miRNA/mRNA RT and qRT-PCR
B
rat cortical neurons
Vehicle
Exosome
Relative to Vehicle miRNA expression
miR-223
miR-132
miR-155
C
rat cortical neurons
Vehicle
Exosome
Relative to Vehicle mRNA expression
Grin2b
Gria2
Adar1
D
miR-223 vs Grin2b (rat cortical neurons)
r = -0.8364
p = 0.0022
Relative to Vehicle miR-223-3p expression
Relative to control Grin2b levels
E
Mouse miR-223 (mouse neurons)
Relative to Vehicle miR-223 expression
Vehicle
Exosome
F
Grin2b
MAP2
Vehicle
Exosome
G
Grin2b protein (mouse neurons)
Relative to Vehicle Grin2b protein intensity
Vehicle
Exosome
H
Grin2b mRNA (mouse neurons)
Relative to Vehicle Grin2b mRNA expression
No-treatment Vehicle
Exosome Anti-Control
Exosome Anti-miR-223
I
Gria2 (mouse neurons)
Relative to Vehicle Gria2 mRNA expression
No-treatment Vehicle
Exosome Anti-Control
Exosome Anti-miR-223
J
Grin2b (mouse neurons)
Relative to Vehicle Grin2b mRNA expression
No-treatment Vehicle
Exosome Vehicle
Exosome Olanzapine

Figure 8: Astrocytic exosomes increase neuronal miR-223 levels and downregulate miR-223-related neuronal gene expression. a Schematic of experimental design. **b** Graph showing mean ± SEM mature miR-223, miR-132, and miR-155 expression (based on mature miRNA qRT-PCR and normalized to highly expressed and unaltered let-7e—see Fig. S5a) in rat neurons treated with mouse astrocytic exosomes for 1–2 days relative to vehicle-treated rat neurons. **c** Graph showing mean ± SEM rat neuronal gene levels following mouse exosomal treatment for rat *Grin2b, Gria2*, and *Adar2* mRNAs (all based on qRT-PCR and normalized to *18S rRNA*—see Fig. S5b). Data are shown as ratios relative to the mean of vehicle. **d** Correlation between relative-to-vehicle miR-223 (mouse primer) and rat *Grin2b* mRNA expression. Spearman's correlation coefficients and two-tailed *p*-values are shown in the graphs. Vehicle = purple circles, exosome treatment = green circles. **e** Graph showing mean ± SEM mouse mature miR-223 expression (based on mature miRNA qRT-PCR and normalized to let-7e) in mouse cortical neurons treated with mouse astrocytic exosomes for 2 days relative to vehicle-treated rat neurons. For (**b**, **c**, **e**) $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, based on two-tailed one-sample *t* test compared with vehicle. **f** Representative images following immunostaining of mouse cortical neurons with anti-Grin2b (red) and anti-MAP2 antibodies (green) after 2 days of treatment with astrocytic exosomes (Exosome) or no treatment (Vehicle). Scale bar = 50 µm. **g** Graph showing mean ± SEM relative to no-treatment vehicle Grin2b immunostaining intensity in mouse cortical neurons positive for MAP2 treated with mouse astrocytic exosomes for 1 day relative to vehicle-treated rat neurons (data from 3 to 4 images were averaged for each well/coverslip). $^{**}p < 0.01$, based on two-tailed one-sample *t* test compared with vehicle. **h**, **i** Graphs showing mean ± SEM mouse neuronal gene levels following for mouse *Grin2b* (**h**) and *Gria2* (**i**) mRNAs (all based on qRT-PCR and normalized to *18S rRNA*) following 1 day of treatment with astrocytic exosomes treated with locked nucleic acid (LNA)-based miRNA inhibitors against mouse miR-223 (Anti-miR-223) or scrambled control (Anti-Control) astrocytic exosomes. **j** Graph showing mean ± SEM relative to no-treatment vehicle mouse *Grin2b* mRNA levels (based on qRT-PCR and normalized to *18S rRNA*) following 2 days of treatment with exosomes from astrocytes treated with olanzapine or vehicle, or no exosome treatment. For (**h**–**j**): $^{\#}0.05 < p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, based on ANOVA with Tukey's multiple comparisons test. The number of biological replicates is shown in each graph.

CHAPTER 4: DISCUSSION

Mounting evidence has linked glutamatergic synaptic transmission and GABAergic and inflammatory gene expression in SCZ and BD (Merikangas et al. 2007; Coyle 2006; Akbarian et al. 1995; Fatemi et al. 2005; Guidotti et al. 2000; Hashimoto et al. 2003; Mellios et al. 2009; Volk et al. 2000; Fillman et al. 2013; Horváth and Mirnics 2014; Hwang et al. 2013; Saetre et al. 2007; Trépanier et al. 2016; Zhang et al. 2016; Arion et al. 2007; Fillman et al. 2014). Here we show that miR-223, a known exosome-enriched miRNA, is significantly increased in the OFC of subjects with SCZ and BD with psychosis, and is negatively correlated to the mRNA levels of its targets *GRIN2B* and *GRIA2*, which are also significantly downregulated. Moreover, we find that changes in miR-223 in the OFC of BD and SCZ patients are positively associated with *SERPINA3* mRNA levels but was negatively associated with alteration in *GAD1* mRNA expression despite the latter not being miR-223 target. Furthermore, reductions in miRNA-processing inhibitors ADAR1/2 also display a negative correlation with miR-223, which is unaltered at the pri-miRNA level. In addition, we show that miR-223 is highly expressed in astrocytes, and is enriched in cortical glial and neuronal exosomes, and that antipsychotic treatment regulates cellular and exosomal miR-223 abundance in a cell-specific manner. Lastly, we demonstrate that addition of astrocytic exosomes containing miR-223 to cortical neuronal cultures results in increased neuronal miR-223 expression and reductions in neuronal *Grin2b*, which are corrected following inhibition of miR-223 in astrocytes. Taken together, our data suggest that a glia-enriched exosome-secreted miRNA regulated by antipsychotics is dysregulated in

the frontal cortex of subjects with psychosis and associated with alterations in glutamate receptor gene expression.

Previous work has shown that miR-223 specifically controls Grin2b and Gria2 protein levels in mouse hippocampal neurons by directly repressing their expression through binding to highly conserved complementary mRNA sites in their 3′UTRs in mouse, rat, and human (Harraz et al. 2012). The same study also found that overexpression of miR-223 resulted in reduced NMDA-mediated calcium influx and miniature excitatory postsynaptic currents in hippocampal neurons, and that hippocampal miR-223 was an important modulator of contextual memory (Harraz et al. 2012). An additional study from the same group also found that inhibition of miR-223 in human stem cell-derived neuronal cultures increased NMDA-induced calcium influx, suggesting a conserved action of miR-223 on NMDA-mediated synaptic function (Harraz et al. 2014). It is tempting to hypothesize that the observed upregulation of miR-223 could contribute to chronic NMDA receptor hypofunction and reduced synaptic activity, a proposed component of SCZ pathophysiology (Coyle 2006; Egan and Weinberger 1997). Furthermore, previous studies have suggested that miR-223 is an inflammation-induced miRNA that acts to limit inflammation by targeting numerous immune-related molecular nodules (Chen et al. 2012; Liu et al. 2011; Yang et al. 2015). Given the positive correlation between miR-223 and inflammation-associated astrocyte-enriched *SERPINA3*, which was also shown to be increased in both SCZ and BD patients with psychosis, it is possible that inflammation and glial activation could contribute to the expression of miR-223 in the OFC. Additional

work is needed to determine the effects of neuroinflammation on miR-223 alterations in psychiatric disorders.

Given the developmentally regulated miRNA expression in neurogenesis and brain development, it is essential to determine the temporal expression of both miR-223 and miR-132 to ascertain their developmental contributions. We decided to use the human induced pluripotent stem cells (iPCSs)-derived neuroprogenitor cells (NPCs) differentiated over a period. Our data indicate that miR-223 was barely expressed in the NPCs and the expression level was maintained over the six-week differentiation period. However, miR-132 was robustly expressed in the NPCs and increased over the six-week period in accordance with earlier studies associating miR-132 with neuronal fate (Reemst et al. 2016). The higher prenatal miR-223 expression may indicate a high permeability of the prenatal blood-brain barrier enabling peripheral leucocyte trafficking since mouse astrogenesis commences on prenatal day E18 (the day fetal brains were harvested). The robust expression of neuronal enriched miR-132, responsible for synaptic plasticity, in adult brain indicates the establishment of neuronal maturation and plasticity in the adult brain.

Maternal immune activation is implicated in the development of multiple brain disorders and warrants the investigation of associated miRNAs. Interestingly, miR-223 is elevated in the prenatal brain during neurogenesis and may contribute to the posttranscriptional mechanisms associated with the establishment of the reported schizophrenia-like features (Batinić et al. 2016; Mattei, Schweibold, and

Wolf 2015). Priming of microglia and altering of neuronal developmental paradigms may contribute to these deficits (Ślusarczyk et al. 2015; Vasistha et al. 2019).

For miR-223 to be able to influence both glial and neuronal gene expression, it is imperative that it is either abundantly expressed in all brain cell types or that it can be transferred from one cell type to the other. Our data suggest that miR-223 is enriched in astrocytes, but displays moderate expression in neurons. In accordance with numerous papers showing miR-223 to participate in cell-to-cell communication through its secretion via exosomes (Zhu et al. 2019; Chen et al. 2017; Yang et al. 2011), our data suggest that secretion of miR-223 from astrocytes allows it to regulate NMDA receptor gene expression in recipient neurons. Of note, a recent study that screened for miRNAs that are enriched in exosomes suggested that miR-223 was among the most enriched and efficiently packaged in exosome miRNAs, with very low abundance outside of exosome fractions in HEK229T cells (Shurtleff et al. 2016). On the other hand, having miR-223 secreted from peripheral monocytes and macrophages, might allow some peripherally generated mature miR-223 molecules to cross the blood–brain barrier (BBB) and influence brain gene expression, especially in cases where the BBB permeability is increased. Future studies are needed to determine the exact balance of peripheral and central miR-223 production in response to inflammation.

Although our study focused on miR-223, additional upregulation in SCZ and BD OFC miRNAs observed in our study could be of relevance to psychiatric disorders. For example, miR-193a-3p, a miRNA of the same family to miR-193b-3p, which is upregulated in both BD and SCZ in our study, was found to be a

reliable blood biomarker in a study with a large number of patients with SCZ (Wei et al. 2015). On a similar note, miR-330-3p, which is increased in the OFC of BD patients in our study, has also been found to be increased in the blood of subjects with BD and monopolar depression (Maffioletti et al. 2016). Moreover, miR-28a-3p, also increased in our study, is in the same miRNA family as miR-708, a miRNA shown to be linked to BD in GWAS analyses (Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011).

Limitations

One of the limitations of our study is that we did not observe miR-223 increases in our dorsolateral prefrontal cortex (DLPFC) cohort despite a previously reported miR-223 upregulation in the DLPFC of an earlier study (Beveridge and Cairns 2012) suggesting differential miRNA gene expression in diverse cohorts. This calls for larger multi-center studies to determine the consistency of miRNA dysregulations of various brain regions from different cohorts. However, we did see that only in the OFC where miR-223 was significantly elevated did upstream (ADAR2) and downstream (GLUR2) genes display altered expression.

Another limitation of our study is that the significant reported alterations in our NanoString miRNA profiling cannot survive correction for multiple comparisons and demographics. However, using mature miRNA-specific qRT-PCR, which is more accurate than any screening method, we have validated the changes shown in the screen following statistical correction for multiple postmortem demographics. Moreover, given the differences in structure, function, and expression of primary

neuronal and glial cultures in comparison with neurons and astrocytes in the brain, the observed differential effects on the expression and exosomal secretion of miR-223 in mouse neuronal and astrocytic cultures following short-term treatment with antipsychotics cannot be extrapolated to occur in the brain. Additional *in vivo* studies are needed to further explore the influence of antipsychotics on miR-223 neuronal and glial cellular and exosomal expression.

Furthermore, although miR-223 expression in human OFC was not significantly associated with overall duration of antipsychotic treatment in our cohort (shown as mg of fluphenazine equivalents), we cannot confidently assume that antipsychotic treatment has no effects on miR-223 expression. Indeed a previous study in mice has shown that although chronic treatment with haloperidol or clozapine does not affect the expression of miR-223 in the brain, olanzapine treatment can result in a significant reduction in brain miR-223 levels (Santarelli et al. 2013). It is, therefore, possible that the observed increase in miR-223 expression in the OFC of subjects with SCZ or BD with the presence of psychosis at the time of death could be ameliorated in a subset of patients that were treated with olanzapine.

Future Directions

Extensive research is required to elucidate the posttranscriptional impact of miR-223 and its associated genes utilizing postmortem brains, iPSC-derived neurons, model animals and cell culture systems, to further study miRNA-mediated impact on neuropsychiatric conditions expounded below. This will require analyzing miR-

223 levels and associated genes such as NFκB, IRAK, NLPR3, CD11b, TLR, NFAT5, IGF1R, ICAM1, SDF-1, IL1b, MEF2C, PAX6, GRIA2, and GRIN2B.

Information on the patients antipsychotics, may clarify the antipsychotic involvement with miR-223 associated gene alterations within the brain.

Given that miR-223 is enriched in peripheral leucocytes and first episode drug-naïve patients with schizophrenia have reportedly high miR-223 levels within their plasma, it will be interesting to analyze peripheral miR-223 effects on neuronal targets utilizing *in vivo* and *in vitro* systems.

Most of the miR-223 validated targets are expressed within microglia, hence characterizing the extent to which exosomal miR-223 originating from astrocytes and peripheral leucocytes might alter these inflammatory targets and the subsequent impact on brain conditions might illuminate posttranscriptional effect on diverse neuroinflammation conditions such as psychosis, Alzheimer's disease, stroke, multiple sclerosis, glioblastoma, and Parkinsonism among others.

The LPS psychosis-like induction model warrants further investigation of miR-223 and miR-132, and relevant gene levels in rodents at time points such as E18, P0, P14 (adolescence), P30 (early adulthood), P60, P180, P360, P720, to assess temporal miR-223 levels and behavior outcomes. Postnatal LPS administration at either P14 or P30 may enlighten the double hit SCZ hypothesis.

Determination of miR-223 levels within oligodendrocytes, ependymal cells, and Schwann cells may ascertain other endogenous nervous system sources. Analyzing miR-223 and miR-132 and associated genes levels during neurogenesis might further enlighten their developmental posttranscriptional modulation.

APPENDIX I: SUPPLEMENTARY MATERIAL

Supplementary Figure 1

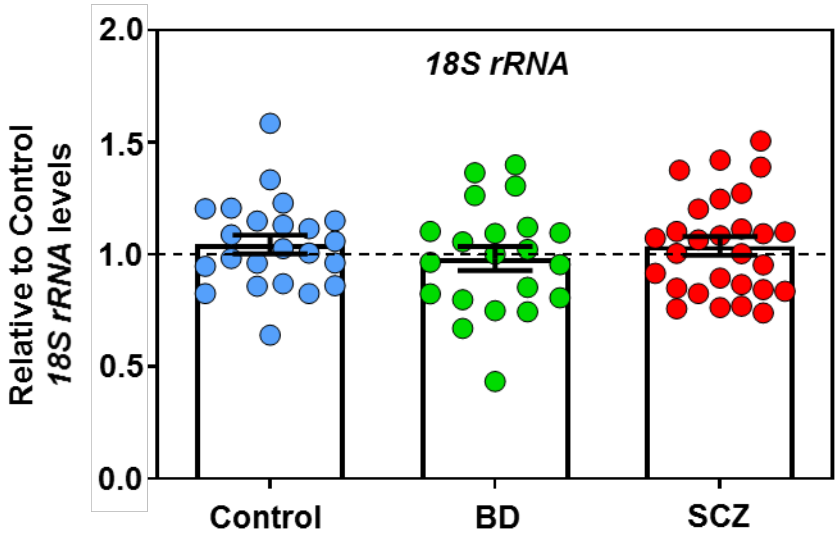

Fig. S1. Expression of *18S rRNA* in BD and SCZ OFC. Graph showing mean ± SEM relative to the mean of unaffected controls mRNA levels in SCZ, BD, and Control OFC for *18S rRNA* (Based on qRT-PCR in 20 fold diluted cDNA and without normalization). Data from each case are also depicted in the graph as blue circles (Control), green circles (BD), and red circles (SCZ).

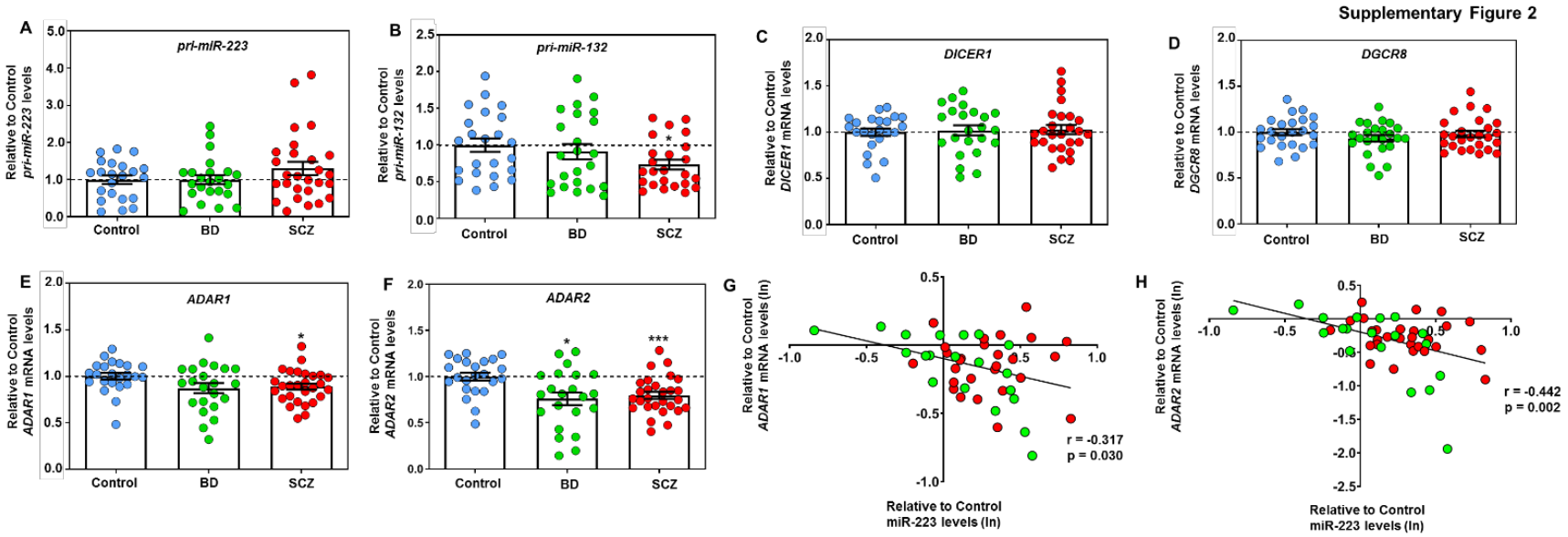

Fig. S2. Expression miRNA biogenesis-associated genes and pri-miR-RNAs in the OFC of SCZ and BD patients. a-f Graphs showing mean ± SEM relative to the mean of unaffected controls mRNA levels in SCZ, BD, and Control OFC for *pri-miR-223* (**a**) *pri-miR-132* **(b)**, *DICER1* **(c)**, *DGCR8* **(d)**, *ADAR1* **(e)**, and *ADAR2* **(f)** mRNA expression, based on qRT-PCR with the unaltered in SCZ and BD *18S rRNA* as a normalizer (see also methods and materials). *p < 0.05, ***p < 0.001, based on a univariate general linear model which corrects for RIN, Brain pH, PMI, and Refrigeration Interval (see also methods and materials). **g-h** Correlations between changes in miR-223 and *ADAR1* **(g)** and *ADAR2* **(h)** mRNA expression in the OFC of subjects with SCZ and BD. Spearman's correlation coefficients and two-tailed p-values are shown in the graph. Relative to Control individual data are also shown in the graphs: SCZ = red circles, BD = green circles.

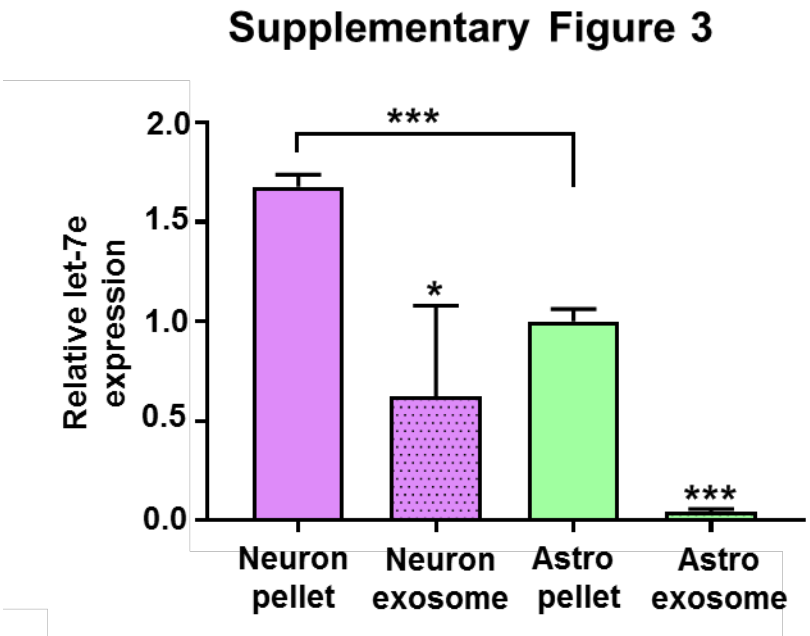

Fig. S3. Cell specificity of mouse let-7e expression. Mean ± SEM let-7e relative expression in mouse cortical neuronal (2 weeks of differentiation) and astrocytic pellets and exosomes (based on mature miRNA qRT-PCR without normalization and shown as ratios relative to the highest expression in mouse astrocytic pellets). *p < 0.05, ***p < 0.001, based on two-tailed one sample *t*-test compared to pellet expression of the same cell culture (stars above bars) or compared to pellet expression between different cell types (stars with connecting line).

Supplementary Figure 4

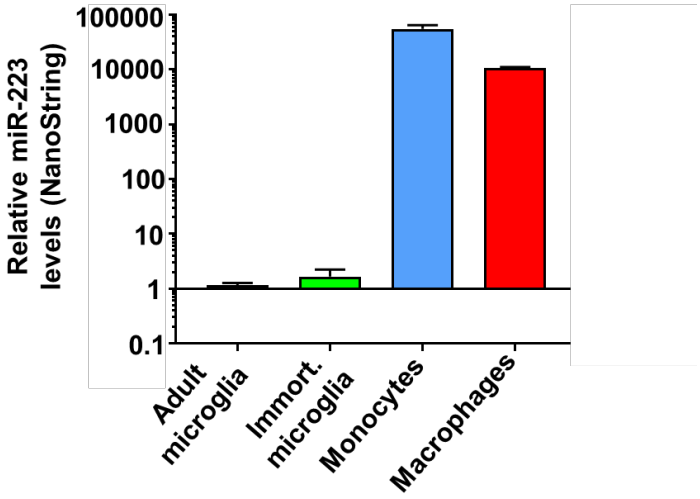

Fig. S4. Expression of miR-223-3p in human microglia and peripheral monocytes and macrophages. Mean ± SEM relative miR-223 expression in human adult (N=4) and immortalized (Immort., N=2) microglia, as well as peripheral monocytes (N=4), and macrophages (N=2), based on Nanostring miRNA profiling (see also methods and materials).

Supplementary Figure 5

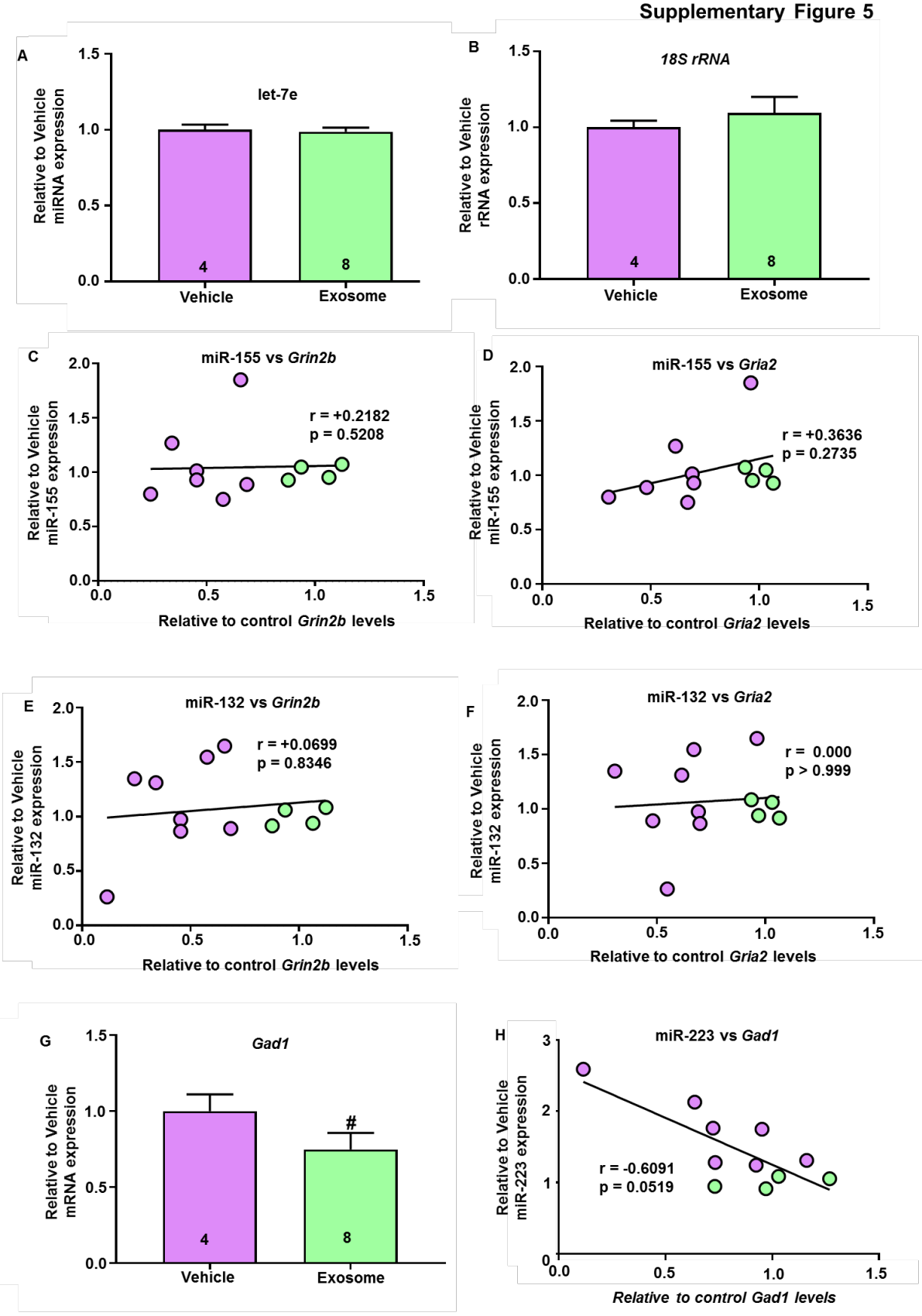

Fig. S5. Expression of let-7e, *18S rRNA*, and *Gad1* mRNA levels in exosome-treated rat cortical neuronal cultures and correlations between miR-132/miR-155 and *Grin2b/Gria2* mRNA expression. a-b Graph showing mean ± SEM mature let-7e **(a)** and *18S rRNA* **(b)** expression (based on qRT-PCR without normalization) in rat neurons treated with mouse astrocytic exosomes relative to vehicle-treated rat neurons. **c-d** Correlations between relative to Vehicle miR-155 and rat *Grin2b* **(e)** and *Gria2* **(f)** mRNA expression **e-f** Correlations between relative to Vehicle miR-132 and rat *Grin2b* **(e)** and *Gria2* **(f)** mRNA expression. **g** Graph showing mean ± SEM rat neuronal gene levels following mouse exosomal treatment for *Gad1* mRNA (based on qRT-PCR and normalized to *18S rRNA*). Data are shown as ratios relative to the mean of Vehicle. **h** Correlation between relative to Vehicle miR-223 and rat *Gad1* mRNA expression. For **(c,d,e,f,h)** Spearman's correlation coefficients and two-tailed p-values are shown in the graph. Vehicle = purple circles, Exosome treatment = green circles. For **(a,b,g)** $^{\#}0.05 < p < 0.10$, based on two-tailed one sample *t*-test compared to Vehicle. The number of biological replicates is shown in each graph.

APPENDIX II: SUPPLEMENTARY TABLES

Table S1. The demographic information of postmortem brain OFC samples of Control, BD, and SCZ cases. Summary of demographics for postmortem interval (PMI), RNA integrity number (RIN), brain pH, refrigeration interval (Refr. Int.), age, and sex. The results are presented as mean ± S.E.M. * $p < 0.05$ relative to unaffected controls based on two-tailed

Diagnosis (N)	Control (N=25)	Bipolar Disorder (N=26)	Schizophrenia (N=29)
PMI (Mean ± S.E.M)	31.00 ± 2.39	36.27 ± 3.34	30.00 ± 2.82
RIN (Mean ± S.E.M)	7.63 ± 0.11	7.63 ± 0.12	7.46 ± 0.09
Brain pH (Mean ± S.E.M)	6.64 ± 0.05	6.47 ± 0.05	6.53 ± 0.04
Refr. Int. (Mean ± S.E.M)	6.45 ± 0.79	9.19 ± 1.52*	6.45 ± 0.79
Age (Mean ± S.E.M)	45.08 ± 1.37	42.58 ± 1.99	42.28 ± 1.59
Sex	21 M / 4 F	12M / 14F*	20M / 9F

Table S2. Detailed demographic information of postmortem brain OFC samples of all Control, BD, and SCZ cases used in this study. DX = DSM IV diagnosis, RIN = RNA integrity number (RIN), Age = years at time of death, Sex: male (1) or female (2), Race: White (1), Hispanic (2), Native American (3), Suic. = Suicide status (1 = presence and 0 = absence), Cause of Death: cardiac (card), suicide (suic), overdose (OD), myocarditis (myoc), cirrhosis (cirrh), pneumonia (pneum), possible pulmonary thrombosis (pulm thr), RI = refrigeration interval (in hours), PMI = Postmortem interval (in hours), pH = brain pH, L/R = left (1) or right (2) hemisphere, BW = brain weight in gr, Dur. Of Illn. = duration of illness in years, TIH = time in hospital for psychiatric disease in years, LAU = lifetime of Alcohol use (0 = little or none, 1 = social, 2 = moderate in the past, 3 = moderate in the present, 4 = heavy in the past, 4 = heavy in the present, blank = insufficient info, Sm. At TOD = smoking at time of death (1 = presence and 0 = absence), Psych. Feat. = psychotic features at time of death (1 = presence and 0 = absence), Lifetime Antips. = lifetime Antipsychotic treatment as fluphenazine equivalents (mg).

Sam. #	DX	RIN	Age	Sex	Race	Suic.	Cause Of Death	RI	PMI	pH	L/R	BW	Age of Ons.	Dur. Of Illn.	TIH	LAU	LDU	Sm. At. TOD	Psy. Feat.	Lifetime Antips.
1	SCZ	7	52	1	1	0	PNEUM	2	16	6.52	2	1340	19	33	0.5	1	0	1	1	60000
2	SCZ	7.4	42	1	1	0	CARD	3	19	6.48	2	1310	18	24	0.8	4	4	1	1	18000
3	SCZ	7.6	41	1	1	0	CARD	5	54	6.18	1	1629	20	21	1.2	0	0	0	1	115000
4	SCZ	7.6	38	1	2	0	OD	8	35	6.68	1	1210	17	21	1	5	5	1	1	15000
5	SCZ	7	47	2	1	0	OD	3	30	6.47	2	1430	23	24	0.5	1	0	1	1	15000
6	SCZ	7.7	54	2	1	0	PNEUM	13	42	6.65	2	1170	17	37	4	0	0	1	1	400000
7	SCZ	6.6	54	1	1	0	CARD	13	38	6.17	2	1400	23	30	1	2		1	1	120000
8	SCZ	7.4	44	1	1	0	CARD	4	32	6.67	1	1560	9	35	0	5	2	1	1	20000
9	SCZ	7.3	35	1	1	0	CARD	6	47	6.4	2	1370	14	21	0.1	0	0	1	1	200000
10	SCZ	7.1	43	1	1	0	CIRRH	2	18	6.3	2	1520	18	25	0.2	5	5	1	1	90000
11	SCZ	7.5	33	1	1	0	CARD	5	29	6.5	1	1470	19	14	1.5	1	0	1	1	20000
12	SCZ	7.2	39	1	1	0	MVA	8	80	6.6	1	1355	17	22	0.2	1	1		1	120000
13	SCZ	8.5	53	2	1	0	CARD	3	13	6.49	1	1345	29	24	0.6	5	0	1	1	15000
14	SCZ	8.2	45	2	1	1	SUIC	12	52	6.51	2	1510	34	11	0.3	4	4		1	20000
15	SCZ	7.8	43	1	1	0	PNEUM	4	26	6.42	1	1620	21	22	0.1	0	0	0	1	180000
16	SCZ	7.2	59	2	1	0	CARD	10	38	6.93	2	1515	14	45	0.2	4	0	1	1	30000
17	SCZ	7.2	46	1	1	0	PNEUM	9	30	6.72	1	1630	22	24	1.5	2	3	1	1	200000
18	SCZ	7.4	47	2	1	0	CARD	10	35	6.5	1	1575	20	27	0.5	1		1	1	90000
19	SCZ	7.3	42	1	1	1	SUIC	2	26	6.19	2	1410	24	18	0.3	5	5		1	10000
20	SCZ	7.9	43	1	1	1	SUIC	19	65	6.67	2	1490	25	18	0.3	1	1		1	70000

21	SCZ	7.8	39	1	1	1	SUIC	6	26	6.8	2	1470	34	5	0.4	0	0	0	1	48000
22	SCZ	8.2	44	2	1	0	PULM THR	2	26	6.58	1	1490	16	28	2.5	0	0	1	1	50000
23	SCZ	7.6	36	2	1	1	SUIC	4	27	6.49	1	1480	33	3	0.1	0	2		1	600
24	SCZ	6.8	45	1	1	0	CARD	9	35	6.66	1	1390	15	30	0	5	2	1	1	50
25	SCZ	8.4	32	2	1	1	SUIC	5	36	6.8	1	1340	29	3	0.2	0	0		1	10000
26	SCZ	7	50	1	1	0	CARD	1	9	6.2	2	1400	31	19	0	0	0	1	1	34000
27	SCZ	7	24	1	1	1	SUIC	5	15	6.2	2	1505	20	4	0.3	5	5	1	1	12000
28	SCZ	7.1	37	1	1	0	CARD	3	30	6.8	2	1550	13	24	1.2	5	5		1	20000
29	SCZ	7.6	19	1	1	0	OD	11	28	6.73	1	1465	18	1	0	1	5	0	1	2500
30	C	7.5	48	1	1	0	CARD	6	24	6.91	2	1321			0	1	1		0	0
31	C	7.2	51	1	1	0	CARD	7	22	6.71	1	1900			0	1	0		0	0
32	C	7.7	32	1	1	0	CARD	6	13	6.57	2	1410			0	0	0		0	0
33	C	7.2	48	1	1	0	CARD	3	31	6.86	2	1580			0	0	0		0	0
34	C	7.1	49	2	1	0	CARD	3	45	6.72	1	1435			0	0	0	1	0	0
35	C	8.8	32	1	1	0	CARD	2	24	7.03	1	1415			0	2	0	0	0	0
36	C	7.7	49	1	1	0	CARD	4	23	6.93	1	1390			0	1	0	0	0	0
37	C	7.1	34	1	1	0	CARD	1	22	6.48	2	1480			0	0	0		0	0
38	C	7.2	35	1	1	0	MYOC	3	52	6.7	2	1700			0	0	0		0	0
39	C	7.4	38	2	1	0	CARD	3	33	6	2	1120			0	3	0		0	0
40	C	6.7	53	1	1	0	CARD	2	28	6	1	1340			0	0	0		0	0
41	C	8.1	37	1	1	0	CARD	2	13	6.5	1	1600			0	0	0	1	0	0
42	C	8	49	1	1	0	CARD	3	46	6.5	2	1605			0	0	0	0	0	0
43	C	8.1	44	2	1	0	CARD	3	28	6.59	2	1330			0	3	0		0	0
44	C	7.6	39	2	1	0	CARD	14	58	6.46	2	1260			0	4	0	1	0	0
45	C	8.7	40	1	1	0	CARD	9	38	6.67	1	1498			0	1	0	1	0	0
46	Ctrl.	8.5	46	1	1	0	CARD	4	31	6.67	1	1360			0	1	0		0	0
47	Ctrl.	8.5	47	1	1	0	CARD	3	11	6.6	1	1495			0	0	1	0	0	0
48	Ctrl.	7.9	50	1	1	0	CARD	6	49	6.75	2	1645			0	1	0	1	0	0
49	Ctrl.	7	55	1	1	0	CARD	4	31	6.7	1	1515			0	1	0	1	0	0
50	C	7.4	42	1	1	0	CARD	12	37	6.91	1	1340			0	4	3	1	0	0

51	C	7.5	45	1	1	0	CARD	4	29	6.94	2	1405			0	1	0	1	0	0
52	C	7.7	60	1	1	0	CARD	4	47	6.8	2	1460			0	0	0		0	0
53	C	6.6	51	1	1	0	CARD	2	31	6.7	2	1400			0	1	0	0	0	0
54	C	7.6	53	1	1	0	CARD	2	9	6.4	1	1500			0	1	0		0	0
55	BD	6.8	42	2	1	0	OD	15	49	6.65	1	1335	20	22	0.7	4	3	1	1	15000
56	BD	7.2	43	2	1	0	OD	15	57	5.92	1	1340	29	14	0.3	4	4	1	1	10000
57	BD	8.5	50	2	1	1	SUIC OD	14	62	6.51	1	1400	25	25	0.2	1	2	0	1	15000
58	BD	8	43	2	1	1	SUIC OD	24	39	6.74	1	1505	25	18	0.2	2	1	0	1	4500
59	BD	7.7	51	1	1	0	CARD	4	23	6.67	2	1590	23	28	0.5	3	0	1	1	1200
60	BD	6.9	35	2	1	1	SUIC OD	3	17	6.1	2	1250	21	14	0.1	1	0		1	3000
61	BD	8.2	54	1	1	1	SUIC OD	29	44	6.5	1	1510	45	9	0.1	2	2		0	0
62	BD	6.7	49	2	1	1	SUIC	10	19	5.87	2	1380	22	27	0.1	0	0	1	1	4000
63	BD	8.5	41	1	3	1	SUIC OD	4	70	6.71	1	1625	22	19	0.5	5	4	1	0	0
64	BD	8	19	1	1	0	OD	8	12	5.97	2	1484	17	2	0	2	5		0	2000
65	BD	7.8	48	1	1	1	SUIC	6	23	6.9	1	1466	31	17	0.3	5	2	1	0	0
66	BD	6.7	41	2	1	0	CARDI	14	28	6.44	1	1360	14	27	2	4	4	1	0	3000
67	BD	8.7	33	2	1	1	SUIC	4	24	6.51	1	1450	15	18	0.1	5	2		0	3000
68	BD	7.8	49	2	1	0	OD	2	38	6.39	2	1190	20	29		5	1	1	1	0
69	BD	7.6	35	1	1	0	DROWNING	4	22	6.58	2	1390	14	21	0.3	2	2	1	1	2000
70	BD	7.3	56	2	1	0	DROWNING	10	26	6.58	1	1170	14	42	0.5	5	4		0	25000
71	BD	7.9	58	2	1	1	SUIC	7	35	6.5	1	1440	27	31	0.4	1	1	0	1	12000
72	BD	7.6	59	2	1	1	SUIC	27	53	6.2	2	1410	48	11	0.1	1	0		0	0
73	BD	8	35	1	1	0	CARDIAC	6	35	6.3	1	1490	19	16	0.1	1	2	1	1	30000
74	BD	8.2	42	1	1	0	DROWNING	3	32	6.65	2	1470	18	24	0	5	5	1		0
75	BD	7.8	48	2	1	0	CARD	4	18	6.5	1	1205	33	15	0.1	1	3	1		0
76	BD	7.3	44	1	1	1	SUI	5	19	6.74	2	1660	33	11	0.1	2	1		0	0
77	BD	6.8	29	2	1	0	OD	5	62	6.74	1	1330	18	11	0.2	3	5	1	1	0
78	BD	7.6	45	1	1	0	CARD	3	28	6.35	2	1480	35	10	0.1		5		1	10000
79	BD	7.9	29	1	1	1	SUIC CO	10	60	6.7	1	1430	17	12	0.1	5	5		0	0

Table S3. Altered mature miRNA expression in the OFC of subjects with SCZ. Table showing fold changes (relative to the mean of Controls) and two-tailed Student's t-test p-values (un-corrected) based Nanostring miRNA profiling. miRNAs with $p < 0.05$ are highlighted with yellow.

Gene Name	Average expression	Fold change (SCZ vs C)	p-value
hsa-miR-132-3p	5589.05	-1.27	0.0003
hsa-miR-28-5p	259.45	1.13	0.0004
hsa-miR-223-3p	797.57	1.24	0.0014
hsa-miR-548ar-3p	3.20	-2.17	0.0022
hsa-miR-1268a	20.04	3.16	0.0023
hsa-miR-28-3p	101.22	1.20	0.0025
hsa-miR-874-5p	36.12	1.72	0.0032
hsa-miR-15b-5p	1414.50	1.13	0.0034
hsa-miR-193a-5p+hsa-miR-193b-5p	42.41	1.28	0.0037
hsa-miR-548b-3p	6.84	-2.09	0.0037
hsa-miR-326	4.42	-1.93	0.0039
hsa-miR-1291	2.27	2.04	0.0044
hsa-miR-374b-5p	1707.39	1.18	0.0051
hsa-miR-198	2.01	-1.78	0.0053
hsa-miR-493-3p	33.13	2.00	0.0068
hsa-miR-193b-3p	175.89	1.43	0.0071
hsa-miR-522-3p	22.56	1.31	0.0075
hsa-miR-374c-5p	6.04	2.50	0.0097
hsa-miR-361-5p	2045.92	1.07	0.0101
hsa-miR-454-3p	288.51	1.18	0.0108
hsa-miR-936	9.08	-1.90	0.0112
hsa-miR-152-3p	146.14	1.18	0.0113
hsa-miR-1908-5p	11.08	-1.87	0.0118
hsa-miR-365b-5p	1.84	-1.67	0.0119
hsa-miR-4755-5p	8.42	-1.76	0.0121
hsa-miR-155-5p	75.06	1.17	0.0122
hsa-miR-1245b-3p	2.96	1.70	0.0122
hsa-miR-924	1.19	1.25	0.0124
hsa-miR-3136-5p	11.39	1.93	0.0125
hsa-miR-23a-3p	4104.07	1.09	0.0129
hsa-miR-320a	39.97	1.23	0.0130
hsa-miR-1290	74.59	1.33	0.0135
hsa-miR-204-5p	1376.80	1.13	0.0141
hsa-miR-892a	2.12	-1.64	0.0161
hsa-miR-181b-2-3p	25.49	-1.26	0.0165
hsa-miR-4454+hsa-miR-7975	29117.16	2.14	0.0174
hsa-miR-1185-1-3p	3.05	-1.80	0.0178

hsa-let-7c-5p	18457.15	1.07	0.0201
hsa-miR-203a-3p	153.40	-1.16	0.0204
hsa-miR-3161	28.61	1.53	0.0209
hsa-let-7b-5p	18878.59	1.12	0.0215
hsa-miR-592	222.33	-1.16	0.0234
hsa-miR-411-5p	733.04	-1.10	0.0237
hsa-miR-630	62.58	1.72	0.0240
hsa-miR-211-5p	3.21	-1.76	0.0242
hsa-let-7d-5p	7865.31	1.06	0.0271
hsa-miR-154-5p	394.34	-1.07	0.0271
hsa-miR-1205	1.30	-1.24	0.0293
hsa-miR-378b	19.38	1.70	0.0295
hsa-miR-487a-3p	737.87	-1.15	0.0311
hsa-miR-580-3p	1.25	1.27	0.0321
hsa-miR-532-5p	78.17	1.15	0.0326
hsa-miR-3613-5p	4.89	-1.57	0.0334
hsa-miR-4461	2.58	-1.61	0.0336
hsa-miR-874-3p	161.00	1.29	0.0344
hsa-miR-3605-3p	5.99	-1.65	0.0345
hsa-miR-125a-5p	6260.63	-1.10	0.0349
hsa-miR-543	918.29	-1.09	0.0352
hsa-miR-4521	5.90	2.25	0.0352
hsa-miR-10a-5p	41.64	1.18	0.0366
hsa-miR-513c-5p	4.62	-1.71	0.0376
hsa-miR-143-3p	2577.23	1.25	0.0379
hsa-miR-624-3p	4.24	-1.69	0.0383
hsa-miR-498	3.22	1.86	0.0384
hsa-miR-199a-3p+hsa-miR-199b-3p	381.84	1.21	0.0385
hsa-miR-16-5p	7915.06	1.15	0.0393
hsa-miR-671-3p	3.31	1.85	0.0401
hsa-miR-361-3p	449.44	1.08	0.0426
hsa-miR-199a-5p	171.54	1.22	0.0443
hsa-miR-608	7.11	-1.59	0.0444
hsa-miR-4284	161.90	1.46	0.0465
hsa-miR-196a-5p	12.96	1.35	0.0466
hsa-miR-106a-5p+hsa-miR-17-5p	848.09	1.14	0.0472
hsa-miR-561-5p	2.04	1.59	0.0485
hsa-miR-483-5p	1.22	1.20	0.0496
hsa-miR-627-5p	1.28	1.52	0.0498
hsa-miR-200b-3p	31.69	1.35	0.0514
hsa-miR-574-3p	231.33	1.22	0.0518

hsa-miR-4741	3.30	-1.68	0.0550
hsa-miR-939-5p	15.67	-1.79	0.0575
hsa-miR-24-3p	957.04	1.10	0.0578
hsa-miR-25-3p	767.61	1.13	0.0583
hsa-miR-219a-1-3p	2.61	1.66	0.0593
hsa-miR-342-5p	14.45	1.38	0.0602
hsa-miR-409-5p	133.52	-1.12	0.0627
hsa-miR-378h	6.31	-1.56	0.0645
hsa-miR-548h-5p	12.41	-1.48	0.0656
hsa-miR-4458	1.23	1.22	0.0665
hsa-miR-1305	48.46	1.36	0.0677
hsa-miR-548ar-5p	1.19	1.33	0.0704
hsa-miR-638	1.17	1.16	0.0704
hsa-miR-4488	35.96	-1.89	0.0705
hsa-miR-1260a	290.48	1.44	0.0712
hsa-miR-374a-3p	1.70	-1.35	0.0712
hsa-miR-661	1.62	-1.40	0.0713
hsa-miR-7-5p	3039.31	-1.15	0.0717
hsa-miR-320b	2.20	1.52	0.0727
hsa-miR-345-3p	11.00	-1.36	0.0731
hsa-miR-145-5p	6039.74	1.22	0.0732
hsa-miR-142-5p	2.47	1.49	0.0735
hsa-miR-100-5p	3748.59	1.12	0.0740
hsa-miR-134-3p	4.97	-1.56	0.0759
hsa-miR-519b-5p+hsa-miR-519c-5p+hsa-miR-523-5p+hsa-miR-518e-5p+hsa-miR-522-5p+hsa-miR-519a-5p	2.56	1.59	0.0765
hsa-miR-30e-3p	273.02	1.05	0.0786
hsa-miR-181d-3p	1.98	-1.47	0.0806
hsa-miR-548n	10.27	1.67	0.0815
hsa-miR-1299	34.25	1.15	0.0824
hsa-miR-1233-3p	16.28	1.53	0.0851
hsa-miR-4532	4.80	-1.72	0.0852
hsa-miR-1268b	4.87	-1.57	0.0869
hsa-miR-758-3p+hsa-miR-411-3p	111.39	-1.08	0.0874
hsa-miR-4536-5p	18.45	1.29	0.0879
hsa-miR-10b-5p	31.16	1.19	0.0889
hsa-miR-379-5p	1225.30	-1.06	0.0891
hsa-miR-210-3p	49.28	1.15	0.0906
hsa-miR-4443	123.69	1.14	0.0917
hsa-miR-601	34.94	1.51	0.0928

hsa-miR-544a	10.63	-1.43	0.0959
hsa-miR-548j-3p	1.74	1.48	0.0967
hsa-miR-1298-5p	31.42	1.13	0.0973
hsa-miR-191-5p	3482.02	1.04	0.0989
hsa-miR-548aa+hsa-miR-548t-3p	1.66	1.66	0.1003
hsa-miR-495-5p	34.54	-1.12	0.1009
hsa-miR-365a-3p+hsa-miR-365b-3p	1878.64	1.13	0.1051
hsa-miR-642a-3p	7.57	1.54	0.1053
hsa-miR-193a-3p	20.68	1.28	0.1081
hsa-miR-561-3p	1.16	1.09	0.1093
hsa-miR-485-3p	835.36	-1.09	0.1100
hsa-miR-3690	17.98	1.37	0.1101
hsa-miR-20a-5p+hsa-miR-20b-5p	1245.97	1.11	0.1102
hsa-miR-33a-5p	55.81	-1.82	0.1112
hsa-miR-610	3.31	1.61	0.1117
hsa-miR-423-5p	634.49	1.10	0.1119
hsa-miR-604	1.39	1.28	0.1122
hsa-miR-1261	4.30	-1.48	0.1124
hsa-miR-202-3p	2.25	1.41	0.1128
hsa-miR-450b-3p	4.10	-1.40	0.1173
hsa-miR-200a-3p	34.75	1.22	0.1190
hsa-miR-539-5p	193.57	1.13	0.1198
hsa-miR-499a-3p	1.62	1.31	0.1198
hsa-miR-93-5p	1138.07	1.07	0.1226
hsa-miR-124-3p	10201.84	-1.14	0.1231
hsa-miR-129-5p	1204.79	-1.06	0.1233
hsa-miR-380-3p	4.01	-1.40	0.1257
hsa-miR-208b-5p	1.22	1.16	0.1260
hsa-miR-514a-3p	9.30	-1.31	0.1262
hsa-miR-196a-3p	2.72	-1.44	0.1266
hsa-miR-1286	9.86	-1.35	0.1268
hsa-let-7a-5p	80860.66	1.06	0.1321
hsa-miR-487b-5p	12.16	-1.32	0.1321
hsa-miR-1269b	1.10	1.07	0.1325
hsa-miR-5196-3p+hsa-miR-6732-3p	301.05	1.16	0.1352
hsa-miR-664a-3p	494.97	1.06	0.1354
hsa-miR-296-5p	110.38	1.10	0.1364
hsa-miR-9-5p	66346.11	-1.07	0.1373
hsa-miR-596	4.12	-1.54	0.1383
hsa-miR-1252-5p	1.17	1.18	0.1391
hsa-miR-148a-3p	567.34	1.15	0.1393

hsa-miR-331-5p	6.48	1.45	0.1397
hsa-miR-4787-5p	2.45	-1.39	0.1432
hsa-miR-451a	19643.84	1.19	0.1452
hsa-miR-1279	1.77	-1.29	0.1468
hsa-miR-450b-5p	3.13	-1.45	0.1491
hsa-miR-518e-3p	1.85	1.30	0.1507
hsa-miR-151b	9.67	-1.39	0.1518
hsa-miR-1827	5.90	-1.40	0.1524
hsa-miR-210-5p	6.71	-1.43	0.1532
hsa-miR-3150b-3p	1.20	1.15	0.1535
hsa-miR-582-3p	15.31	1.19	0.1537
hsa-miR-600	2.54	1.45	0.1555
hsa-miR-568	1.61	1.34	0.1579
hsa-miR-510-3p	1.74	-1.30	0.1595
hsa-miR-339-3p	4.73	-1.39	0.1597
hsa-miR-641	1.46	-1.26	0.1599
hsa-miR-628-3p	154.17	1.05	0.1617
hsa-miR-3202	1.15	1.16	0.1620
hsa-miR-509-5p	6.98	1.37	0.1642
hsa-miR-562	1.33	-1.17	0.1645
hsa-miR-127-5p	46.57	-1.15	0.1648
hsa-miR-4455	17.65	1.24	0.1654
hsa-miR-941	8.39	1.39	0.1668
hsa-miR-626	21.04	-1.21	0.1674
hsa-miR-1197	71.15	-1.09	0.1688
hsa-miR-186-5p	262.51	1.14	0.1703
hsa-miR-664b-3p	30.93	1.13	0.1709
hsa-miR-1260b	47.49	1.18	0.1716
hsa-miR-146a-5p	456.16	1.08	0.1724
hsa-miR-122-5p	49.53	-1.60	0.1726
hsa-miR-548q	8.31	1.40	0.1735
hsa-miR-337-5p	99.02	-1.12	0.1749
hsa-miR-944	13.76	1.37	0.1760
hsa-miR-199b-5p	54.34	1.11	0.1761
hsa-miR-2116-5p	25.37	1.28	0.1767
hsa-miR-376b-3p	22.30	-1.29	0.1785
hsa-miR-933	6.42	-1.41	0.1790
hsa-miR-370-5p	2.68	-1.34	0.1833
hsa-miR-551b-3p	209.26	-1.17	0.1837
hsa-miR-487b-3p	1514.06	-1.06	0.1843
hsa-miR-425-5p	335.46	1.04	0.1871

hsa-miR-1283	433.89	-1.49	0.1884
hsa-miR-29c-3p	8484.38	-1.10	0.1891
hsa-miR-513a-5p	1.72	-1.28	0.1907
hsa-miR-620	1.13	1.08	0.1908
hsa-miR-1910-3p	2.96	-1.33	0.1931
hsa-miR-324-5p	1043.53	-1.10	0.1933
hsa-miR-1976	2.73	1.34	0.1943
hsa-miR-1909-3p	1.24	1.17	0.1953
hsa-miR-1289	1.60	1.23	0.1974
hsa-miR-619-3p	1.79	1.32	0.1976
hsa-miR-377-3p	913.27	-1.09	0.2030
hsa-miR-208b-3p	13.28	-1.28	0.2032
hsa-miR-1288-3p	1.17	1.10	0.2056
hsa-miR-26a-5p	17936.89	1.14	0.2061
hsa-miR-1297	3.02	1.35	0.2073
hsa-miR-19b-3p	1488.77	1.11	0.2076
hsa-miR-519e-3p	2.06	1.27	0.2104
hsa-miR-3613-3p	6.83	-1.31	0.2134
hsa-miR-21-5p	2487.87	1.14	0.2138
hsa-miR-1277-3p	8.03	-1.36	0.2148
hsa-miR-615-3p	2.57	-1.34	0.2152
hsa-miR-767-5p	18.04	-1.23	0.2154
hsa-miR-376a-3p	2464.68	-1.08	0.2158
hsa-miR-940	16.77	-1.24	0.2171
hsa-miR-1193	5.37	-1.31	0.2173
hsa-miR-2110	10.63	-1.27	0.2194
hsa-miR-598-3p	1407.54	-1.05	0.2210
hsa-miR-483-3p	97.40	1.16	0.2224
hsa-miR-1469	2.06	-1.36	0.2234
hsa-miR-3605-5p	1.48	-1.19	0.2241
hsa-miR-129-2-3p	5606.03	-1.07	0.2247
hsa-miR-1264	7.00	1.29	0.2252
hsa-miR-381-3p	446.76	-1.06	0.2254
hsa-miR-135a-5p	2305.38	-1.09	0.2266
hsa-miR-323b-3p	13.51	1.18	0.2268
hsa-miR-548l	1.10	1.06	0.2269
hsa-miR-516a-5p	1.16	-1.13	0.2306
hsa-miR-194-5p	127.75	1.09	0.2309
hsa-miR-490-5p	10.14	1.35	0.2311
hsa-miR-136-5p	1748.84	-1.32	0.2332
hsa-miR-4435	2.22	1.27	0.2345

hsa-miR-195-5p	786.95	1.08	0.2349
hsa-miR-942-5p	2.60	-1.33	0.2352
hsa-miR-369-3p	48.31	-1.10	0.2354
hsa-miR-212-3p	9.65	-1.26	0.2361
hsa-miR-3140-5p	1.34	-1.16	0.2403
hsa-miR-889-3p	248.86	-1.06	0.2428
hsa-miR-523-3p	1.16	1.14	0.2429
hsa-miR-30c-5p	1818.36	1.08	0.2438
hsa-miR-146b-5p	208.86	-1.07	0.2444
hsa-miR-302d-3p	11.42	1.62	0.2446
hsa-miR-6511a-3p	3.56	-1.31	0.2458
hsa-miR-330-3p	189.44	1.12	0.2464
hsa-miR-409-3p	519.29	-1.06	0.2466
hsa-miR-299-5p	431.56	-1.05	0.2474
hsa-miR-515-5p	1.91	-1.27	0.2481
hsa-miR-25-5p	3.04	-1.32	0.2497
hsa-miR-1915-3p	30.61	-1.32	0.2498
hsa-miR-324-3p	52.09	1.13	0.2503
hsa-miR-218-5p	3517.85	-1.11	0.2516
hsa-miR-6720-3p	1.80	-1.26	0.2524
hsa-miR-455-5p	50.21	-1.09	0.2525
hsa-miR-215-5p	10.36	-1.18	0.2547
hsa-miR-362-3p	58.66	-1.11	0.2563
hsa-miR-1183	47.09	1.10	0.2569
hsa-miR-548i	11.59	1.22	0.2584
hsa-miR-675-5p	1.47	1.21	0.2603
hsa-miR-502-3p	2.11	1.28	0.2605
hsa-miR-708-5p	164.04	1.07	0.2609
hsa-miR-1275	2.92	-1.29	0.2634
hsa-miR-3168	8.46	-1.27	0.2638
hsa-miR-146b-3p	16.00	-1.28	0.2648
hsa-miR-526a+hsa-miR-518c-5p+hsa-miR-518d-5p	11.51	1.24	0.2677
hsa-miR-671-5p	1.48	1.18	0.2690
hsa-miR-548a-5p	10.19	-1.25	0.2692
hsa-miR-575	71.76	1.17	0.2697
hsa-miR-96-5p	9.01	1.26	0.2711
hsa-miR-539-3p	47.48	-1.21	0.2724
hsa-miR-488-3p	1115.41	-1.14	0.2741
hsa-miR-323a-3p	1614.87	-1.04	0.2742
hsa-miR-1301-3p	21.78	-1.12	0.2778
hsa-miR-1306-5p	89.56	-1.05	0.2790

hsa-miR-4787-3p	3.78	-1.40	0.2806
hsa-miR-4792	1.60	-1.23	0.2810
hsa-miR-495-3p	2874.14	-1.03	0.2826
hsa-miR-4707-5p	3.00	-1.29	0.2833
hsa-miR-520d-3p	1.72	-1.25	0.2854
hsa-miR-518b	262.48	-1.07	0.2875
hsa-miR-644a	9.50	1.32	0.2876
hsa-miR-26b-5p	2566.81	1.08	0.2889
hsa-miR-29b-3p	50637.47	-1.20	0.2890
hsa-miR-650	2.19	-1.25	0.2915
hsa-miR-514a-5p	2.27	1.27	0.2931
hsa-miR-135b-5p	120.09	-1.08	0.2932
hsa-miR-1303	1.31	-1.14	0.2936
hsa-miR-603	1.25	1.27	0.2949
hsa-miR-1206	4.30	1.33	0.2951
hsa-miR-637	1.16	1.09	0.2956
hsa-miR-150-5p	1253.13	1.05	0.2959
hsa-miR-188-3p	1.26	1.11	0.2960
hsa-miR-128-1-5p	7.03	1.33	0.3001
hsa-miR-3614-5p	6.40	-1.28	0.3008
hsa-miR-4451	2.14	1.25	0.3015
hsa-miR-516a-3p+hsa-miR-516b-3p	2.53	1.27	0.3038
hsa-miR-206	6.84	1.30	0.3063
hsa-miR-532-3p	16.14	1.17	0.3082
hsa-miR-449b-5p	4.09	1.29	0.3140
hsa-miR-3192-5p	1.62	-1.16	0.3164
hsa-miR-770-5p	52.87	1.08	0.3174
hsa-miR-520b	1.22	1.09	0.3184
hsa-miR-126-3p	15366.65	1.04	0.3185
hsa-miR-1972	17.49	-1.15	0.3188
hsa-miR-5001-3p	1.11	1.04	0.3191
hsa-miR-510-5p	1.23	1.09	0.3197
hsa-miR-665	3.69	1.25	0.3200
hsa-miR-4448	1.60	1.28	0.3201
hsa-miR-302c-3p	2.09	-1.19	0.3208
hsa-miR-3190-3p	3.31	-1.26	0.3222
hsa-miR-197-5p	38.01	1.12	0.3233
hsa-miR-23b-3p	6042.12	1.06	0.3234
hsa-miR-548ai+hsa-miR-570-5p	4.58	1.32	0.3241
hsa-miR-570-3p	1.60	1.28	0.3245
hsa-miR-548ad-3p	1.12	1.03	0.3249

hsa-miR-517b-3p	1.10	1.03	0.3249
hsa-miR-3140-3p	1.09	1.03	0.3249
hsa-miR-548c-5p+hsa-miR-548o-5p+hsa-miR-548am-5p	1.09	1.03	0.3249
hsa-miR-548e-3p	1.09	1.03	0.3249
hsa-miR-548o-3p+hsa-miR-548ah-3p+hsa-miR-548av-3p	1.09	1.03	0.3249
hsa-miR-550a-5p	1.09	1.03	0.3249
hsa-miR-615-5p	1.09	1.03	0.3249
hsa-miR-652-5p	1.09	1.03	0.3249
hsa-miR-767-3p	1.09	1.03	0.3249
hsa-miR-6511a-5p	1.09	1.03	0.3249
hsa-miR-551a	21.78	1.23	0.3250
hsa-miR-92a-3p	204.50	1.11	0.3258
hsa-miR-328-5p	8.07	-1.23	0.3290
hsa-miR-4421	2.92	-1.25	0.3311
hsa-miR-548y	6.61	-1.26	0.3326
hsa-miR-2117	16.69	1.23	0.3328
hsa-miR-542-3p	1.43	-1.22	0.3332
hsa-miR-1285-3p	6.51	1.23	0.3369
hsa-miR-887-5p	1.37	1.13	0.3375
hsa-miR-34a-5p	1221.04	-1.08	0.3382
hsa-miR-153-3p	151.69	-1.20	0.3383
hsa-miR-6503-5p	1.55	-1.17	0.3384
hsa-miR-3164	2.26	-1.24	0.3388
hsa-miR-190a-5p	261.52	-1.12	0.3407
hsa-miR-567	6.13	1.28	0.3417
hsa-miR-489-3p	22.91	-1.16	0.3426
hsa-miR-769-5p	1470.83	-1.03	0.3429
hsa-miR-758-5p	2.26	-1.25	0.3449
hsa-miR-141-3p	20.60	1.17	0.3466
hsa-miR-450a-5p	149.73	-1.07	0.3468
hsa-miR-4516	79.25	-1.19	0.3516
hsa-miR-423-3p	363.72	1.05	0.3529
hsa-miR-518d-3p	1.18	1.10	0.3534
hsa-miR-147b	5.22	1.26	0.3542
hsa-miR-302f	1.41	1.15	0.3547
hsa-miR-2053	1.81	-1.20	0.3555
hsa-miR-3180	6.60	-1.26	0.3573
hsa-miR-3180-5p	1.64	1.16	0.3579
hsa-miR-1254	1.25	-1.11	0.3585
hsa-miR-130a-3p	2867.39	1.03	0.3597

hsa-miR-942-3p	1.18	1.08	0.3613
hsa-miR-549a	17.03	1.24	0.3626
hsa-miR-378f	16.54	1.18	0.3634
hsa-miR-1249-5p	1.61	1.18	0.3641
hsa-let-7g-5p	17897.00	1.03	0.3642
hsa-miR-371b-5p	1.36	-1.15	0.3644
hsa-miR-3934-5p	10.06	-1.21	0.3646
hsa-miR-98-5p	3655.51	1.04	0.3650
hsa-miR-342-3p	6212.99	1.03	0.3653
hsa-miR-873-3p	99.26	1.07	0.3658
hsa-miR-376c-3p	2624.52	-1.09	0.3694
hsa-miR-3147	5.05	1.23	0.3720
hsa-miR-3179	1.55	1.16	0.3779
hsa-miR-217	3.69	-1.23	0.3786
hsa-miR-877-5p	21.58	-1.29	0.3793
hsa-miR-584-3p	4.59	1.25	0.3823
hsa-miR-133a-5p	7.92	-1.21	0.3861
hsa-miR-494-3p	753.51	-1.45	0.3894
hsa-miR-181a-2-3p	35.95	1.09	0.3894
hsa-miR-2113	1.36	1.11	0.3908
hsa-miR-187-3p	40.46	-1.06	0.3918
hsa-miR-378e	4.08	1.48	0.3938
hsa-miR-107	6251.59	1.05	0.3941
hsa-miR-1180-3p	954.01	-1.03	0.3953
hsa-miR-1262	7.02	-1.19	0.3953
hsa-miR-548g-3p	27.53	-1.11	0.3962
hsa-miR-576-5p	6.55	-1.21	0.3964
hsa-miR-99a-5p	6949.43	1.04	0.3973
hsa-miR-133b	1.38	-1.11	0.3997
hsa-miR-4425	1.41	1.13	0.3999
hsa-miR-1302	3.89	1.25	0.4010
hsa-miR-19a-3p	393.13	1.10	0.4011
hsa-miR-222-3p	956.63	-1.05	0.4025
hsa-miR-1249-3p	88.28	1.07	0.4034
hsa-miR-1296-5p	77.57	1.06	0.4034
hsa-miR-519c-3p	5.85	-1.21	0.4048
hsa-miR-221-5p	77.11	-1.04	0.4059
hsa-miR-378g	32.30	-1.09	0.4085
hsa-miR-3151-5p	360.40	-1.06	0.4095
hsa-miR-147a	2.31	-1.21	0.4114
hsa-miR-5001-5p	1.85	-1.17	0.4124

hsa-miR-296-3p	2.56	-1.22	0.4133
hsa-miR-582-5p	912.37	-1.03	0.4143
hsa-miR-542-5p	187.58	1.12	0.4145
hsa-miR-515-3p	1.75	-1.17	0.4195
hsa-miR-1287-3p	14.03	1.14	0.4205
hsa-miR-1278	2.30	-1.20	0.4205
hsa-miR-5010-3p	3.88	-1.22	0.4217
hsa-miR-506-5p	2.06	-1.18	0.4219
hsa-miR-412-3p	3.67	-1.23	0.4245
hsa-miR-652-3p	76.99	1.04	0.4253
hsa-miR-491-3p	44.39	-1.04	0.4260
hsa-miR-1203	3.71	-1.23	0.4265
hsa-miR-651-3p	1.90	-1.17	0.4281
hsa-miR-128-2-5p	3.87	-1.20	0.4326
hsa-miR-139-3p	366.91	1.03	0.4342
hsa-miR-499b-5p	1.84	1.16	0.4342
hsa-miR-504-5p	279.74	-1.05	0.4346
hsa-miR-1255b-5p	2.83	-1.20	0.4350
hsa-miR-548d-5p	37.81	-1.21	0.4369
hsa-miR-503-5p	25.94	1.07	0.4370
hsa-miR-766-5p	1.25	-1.09	0.4381
hsa-miR-548k	11.65	-1.16	0.4382
hsa-miR-184	11.23	1.24	0.4408
hsa-miR-140-3p	142.84	1.05	0.4423
hsa-miR-500a-5p+hsa-miR-501-5p	42.36	1.06	0.4452
hsa-miR-369-5p	1.62	-1.16	0.4473
hsa-miR-2278	1.28	-1.08	0.4482
hsa-miR-520d-5p+hsa-miR-527+hsa-miR-518a-5p	38.73	1.11	0.4491
hsa-miR-151a-3p	568.80	1.06	0.4500
hsa-miR-1185-5p	131.17	-1.04	0.4627
hsa-miR-383-5p	105.10	1.06	0.4642
hsa-miR-130b-3p	39.99	1.07	0.4663
hsa-miR-363-3p	382.41	-1.03	0.4685
hsa-miR-3127-5p	1.86	1.19	0.4689
hsa-miR-3144-5p	2.77	-1.17	0.4705
hsa-miR-182-3p	4.48	1.20	0.4740
hsa-miR-744-5p	53.09	1.06	0.4777
hsa-miR-23c	36.27	1.07	0.4810
hsa-miR-125b-5p	126265.00	1.03	0.4813
hsa-miR-1269a	1.68	-1.16	0.4823
hsa-miR-362-5p	37.07	1.06	0.4825

hsa-let-7f-5p	5199.72	1.08	0.4828
hsa-miR-301a-5p	10.25	-1.17	0.4839
hsa-miR-6503-3p	1.54	1.12	0.4848
hsa-miR-520h	25.15	-1.10	0.4879
hsa-miR-335-5p	781.53	1.06	0.4886
hsa-miR-1228-3p	3.68	-1.19	0.4899
hsa-miR-219a-2-3p	3743.02	1.12	0.4927
hsa-miR-512-3p	1.28	1.06	0.4928
hsa-miR-631	5.77	-1.17	0.4967
hsa-miR-648	1.14	-1.04	0.4971
hsa-miR-486-3p	2.54	1.17	0.5012
hsa-miR-125a-3p	17.66	1.07	0.5019
hsa-miR-885-5p	1904.56	-1.05	0.5028
hsa-miR-548al	28.05	-1.07	0.5031
hsa-miR-1200	3.22	-1.19	0.5040
hsa-miR-525-3p	4.87	1.27	0.5042
hsa-miR-3158-3p	29.95	1.06	0.5045
hsa-miR-520f-3p	42.18	1.07	0.5074
hsa-miR-606	1.47	-1.10	0.5084
hsa-miR-450a-1-3p	1.25	1.08	0.5096
hsa-miR-548a-3p	1.49	1.15	0.5121
hsa-miR-593-3p	70.54	1.06	0.5141
hsa-miR-1910-5p	10.40	-1.14	0.5168
hsa-miR-429	2.90	1.18	0.5174
hsa-miR-554	1.28	-1.10	0.5177
hsa-miR-3185	2.21	-1.15	0.5195
hsa-miR-629-5p	11.00	1.10	0.5199
hsa-miR-572	1.71	-1.14	0.5213
hsa-miR-196b-5p	1.55	-1.10	0.5218
hsa-miR-5196-5p	2.62	-1.16	0.5222
hsa-miR-192-5p	85.02	1.04	0.5232
hsa-miR-548ah-5p	38.35	1.05	0.5261
hsa-miR-1270	3.72	1.18	0.5272
hsa-miR-643	1.59	1.11	0.5279
hsa-miR-614	1.74	-1.14	0.5315
hsa-miR-499b-3p	1.20	-1.09	0.5319
hsa-miR-517c-3p+hsa-miR-519a-3p	40.29	-1.07	0.5327
hsa-miR-494-5p	1.72	1.13	0.5332
hsa-miR-548m	8.61	-1.18	0.5333
hsa-miR-6724-5p	4.04	1.16	0.5339
hsa-miR-149-5p	3140.58	-1.02	0.5384

hsa-miR-512-5p	3.92	1.18	0.5398
hsa-miR-627-3p	2.56	-1.15	0.5407
hsa-miR-30b-5p	2999.57	1.07	0.5409
hsa-miR-133a-3p	144.99	-1.04	0.5430
hsa-miR-455-3p	34.94	1.08	0.5431
hsa-miR-595	1.81	1.14	0.5447
hsa-miR-1285-5p	60.82	1.08	0.5466
hsa-miR-484	95.28	1.06	0.5480
hsa-miR-302a-3p	6.66	1.14	0.5488
hsa-miR-1258	24.60	1.06	0.5489
hsa-miR-1287-5p	22.01	1.10	0.5491
hsa-miR-1178-3p	1.26	1.07	0.5519
hsa-miR-219a-5p	7812.06	-1.20	0.5530
hsa-miR-508-3p	1.43	1.10	0.5538
hsa-miR-32-5p	489.41	-1.12	0.5540
hsa-miR-4536-3p	2.19	1.15	0.5540
hsa-miR-584-5p	15.08	-1.12	0.5560
hsa-miR-190b	4.08	-1.14	0.5564
hsa-miR-98-3p	1.47	1.08	0.5569
hsa-miR-329-3p	171.40	1.03	0.5594
hsa-miR-152-5p	1.24	-1.06	0.5611
hsa-miR-367-3p	2.12	-1.14	0.5637
hsa-miR-224-5p	1.86	-1.13	0.5645
hsa-miR-506-3p	9.39	1.13	0.5647
hsa-miR-4485-3p	6.15	1.14	0.5695
hsa-miR-579-3p	77.47	1.60	0.5702
hsa-miR-27a-3p	36.70	-1.05	0.5713
hsa-miR-3928-3p	6.66	-1.16	0.5727
hsa-miR-22-3p	3558.58	1.03	0.5755
hsa-miR-524-3p	2.10	-1.12	0.5777
hsa-miR-338-5p	4.58	-1.13	0.5784
hsa-miR-381-5p	45.69	-1.04	0.5795
hsa-miR-18a-5p	62.75	1.05	0.5819
hsa-miR-660-3p	3.99	1.15	0.5820
hsa-miR-363-5p	2.67	1.14	0.5830
hsa-miR-516b-5p	1.55	1.11	0.5841
hsa-miR-1250-5p	28.45	1.11	0.5852
hsa-miR-576-3p	1.66	1.09	0.5860
hsa-miR-517a-3p	2.96	-1.14	0.5908
hsa-miR-421	274.43	1.03	0.5926
hsa-miR-205-5p	1.46	-1.10	0.5941

hsa-miR-890	3.42	-1.14	0.5950
hsa-miR-1236-3p	14.43	-1.06	0.5952
hsa-miR-605-5p	1.88	-1.12	0.5959
hsa-miR-520e	1.25	1.06	0.5997
hsa-miR-891a-5p	13.38	-1.12	0.6013
hsa-miR-1-5p	1.30	-1.08	0.6018
hsa-miR-382-5p	1176.92	-1.01	0.6047
hsa-miR-876-3p	15.37	-1.10	0.6093
hsa-miR-376c-5p	7.04	-1.14	0.6094
hsa-miR-449c-5p	1.32	-1.06	0.6107
hsa-miR-433-3p	1283.19	-1.02	0.6132
hsa-miR-30e-5p	931.82	-1.06	0.6143
hsa-miR-181a-3p	363.67	1.03	0.6154
hsa-miR-520g-3p	28.37	1.05	0.6158
hsa-miR-346	81.66	-1.05	0.6175
hsa-miR-1248	2.07	1.10	0.6182
hsa-miR-892b	1.17	-1.03	0.6195
hsa-miR-3195	23.77	-1.17	0.6197
hsa-miR-99b-5p	2419.02	-1.03	0.6202
hsa-miR-331-3p	627.57	1.02	0.6240
hsa-miR-1293	1.46	-1.08	0.6245
hsa-miR-585-3p	13.51	-1.10	0.6256
hsa-miR-501-3p	8.25	1.12	0.6260
hsa-miR-1295a	8.10	-1.12	0.6270
hsa-miR-370-3p	237.54	-1.03	0.6277
hsa-miR-410-3p	368.94	-1.04	0.6291
hsa-miR-1304-5p	1.94	1.11	0.6291
hsa-miR-3918	1.16	1.05	0.6294
hsa-miR-548j-5p	2.35	-1.14	0.6308
hsa-miR-766-3p	48.89	-1.04	0.6318
hsa-miR-181a-5p	18242.31	1.04	0.6325
hsa-miR-181c-5p	695.58	-1.02	0.6328
hsa-miR-188-5p	8.39	-1.10	0.6336
hsa-miR-548v	21.85	-1.06	0.6377
hsa-miR-1271-3p	5.52	1.13	0.6416
hsa-miR-556-3p	1.13	1.03	0.6416
hsa-miR-300	4.08	1.13	0.6421
hsa-miR-431-5p	28.60	-1.05	0.6432
hsa-miR-134-5p+hsa-miR-6728-5p	1.45	-1.08	0.6473
hsa-miR-519d-3p	2.84	1.14	0.6484
hsa-miR-574-5p	49.72	-1.04	0.6510

hsa-miR-507	1.30	1.05	0.6511
hsa-miR-612	28.36	-1.05	0.6530
hsa-miR-607	5.68	-1.13	0.6560
hsa-miR-31-5p	35.92	-1.04	0.6563
hsa-miR-148b-3p	1645.31	1.02	0.6566
hsa-miR-448	12.48	-1.06	0.6566
hsa-miR-18b-5p	14.72	-1.06	0.6582
hsa-miR-328-3p	275.06	1.03	0.6595
hsa-miR-922	10.12	1.08	0.6601
hsa-miR-422a	33.26	-1.27	0.6606
hsa-miR-587	4.00	-1.12	0.6615
hsa-miR-521	27.35	1.04	0.6634
hsa-miR-1307-3p	41.89	-1.05	0.6670
hsa-miR-4707-3p	1.12	1.03	0.6671
hsa-miR-764	3.69	1.12	0.6695
hsa-miR-513a-3p	6.06	-1.11	0.6704
hsa-miR-875-3p	4.98	1.10	0.6706
hsa-miR-92b-3p	290.93	1.06	0.6716
hsa-miR-3130-3p	1.15	-1.02	0.6723
hsa-miR-301b-5p	1.59	1.09	0.6724
hsa-miR-490-3p	47.83	1.04	0.6725
hsa-miR-3615	1.61	-1.06	0.6741
hsa-miR-564	1.40	-1.07	0.6747
hsa-miR-1255a	11.46	1.08	0.6758
hsa-miR-345-5p	66.94	-1.05	0.6787
hsa-miR-660-5p	112.67	1.03	0.6793
hsa-miR-214-3p	6.62	1.13	0.6806
hsa-miR-323b-5p	1.10	1.02	0.6808
hsa-miR-1226-3p	4.98	-1.12	0.6823
hsa-miR-556-5p	33.40	-1.06	0.6856
hsa-miR-127-3p	1688.28	-1.01	0.6871
hsa-miR-491-5p	284.80	-1.02	0.6874
hsa-miR-3196	1.20	-1.04	0.6896
hsa-miR-525-5p	7.37	1.09	0.6953
hsa-miR-6721-5p	92.04	-1.03	0.6990
hsa-miR-1246	98.91	1.12	0.6998
hsa-miR-340-5p	3310.40	-1.04	0.6999
hsa-miR-375	2.79	1.13	0.7004
hsa-miR-3065-3p	6.88	-1.10	0.7056
hsa-miR-526b-5p	3.07	1.10	0.7065
hsa-miR-566	1.16	1.03	0.7101

hsa-miR-376a-2-5p	1.75	1.07	0.7137
hsa-miR-185-5p	609.15	1.02	0.7138
hsa-miR-1273c	1.48	1.06	0.7144
hsa-miR-548e-5p	5.06	-1.10	0.7154
hsa-miR-663a	22.10	-1.12	0.7173
hsa-miR-325	9.18	-1.07	0.7180
hsa-miR-216a-5p	4.95	1.09	0.7180
hsa-miR-514b-5p	23.64	-1.03	0.7199
hsa-miR-378d	9.72	1.06	0.7214
hsa-miR-301a-3p	568.47	-1.03	0.7230
hsa-miR-664b-5p	1.11	1.01	0.7256
hsa-miR-1245b-5p	2.01	1.08	0.7260
hsa-miR-579-5p	2.37	-1.08	0.7270
hsa-miR-372-3p	3.80	-1.09	0.7320
hsa-miR-519b-3p	1.64	1.07	0.7324
hsa-miR-5010-5p	1.68	1.06	0.7345
hsa-let-7e-5p	5695.25	1.01	0.7353
hsa-miR-520c-3p	3.04	-1.10	0.7358
hsa-miR-935	1.30	-1.04	0.7359
hsa-miR-628-5p	258.61	-1.02	0.7368
hsa-miR-887-3p	1.94	-1.06	0.7371
hsa-miR-373-3p	2.48	1.08	0.7375
hsa-miR-433-5p	13.92	-1.06	0.7379
hsa-miR-301b-3p	15.84	1.06	0.7385
hsa-miR-3614-3p	1.15	1.03	0.7402
hsa-miR-140-5p	1196.63	1.02	0.7415
hsa-miR-181b-5p+hsa-miR-181d-5p	1059.72	1.03	0.7425
hsa-miR-573	1.84	1.07	0.7444
hsa-miR-656-3p	743.53	-1.02	0.7463
hsa-miR-92a-1-5p	1.67	-1.06	0.7467
hsa-miR-520a-5p	3.34	-1.07	0.7470
hsa-miR-3916	1.33	-1.04	0.7478
hsa-miR-208a-3p	3.31	1.08	0.7485
hsa-miR-382-3p	1.57	1.05	0.7500
hsa-miR-329-5p	1.70	-1.06	0.7560
hsa-miR-337-3p	103.14	-1.01	0.7578
hsa-miR-424-5p	73.02	-1.04	0.7579
hsa-miR-106b-5p	634.76	1.03	0.7592
hsa-miR-548d-3p	5.49	-1.08	0.7607
hsa-miR-151a-5p	1097.68	1.03	0.7616
hsa-miR-589-5p	1.62	1.05	0.7621

hsa-miR-885-3p	1.98	-1.06	0.7625
hsa-miR-1296-3p	7.22	1.07	0.7631
hsa-miR-1253	15.82	1.16	0.7646
hsa-miR-1304-3p	1.63	1.05	0.7683
hsa-miR-200c-3p	19.37	-1.05	0.7694
hsa-miR-505-3p	57.48	1.02	0.7698
hsa-miR-4647	6.07	-1.08	0.7712
hsa-miR-553	1.27	-1.03	0.7715
hsa-miR-320d	2.95	-1.08	0.7719
hsa-miR-320c	6.40	-1.09	0.7728
hsa-miR-502-5p	5.89	1.14	0.7771
hsa-miR-1234-3p	30.83	1.05	0.7787
hsa-miR-221-3p	2710.45	1.02	0.7804
hsa-miR-33b-5p	8.05	1.07	0.7816
hsa-miR-577	202.33	1.05	0.7825
hsa-miR-1244	9.47	1.08	0.7826
hsa-miR-654-5p	20.84	-1.02	0.7846
hsa-miR-1272	4.40	1.07	0.7871
hsa-miR-432-5p	157.94	-1.01	0.7908
hsa-miR-548ak	3.82	1.07	0.7923
hsa-miR-30a-3p	159.71	-1.01	0.7929
hsa-miR-4286	16037.45	1.05	0.7966
hsa-miR-563	4.23	-1.07	0.7971
hsa-miR-34b-3p	5.14	1.07	0.7980
hsa-miR-3074-3p	1.42	1.03	0.8022
hsa-miR-1257	15.86	1.05	0.8024
hsa-miR-617	6.64	1.06	0.8025
hsa-miR-1245a	2.01	-1.06	0.8027
hsa-miR-3131	1.45	-1.04	0.8052
hsa-miR-651-5p	18.47	1.04	0.8059
hsa-miR-485-5p	11.65	1.05	0.8082
hsa-miR-541-3p	1.53	1.04	0.8083
hsa-miR-30d-5p	1896.40	1.01	0.8111
hsa-miR-1271-5p	13.05	-1.05	0.8127
hsa-miR-761	21.38	-1.03	0.8140
hsa-miR-642a-5p	38.02	1.06	0.8141
hsa-miR-139-5p	360.46	1.02	0.8163
hsa-miR-378c	1.66	-1.05	0.8165
hsa-miR-590-3p	1.19	1.02	0.8166
hsa-miR-27b-3p	5085.66	1.01	0.8183
hsa-miR-514b-3p	1.46	-1.03	0.8183

hsa-miR-105-5p	67.55	-1.03	0.8188
hsa-miR-3144-3p	1.44	1.04	0.8189
hsa-miR-760	1.11	-1.01	0.8189
hsa-let-7i-5p	4762.08	1.01	0.8197
hsa-miR-513c-3p	1.12	-1.01	0.8203
hsa-miR-765	1.91	1.05	0.8245
hsa-miR-597-5p	49.86	1.02	0.8248
hsa-miR-384	2.92	-1.06	0.8260
hsa-miR-639	4.40	-1.05	0.8302
hsa-miR-103a-3p	22.40	-1.03	0.8333
hsa-miR-937-3p	11.02	-1.04	0.8362
hsa-miR-3180-3p	1.80	-1.04	0.8370
hsa-miR-599	1.33	1.03	0.8376
hsa-miR-1185-2-3p	24.56	-1.02	0.8401
hsa-miR-513b-5p	8.02	-1.05	0.8419
hsa-miR-654-3p	6.53	1.04	0.8439
hsa-miR-655-3p	13.84	1.04	0.8495
hsa-miR-504-3p	1.47	-1.03	0.8521
hsa-miR-371a-5p	5.79	1.06	0.8543
hsa-miR-452-5p	1.51	-1.03	0.8545
hsa-miR-339-5p	3.49	1.05	0.8564
hsa-miR-492	1.47	1.04	0.8567
hsa-miR-330-5p	69.50	1.01	0.8594
hsa-miR-625-5p	84.84	1.02	0.8612
hsa-miR-15a-5p	2281.74	1.01	0.8621
hsa-miR-1202	1.82	1.03	0.8648
hsa-miR-509-3p	1.53	1.03	0.8674
hsa-miR-3065-5p	66.80	1.02	0.8681
hsa-miR-4531	22.37	-1.02	0.8696
hsa-miR-297	20.48	1.02	0.8725
hsa-miR-1537-3p	9.26	-1.04	0.8752
hsa-miR-545-3p	5.82	-1.05	0.8752
hsa-miR-591	2.00	1.03	0.8767
hsa-miR-1204	2.09	-1.03	0.8776
hsa-miR-182-5p	2.54	-1.04	0.8782
hsa-miR-374a-5p	3402.05	1.01	0.8868
hsa-miR-769-3p	142.18	1.01	0.8896
hsa-miR-552-3p	1.59	-1.03	0.8906
hsa-miR-1908-3p	1.98	-1.03	0.8913
hsa-miR-203a-5p	11.59	1.03	0.8915
hsa-miR-1266-5p	1.41	-1.02	0.8927

hsa-miR-320e	414.94	1.02	0.8959
hsa-miR-219b-3p	4.63	1.03	0.8965
hsa-miR-508-5p	2.35	-1.03	0.8977
hsa-miR-802	5.85	-1.04	0.8978
hsa-miR-1247-5p	3.44	-1.03	0.8994
hsa-miR-4431	1.45	1.02	0.8997
hsa-miR-518c-3p	4.52	-1.04	0.8999
hsa-miR-450a-2-3p	9.80	-1.02	0.9014
hsa-miR-29a-3p	12785.35	-1.01	0.9096
hsa-miR-578	8.07	-1.03	0.9111
hsa-miR-138-5p	164.62	1.01	0.9123
hsa-miR-1224-5p	1.77	1.02	0.9129
hsa-miR-876-5p	13.01	-1.03	0.9155
hsa-miR-197-3p	295.13	-1.02	0.9167
hsa-miR-1307-5p	16.65	1.02	0.9171
hsa-miR-95-3p	892.01	-1.00	0.9176
hsa-miR-4524a-5p	1.15	-1.01	0.9185
hsa-miR-299-3p	274.73	1.01	0.9188
hsa-miR-1322	23.81	1.01	0.9202
hsa-miR-1306-3p	3.08	1.02	0.9241
hsa-miR-302e	2.24	-1.02	0.9242
hsa-miR-1973	21.92	-1.02	0.9247
hsa-miR-101-3p	82.15	-1.01	0.9256
hsa-miR-190a-3p	20.58	1.02	0.9263
hsa-miR-497-5p	919.44	-1.01	0.9293
hsa-miR-503-3p	25.62	-1.01	0.9308
hsa-miR-496	29.61	1.01	0.9313
hsa-miR-144-3p	835.13	1.02	0.9314
hsa-miR-30a-5p	1485.79	1.01	0.9329
hsa-miR-518f-3p	29.68	1.01	0.9332
hsa-miR-449a	1.16	-1.01	0.9338
hsa-miR-616-3p	2.53	-1.02	0.9342
hsa-miR-499a-5p	17.13	-1.02	0.9351
hsa-miR-2682-5p	22.41	1.01	0.9369
hsa-miR-613	2.63	1.02	0.9376
hsa-miR-548z+hsa-miR-548h-3p	18.28	-1.01	0.9395
hsa-miR-640	2.42	1.02	0.9410
hsa-miR-137	3899.99	-1.01	0.9423
hsa-miR-1-3p	323.27	-1.01	0.9441
hsa-miR-934	2.29	-1.01	0.9477
hsa-miR-34c-5p	64.29	-1.01	0.9485

hsa-miR-211-3p	1.12	-1.00	0.9497
hsa-miR-1224-3p	2.56	1.02	0.9520
hsa-miR-302b-3p	15.70	1.01	0.9538
hsa-miR-216b-5p	87.65	-1.00	0.9552
hsa-miR-302a-5p	5.62	-1.02	0.9587
hsa-miR-649	1.50	1.01	0.9591
hsa-miR-298	1.14	1.00	0.9591
hsa-miR-509-3-5p	1.88	-1.01	0.9638
hsa-miR-323a-5p	1.47	1.01	0.9653
hsa-miR-520a-3p	1.21	1.00	0.9699
hsa-miR-378i	129.48	-1.00	0.9714
hsa-miR-590-5p	178.62	-1.00	0.9770
hsa-miR-1281	8.82	1.01	0.9800
hsa-miR-511-5p	3.54	-1.01	0.9807
hsa-miR-555	2.61	-1.01	0.9823
hsa-miR-891b	19.98	1.00	0.9829
hsa-miR-3182	1.78	1.00	0.9847
hsa-miR-183-5p	13.36	1.00	0.9883
hsa-miR-888-5p	21.50	1.00	0.9886
hsa-miR-873-5p	168.68	-1.00	0.9903
hsa-miR-1276	8.34	1.00	0.9912
hsa-miR-571	1.59	1.00	0.9923
hsa-miR-142-3p	1232.64	-1.00	0.9956
hsa-miR-128-3p	17984.93	1.00	0.9974
hsa-miR-34c-3p	9.96	-1.00	0.9975
hsa-miR-1323	11.60	1.00	0.9993

Table S4. Altered mature miRNA expression in the OFC of subjects with BD. Table showing fold changes (relative to the mean of Controls) and two-tailed Student's t-test p-values (un-corrected) based Nanostring miRNA profiling. miRNAs with $p < 0.05$ are highlighted with yellow.

Gene Name	Average expression	Fold change (BD/C)	p-value
hsa-miR-1268a	20.04	4.13	0.0002
hsa-let-7c-5p	18457.15	1.09	0.0004
hsa-miR-425-5p	335.46	1.12	0.0013
hsa-miR-28-3p	101.22	1.24	0.0016
hsa-miR-490-5p	10.14	1.85	0.0018
hsa-miR-16-5p	7915.06	1.30	0.0022
hsa-miR-1305	48.46	1.67	0.0023
hsa-miR-152-3p	146.14	1.24	0.0027
hsa-miR-193b-3p	175.89	1.54	0.0029
hsa-miR-330-3p	189.44	1.34	0.0034
hsa-miR-146a-5p	456.16	1.18	0.0037
hsa-miR-130b-3p	39.99	1.30	0.0039
hsa-miR-302d-3p	11.42	3.20	0.0041
hsa-miR-664b-3p	30.93	1.30	0.0046
hsa-miR-575	71.76	1.53	0.0059
hsa-miR-193a-5p+hsa-miR-193b-5p	42.41	1.25	0.0059
hsa-miR-543	918.29	-1.10	0.0062
hsa-miR-361-5p	2045.92	1.09	0.0070
hsa-miR-10a-5p	41.64	1.31	0.0071
hsa-miR-630	62.58	2.00	0.0078
hsa-miR-25-3p	767.61	1.25	0.0081
hsa-miR-423-5p	634.49	1.22	0.0084
hsa-miR-1287-5p	22.01	1.51	0.0093
hsa-miR-874-3p	161.00	1.35	0.0095
hsa-miR-601	34.94	1.87	0.0096
hsa-miR-451a	19643.84	1.38	0.0098
hsa-let-7d-5p	7865.31	1.08	0.0125
hsa-miR-1976	2.73	1.69	0.0131
hsa-miR-374b-5p	1707.39	1.22	0.0133
hsa-miR-532-5p	78.17	1.17	0.0135
hsa-miR-644a	9.50	1.80	0.0139
hsa-miR-2117	16.69	1.64	0.0142
hsa-miR-15b-5p	1414.50	1.17	0.0159
hsa-miR-132-3p	5589.05	-1.17	0.0162
hsa-miR-6724-5p	4.04	1.77	0.0163

hsa-miR-1290	74.59	1.35	0.0175
hsa-miR-7-5p	3039.31	-1.19	0.0182
hsa-miR-379-5p	1225.30	-1.10	0.0188
hsa-miR-299-5p	431.56	-1.13	0.0193
hsa-miR-378f	16.54	1.41	0.0194
hsa-miR-24-3p	957.04	1.16	0.0202
hsa-miR-423-3p	363.72	1.15	0.0202
hsa-miR-19b-3p	1488.77	1.26	0.0224
hsa-miR-20a-5p+hsa-miR-20b-5p	1245.97	1.22	0.0232
hsa-miR-378b	19.38	1.82	0.0238
hsa-miR-342-5p	14.45	1.41	0.0255
hsa-miR-1291	2.27	1.67	0.0255
hsa-miR-3161	28.61	1.41	0.0259
hsa-miR-19a-3p	393.13	1.35	0.0260
hsa-miR-642a-3p	7.57	1.93	0.0273
hsa-miR-200a-3p	34.75	1.22	0.0279
hsa-miR-18a-5p	62.75	1.26	0.0291
hsa-miR-323a-3p	1614.87	-1.08	0.0293
hsa-miR-1296-5p	77.57	1.17	0.0294
hsa-miR-106a-5p+hsa-miR-17-5p	848.09	1.21	0.0300
hsa-miR-331-5p	6.48	1.68	0.0311
hsa-miR-194-5p	127.75	1.16	0.0341
hsa-miR-1248	2.07	1.65	0.0349
hsa-miR-186-5p	262.51	1.27	0.0352
hsa-miR-1285-5p	60.82	1.31	0.0363
hsa-miR-3690	17.98	1.49	0.0370
hsa-miR-874-5p	36.12	1.42	0.0374
hsa-miR-185-5p	609.15	1.18	0.0381
hsa-miR-4755-5p	8.42	-1.41	0.0394
hsa-miR-22-3p	3558.58	1.15	0.0402
hsa-miR-1260a	290.48	1.48	0.0410
hsa-miR-497-5p	919.44	1.13	0.0427
hsa-miR-889-3p	248.86	-1.11	0.0427
hsa-miR-140-3p	142.84	1.18	0.0428
hsa-let-7b-5p	18878.59	1.14	0.0444
hsa-miR-206	6.84	1.72	0.0444
hsa-miR-141-3p	20.60	1.24	0.0472
hsa-miR-1285-3p	6.51	1.48	0.0473
hsa-miR-10b-5p	31.16	1.21	0.0486
hsa-miR-98-5p	3655.51	1.10	0.0488

hsa-miR-192-5p	85.02	1.13	0.0504
hsa-miR-125a-5p	6260.63	-1.10	0.0511
hsa-miR-885-3p	1.98	1.57	0.0511
hsa-miR-3180-5p	1.64	1.45	0.0512
hsa-miR-374c-5p	6.04	1.92	0.0517
hsa-miR-296-5p	110.38	1.16	0.0534
hsa-miR-96-5p	9.01	1.43	0.0547
hsa-miR-1268b	4.87	-1.63	0.0550
hsa-miR-100-5p	3748.59	1.17	0.0551
hsa-miR-208a-3p	3.31	1.57	0.0557
hsa-miR-652-3p	76.99	1.10	0.0561
hsa-miR-485-3p	835.36	-1.12	0.0564
hsa-miR-513a-5p	1.72	-1.42	0.0564
hsa-miR-574-3p	231.33	1.25	0.0566
hsa-miR-219b-3p	4.63	-1.59	0.0574
hsa-miR-664a-3p	494.97	1.08	0.0577
hsa-miR-28-5p	259.45	1.09	0.0587
hsa-miR-501-3p	8.25	1.54	0.0603
hsa-miR-504-5p	279.74	-1.15	0.0605
hsa-miR-433-3p	1283.19	-1.08	0.0608
hsa-miR-4286	16037.45	1.40	0.0611
hsa-miR-181a-2-3p	35.95	1.26	0.0645
hsa-miR-4787-3p	3.78	-1.87	0.0652
hsa-miR-592	222.33	-1.13	0.0656
hsa-miR-936	9.08	-1.58	0.0672
hsa-miR-361-3p	449.44	1.09	0.0676
hsa-miR-200b-3p	31.69	1.25	0.0685
hsa-miR-93-5p	1138.07	1.10	0.0704
hsa-miR-411-5p	733.04	-1.10	0.0704
hsa-miR-198	2.01	-1.51	0.0708
hsa-miR-375	2.79	-1.55	0.0712
hsa-miR-1271-3p	5.52	1.61	0.0725
hsa-miR-365a-3p+hsa-miR-365b-3p	1878.64	1.15	0.0728
hsa-miR-4454+hsa-miR-7975	29117.16	1.66	0.0775
hsa-miR-516a-5p	1.16	-1.18	0.0779
hsa-miR-503-3p	25.62	1.14	0.0793
hsa-let-7a-5p	80860.66	1.09	0.0798
hsa-miR-6511a-3p	3.56	-1.55	0.0804
hsa-miR-4521	5.90	1.84	0.0807
hsa-miR-1197	71.15	-1.13	0.0811

hsa-miR-578	8.07	1.46	0.0815
hsa-miR-378e	4.08	2.33	0.0851
hsa-miR-556-5p	33.40	1.27	0.0853
hsa-miR-25-5p	3.04	-1.53	0.0874
hsa-miR-526a+hsa-miR-518c-5p+hsa-miR-518d-5p	11.51	1.40	0.0882
hsa-miR-151b	9.67	1.43	0.0883
hsa-miR-516a-3p+hsa-miR-516b-3p	2.53	1.48	0.0890
hsa-miR-337-5p	99.02	-1.16	0.0903
hsa-miR-195-5p	786.95	1.11	0.0907
hsa-miR-338-5p	4.58	-1.50	0.0916
hsa-miR-941	8.39	1.52	0.0920
hsa-miR-561-3p	1.16	1.13	0.0929
hsa-miR-520d-5p+hsa-miR-527+hsa-miR-518a-5p	38.73	1.28	0.0933
hsa-miR-382-3p	1.57	1.37	0.0936
hsa-miR-154-5p	394.34	-1.10	0.0940
hsa-miR-454-3p	288.51	1.15	0.0943
hsa-miR-200c-3p	19.37	-1.22	0.0945
hsa-miR-944	13.76	1.42	0.0947
hsa-miR-596	4.12	-1.63	0.0953
hsa-miR-518e-3p	1.85	1.38	0.0964
hsa-miR-149-5p	3140.58	-1.07	0.0966
hsa-miR-544a	10.63	-1.46	0.0972
hsa-miR-30c-5p	1818.36	1.12	0.0975
hsa-miR-203a-3p	153.40	-1.12	0.0975
hsa-miR-1469	2.06	-1.50	0.0987
hsa-miR-891b	19.98	1.22	0.1001
hsa-miR-92a-3p	204.50	1.21	0.1041
hsa-miR-320e	414.94	1.40	0.1046
hsa-miR-1261	4.30	-1.49	0.1066
hsa-miR-1180-3p	954.01	-1.08	0.1070
hsa-miR-182-3p	4.48	1.49	0.1076
hsa-miR-3928-3p	6.66	1.44	0.1102
hsa-miR-151a-5p	1097.68	1.19	0.1116
hsa-miR-26b-5p	2566.81	1.18	0.1123
hsa-miR-320a	39.97	1.15	0.1140
hsa-miR-301b-5p	1.59	-1.29	0.1145
hsa-miR-625-5p	84.84	1.26	0.1157
hsa-miR-1249-3p	88.28	1.14	0.1160

hsa-miR-125b-5p	126265.00	1.06	0.1167
hsa-miR-500a-5p+hsa-miR-501-5p	42.36	1.15	0.1182
hsa-miR-450b-5p	3.13	-1.51	0.1197
hsa-miR-151a-3p	568.80	1.16	0.1206
hsa-miR-503-5p	25.94	-1.16	0.1235
hsa-miR-504-3p	1.47	-1.23	0.1241
hsa-miR-1185-5p	131.17	-1.11	0.1245
hsa-miR-1272	4.40	1.48	0.1252
hsa-miR-432-5p	157.94	-1.10	0.1260
hsa-miR-148b-3p	1645.31	1.08	0.1262
hsa-miR-135b-5p	120.09	-1.09	0.1282
hsa-miR-744-5p	53.09	1.14	0.1285
hsa-miR-302b-3p	15.70	1.28	0.1301
hsa-miR-499b-3p	1.20	-1.17	0.1308
hsa-miR-651-5p	18.47	1.23	0.1315
hsa-miR-587	4.00	1.48	0.1319
hsa-miR-128-2-5p	3.87	-1.43	0.1328
hsa-miR-1257	15.86	1.26	0.1329
hsa-miR-1193	5.37	-1.43	0.1362
hsa-miR-210-3p	49.28	1.15	0.1378
hsa-miR-2116-5p	25.37	1.35	0.1379
hsa-miR-181b-2-3p	25.49	1.13	0.1380
hsa-miR-940	16.77	-1.26	0.1415
hsa-miR-218-5p	3517.85	-1.14	0.1421
hsa-miR-219a-2-3p	3743.02	1.32	0.1451
hsa-miR-607	5.68	-1.47	0.1471
hsa-miR-422a	33.26	2.06	0.1514
hsa-miR-431-5p	28.60	-1.18	0.1517
hsa-miR-409-5p	133.52	-1.10	0.1563
hsa-let-7g-5p	17897.00	1.06	0.1577
hsa-miR-106b-5p	634.76	1.17	0.1585
hsa-miR-532-3p	16.14	1.25	0.1597
hsa-miR-1286	9.86	-1.32	0.1603
hsa-miR-21-5p	2487.87	1.20	0.1606
hsa-miR-29a-3p	12785.35	1.11	0.1624
hsa-miR-4435	2.22	1.36	0.1662
hsa-miR-324-3p	52.09	1.16	0.1672
hsa-miR-188-5p	8.39	-1.34	0.1685
hsa-miR-539-5p	193.57	1.09	0.1696
hsa-miR-604	1.39	1.18	0.1704
hsa-miR-493-3p	33.13	1.41	0.1730

hsa-miR-323a-5p	1.47	1.25	0.1749
hsa-miR-150-5p	1253.13	-1.08	0.1752
hsa-miR-184	11.23	1.40	0.1775
hsa-miR-519e-3p	2.06	1.32	0.1778
hsa-miR-449b-5p	4.09	1.41	0.1793
hsa-miR-924	1.19	1.10	0.1799
hsa-miR-3615	1.61	1.29	0.1803
hsa-miR-34c-3p	9.96	1.34	0.1823
hsa-miR-297	20.48	-1.27	0.1843
hsa-miR-549a	17.03	1.34	0.1849
hsa-miR-1185-1-3p	3.05	-1.42	0.1867
hsa-miR-624-3p	4.24	-1.42	0.1872
hsa-miR-487b-3p	1514.06	-1.07	0.1873
hsa-miR-363-5p	2.67	-1.34	0.1886
hsa-miR-514a-5p	2.27	1.42	0.1899
hsa-miR-512-3p	1.28	1.16	0.1903
hsa-miR-204-5p	1376.80	1.08	0.1977
hsa-miR-30e-3p	273.02	1.05	0.1979
hsa-miR-302c-3p	2.09	1.35	0.1991
hsa-miR-181a-5p	18242.31	1.15	0.2007
hsa-miR-758-3p+hsa-miR-411-3p	111.39	-1.07	0.2020
hsa-miR-1183	47.09	1.11	0.2023
hsa-miR-4284	161.90	1.25	0.2046
hsa-miR-571	1.59	1.24	0.2048
hsa-miR-202-3p	2.25	1.33	0.2051
hsa-miR-1289	1.60	1.27	0.2053
hsa-miR-495-3p	2874.14	-1.04	0.2068
hsa-miR-23c	36.27	1.12	0.2068
hsa-miR-2682-5p	22.41	1.11	0.2081
hsa-miR-3144-3p	1.44	1.26	0.2095
hsa-miR-628-3p	154.17	1.05	0.2104
hsa-miR-495-5p	34.54	-1.10	0.2111
hsa-miR-133a-5p	7.92	-1.31	0.2121
hsa-miR-128-1-5p	7.03	1.40	0.2148
hsa-miR-26a-5p	17936.89	1.13	0.2149
hsa-miR-708-5p	164.04	1.08	0.2176
hsa-miR-876-3p	15.37	1.18	0.2192
hsa-let-7i-5p	4762.08	1.06	0.2195
hsa-miR-498	3.22	1.41	0.2207
hsa-miR-1246	98.91	1.36	0.2221
hsa-miR-339-5p	3.49	1.40	0.2230

hsa-miR-615-3p	2.57	-1.31	0.2233
hsa-miR-502-5p	5.89	1.84	0.2239
hsa-miR-519d-3p	2.84	-1.40	0.2262
hsa-miR-330-5p	69.50	1.14	0.2275
hsa-miR-484	95.28	1.15	0.2296
hsa-miR-1299	34.25	1.12	0.2297
hsa-miR-365b-5p	1.84	-1.29	0.2298
hsa-miR-329-3p	171.40	1.09	0.2302
hsa-miR-488-3p	1115.41	-1.14	0.2305
hsa-miR-1258	24.60	1.12	0.2307
hsa-miR-548h-5p	12.41	-1.31	0.2312
hsa-miR-4421	2.92	-1.34	0.2318
hsa-miR-510-3p	1.74	-1.27	0.2320
hsa-miR-1276	8.34	1.35	0.2344
hsa-miR-31-5p	35.92	1.09	0.2354
hsa-miR-346	81.66	1.11	0.2400
hsa-miR-1273c	1.48	1.23	0.2408
hsa-miR-3605-3p	5.99	-1.31	0.2414
hsa-miR-614	1.74	-1.25	0.2416
hsa-miR-369-3p	48.31	-1.11	0.2422
hsa-miR-520b	1.22	1.17	0.2427
hsa-miR-597-5p	49.86	1.11	0.2428
hsa-miR-193a-3p	20.68	1.21	0.2434
hsa-miR-1-5p	1.30	-1.17	0.2451
hsa-miR-506-3p	9.39	1.24	0.2455
hsa-miR-627-5p	1.28	1.07	0.2471
hsa-miR-448	12.48	-1.20	0.2484
hsa-miR-671-5p	1.48	1.20	0.2511
hsa-miR-107	6251.59	1.08	0.2518
hsa-miR-1252-5p	1.17	1.06	0.2528
hsa-miR-320b	2.20	1.29	0.2530
hsa-miR-33b-5p	8.05	1.33	0.2544
hsa-miR-325	9.18	1.26	0.2554
hsa-miR-3136-5p	11.39	1.37	0.2576
hsa-miR-335-5p	781.53	1.10	0.2582
hsa-miR-142-5p	2.47	1.31	0.2582
hsa-miR-584-3p	4.59	1.32	0.2597
hsa-miR-181a-3p	363.67	1.12	0.2612
hsa-miR-542-3p	1.43	-1.27	0.2612
hsa-miR-3074-3p	1.42	1.19	0.2617
hsa-miR-326	4.42	-1.28	0.2640

hsa-miR-548y	6.61	-1.33	0.2648
hsa-miR-876-5p	13.01	-1.43	0.2659
hsa-miR-1297	3.02	1.27	0.2659
hsa-miR-567	6.13	1.32	0.2676
hsa-miR-548ad-3p	1.12	1.09	0.2684
hsa-miR-554	1.28	-1.15	0.2687
hsa-miR-509-3p	1.53	-1.18	0.2707
hsa-miR-376a-2-5p	1.75	1.25	0.2735
hsa-miR-136-5p	1748.84	-1.28	0.2754
hsa-miR-301b-3p	15.84	1.19	0.2774
hsa-miR-23b-3p	6042.12	1.10	0.2781
hsa-miR-452-5p	1.51	-1.19	0.2783
hsa-miR-942-3p	1.18	1.11	0.2802
hsa-miR-328-3p	275.06	1.07	0.2803
hsa-miR-620	1.13	1.08	0.2816
hsa-miR-660-5p	112.67	1.07	0.2824
hsa-miR-483-5p	1.22	1.08	0.2831
hsa-miR-890	3.42	-1.32	0.2848
hsa-miR-551b-3p	209.26	-1.13	0.2858
hsa-miR-577	202.33	1.22	0.2889
hsa-miR-505-3p	57.48	1.10	0.2896
hsa-miR-1301-3p	21.78	1.11	0.2914
hsa-miR-517a-3p	2.96	-1.31	0.2920
hsa-miR-27b-3p	5085.66	1.09	0.2926
hsa-miR-124-3p	10201.84	-1.09	0.2929
hsa-miR-1304-5p	1.94	-1.23	0.2930
hsa-miR-1307-3p	41.89	1.12	0.2931
hsa-miR-1234-3p	30.83	1.16	0.2937
hsa-miR-642a-5p	38.02	1.30	0.2939
hsa-miR-1264	7.00	-1.29	0.2940
hsa-miR-507	1.30	1.15	0.2960
hsa-miR-2110	10.63	-1.22	0.2983
hsa-miR-1226-3p	4.98	1.34	0.2987
hsa-miR-34c-5p	64.29	1.21	0.2996
hsa-miR-2113	1.36	1.17	0.3014
hsa-miR-1298-5p	31.42	1.09	0.3026
hsa-miR-628-5p	258.61	-1.07	0.3027
hsa-miR-654-5p	20.84	-1.10	0.3052
hsa-miR-1279	1.77	-1.21	0.3065
hsa-miR-205-5p	1.46	-1.20	0.3094
hsa-miR-548b-3p	6.84	-1.25	0.3101

hsa-miR-6720-3p	1.80	-1.23	0.3123
hsa-miR-320c	6.40	-1.39	0.3133
hsa-miR-208b-3p	13.28	-1.21	0.3137
hsa-miR-370-3p	237.54	-1.07	0.3153
hsa-miR-513b-5p	8.02	-1.24	0.3186
hsa-miR-331-3p	627.57	1.05	0.3189
hsa-miR-524-3p	2.10	1.26	0.3199
hsa-miR-377-3p	913.27	-1.06	0.3202
hsa-miR-942-5p	2.60	-1.28	0.3208
hsa-miR-371b-5p	1.36	-1.16	0.3210
hsa-miR-802	5.85	1.32	0.3212
hsa-miR-556-3p	1.13	-1.05	0.3214
hsa-miR-521	27.35	1.11	0.3235
hsa-miR-566	1.16	1.11	0.3242
hsa-miR-551a	21.78	1.21	0.3244
hsa-miR-1306-5p	89.56	1.05	0.3247
hsa-miR-641	1.46	-1.19	0.3260
hsa-miR-455-5p	50.21	-1.08	0.3279
hsa-miR-3195	23.77	1.34	0.3287
hsa-miR-219a-1-3p	2.61	1.25	0.3300
hsa-miR-4488	35.96	-1.43	0.3314
hsa-miR-1296-3p	7.22	1.23	0.3334
hsa-miR-875-3p	4.98	-1.26	0.3336
hsa-miR-663a	22.10	1.33	0.3354
hsa-miR-129-5p	1204.79	-1.05	0.3356
hsa-miR-148a-3p	567.34	1.08	0.3356
hsa-miR-302a-5p	5.62	1.30	0.3357
hsa-miR-3918	1.16	-1.07	0.3389
hsa-miR-1202	1.82	1.23	0.3399
hsa-miR-15a-5p	2281.74	1.08	0.3412
hsa-miR-4443	123.69	1.07	0.3418
hsa-miR-9-5p	66346.11	-1.05	0.3440
hsa-miR-296-3p	2.56	-1.25	0.3491
hsa-miR-30d-5p	1896.40	1.02	0.3511
hsa-miR-590-5p	178.62	1.13	0.3531
hsa-miR-98-3p	1.47	1.16	0.3533
hsa-miR-1322	23.81	-1.10	0.3535
hsa-miR-526b-5p	3.07	-1.29	0.3535
hsa-miR-1254	1.25	-1.12	0.3543
hsa-miR-517b-3p	1.10	1.04	0.3557
hsa-miR-1275	2.92	-1.25	0.3570

hsa-miR-638	1.17	1.08	0.3574
hsa-miR-140-5p	1196.63	1.06	0.3580
hsa-miR-5196-5p	2.62	-1.22	0.3587
hsa-miR-363-3p	382.41	1.03	0.3591
hsa-miR-483-3p	97.40	1.11	0.3591
hsa-miR-4532	4.80	-1.36	0.3602
hsa-miR-5010-5p	1.68	1.20	0.3605
hsa-miR-221-3p	2710.45	1.05	0.3619
hsa-miR-4531	22.37	1.12	0.3622
hsa-miR-509-3-5p	1.88	1.22	0.3624
hsa-miR-1293	1.46	-1.16	0.3630
hsa-miR-548k	11.65	-1.16	0.3643
hsa-miR-126-3p	15366.65	-1.03	0.3654
hsa-miR-887-5p	1.37	1.13	0.3659
hsa-miR-643	1.59	1.19	0.3668
hsa-miR-216a-5p	4.95	-1.25	0.3680
hsa-miR-599	1.33	1.16	0.3685
hsa-miR-1245b-3p	2.96	1.21	0.3700
hsa-miR-299-3p	274.73	1.09	0.3702
hsa-miR-552-3p	1.59	-1.17	0.3710
hsa-miR-449a	1.16	-1.09	0.3712
hsa-miR-1269a	1.68	-1.21	0.3718
hsa-miR-582-5p	912.37	-1.03	0.3728
hsa-miR-129-2-3p	5606.03	-1.06	0.3730
hsa-miR-3182	1.78	-1.20	0.3730
hsa-miR-548v	21.85	1.12	0.3762
hsa-miR-197-5p	38.01	1.11	0.3769
hsa-miR-1288-3p	1.17	1.05	0.3779
hsa-miR-5196-3p+hsa-miR-6732-3p	301.05	1.10	0.3781
hsa-miR-758-5p	2.26	-1.23	0.3810
hsa-miR-203a-5p	11.59	1.18	0.3823
hsa-miR-510-5p	1.23	1.09	0.3845
hsa-miR-433-5p	13.92	-1.17	0.3853
hsa-miR-1908-5p	11.08	1.19	0.3864
hsa-miR-548ah-5p	38.35	1.07	0.3874
hsa-miR-34b-3p	5.14	1.27	0.3874
hsa-miR-181c-5p	695.58	1.03	0.3880
hsa-miR-761	21.38	1.12	0.3895
hsa-miR-769-5p	1470.83	-1.03	0.3934
hsa-miR-933	6.42	-1.22	0.3935
hsa-miR-486-3p	2.54	1.21	0.3937

hsa-miR-342-3p	6212.99	1.02	0.3945
hsa-miR-5001-5p	1.85	1.19	0.3945
hsa-miR-639	4.40	1.22	0.3948
hsa-miR-1253	15.82	1.56	0.3953
hsa-miR-95-3p	892.01	-1.04	0.3954
hsa-miR-29b-3p	50637.47	-1.15	0.4003
hsa-miR-381-3p	446.76	-1.04	0.4007
hsa-miR-450a-5p	149.73	-1.07	0.4059
hsa-miR-378g	32.30	-1.10	0.4059
hsa-miR-221-5p	77.11	-1.05	0.4111
hsa-miR-211-5p	3.21	-1.24	0.4153
hsa-miR-99a-5p	6949.43	1.04	0.4179
hsa-miR-650	2.19	-1.20	0.4187
hsa-miR-4741	3.30	-1.25	0.4194
hsa-miR-215-5p	10.36	-1.16	0.4196
hsa-miR-376b-3p	22.30	-1.18	0.4205
hsa-miR-181b-5p+hsa-miR-181d-5p	1059.72	1.08	0.4225
hsa-miR-892b	1.17	1.08	0.4251
hsa-miR-562	1.33	-1.11	0.4264
hsa-miR-499a-3p	1.62	1.15	0.4271
hsa-miR-199b-5p	54.34	-1.07	0.4272
hsa-miR-1249-5p	1.61	1.15	0.4290
hsa-miR-568	1.61	-1.13	0.4298
hsa-let-7f-5p	5199.72	1.10	0.4309
hsa-miR-4431	1.45	-1.14	0.4324
hsa-miR-877-5p	21.58	1.20	0.4328
hsa-miR-548al	28.05	1.09	0.4329
hsa-miR-548ai+hsa-miR-570-5p	4.58	1.22	0.4363
hsa-miR-196b-5p	1.55	1.15	0.4369
hsa-miR-29c-3p	8484.38	-1.06	0.4370
hsa-miR-4516	79.25	1.17	0.4372
hsa-miR-4485-3p	6.15	1.22	0.4374
hsa-miR-153-3p	151.69	-1.14	0.4379
hsa-miR-891a-5p	13.38	1.13	0.4382
hsa-miR-631	5.77	1.20	0.4399
hsa-miR-606	1.47	1.15	0.4475
hsa-miR-1185-2-3p	24.56	-1.09	0.4477
hsa-miR-1236-3p	14.43	1.10	0.4501
hsa-miR-491-3p	44.39	-1.05	0.4507
hsa-miR-147a	2.31	-1.19	0.4515

hsa-miR-496	29.61	-1.06	0.4527
hsa-miR-525-5p	7.37	-1.21	0.4531
hsa-miR-1224-3p	2.56	-1.21	0.4531
hsa-miR-199a-3p+hsa-miR-199b-3p	381.84	-1.05	0.4532
hsa-miR-450b-3p	4.10	-1.19	0.4538
hsa-miR-1307-5p	16.65	1.11	0.4559
hsa-miR-520a-5p	3.34	1.19	0.4565
hsa-miR-1827	5.90	-1.21	0.4592
hsa-miR-421	274.43	1.06	0.4609
hsa-miR-376a-3p	2464.68	-1.04	0.4611
hsa-miR-590-3p	1.19	-1.06	0.4677
hsa-miR-605-5p	1.88	-1.17	0.4685
hsa-miR-548a-3p	1.49	-1.13	0.4711
hsa-miR-603	1.25	-1.07	0.4723
hsa-miR-1909-3p	1.24	-1.05	0.4725
hsa-miR-617	6.64	-1.19	0.4727
hsa-miR-654-3p	6.53	1.18	0.4772
hsa-miR-450a-2-3p	9.80	-1.17	0.4778
hsa-miR-1245b-5p	2.01	-1.16	0.4779
hsa-miR-217	3.69	1.17	0.4795
hsa-miR-143-3p	2577.23	-1.06	0.4796
hsa-miR-492	1.47	-1.15	0.4804
hsa-miR-371a-5p	5.79	-1.28	0.4856
hsa-miR-610	3.31	1.23	0.4889
hsa-miR-489-3p	22.91	-1.12	0.4893
hsa-miR-499a-5p	17.13	1.17	0.4900
hsa-miR-541-3p	1.53	1.14	0.4937
hsa-miR-600	2.54	1.19	0.4948
hsa-miR-378h	6.31	-1.18	0.4953
hsa-miR-664b-5p	1.11	1.04	0.4958
hsa-miR-539-3p	47.48	-1.11	0.4962
hsa-miR-518d-3p	1.18	-1.04	0.4971
hsa-miR-671-3p	3.31	1.21	0.4972
hsa-miR-576-3p	1.66	1.14	0.4989
hsa-miR-199a-5p	171.54	1.05	0.4992
hsa-miR-3614-5p	6.40	-1.19	0.4999
hsa-miR-548m	8.61	1.16	0.5002
hsa-miR-3934-5p	10.06	1.15	0.5009
hsa-miR-3140-5p	1.34	-1.10	0.5017
hsa-miR-626	21.04	-1.12	0.5034
hsa-miR-3144-5p	2.77	1.17	0.5046

hsa-miR-424-5p	73.02	1.09	0.5070
hsa-miR-134-5p+hsa-miR-6728-5p	1.45	-1.12	0.5078
hsa-miR-196a-3p	2.72	-1.18	0.5081
hsa-miR-582-3p	15.31	1.10	0.5129
hsa-miR-211-3p	1.12	-1.03	0.5144
hsa-miR-409-3p	519.29	-1.04	0.5148
hsa-miR-382-5p	1176.92	-1.02	0.5164
hsa-miR-373-3p	2.48	1.15	0.5193
hsa-miR-518b	262.48	-1.05	0.5196
hsa-miR-223-3p	797.57	1.05	0.5210
hsa-miR-378d	9.72	-1.14	0.5210
hsa-miR-629-5p	11.00	-1.12	0.5211
hsa-miR-520g-3p	28.37	-1.08	0.5231
hsa-miR-661	1.62	-1.14	0.5240
hsa-miR-1281	8.82	1.16	0.5249
hsa-miR-887-3p	1.94	1.16	0.5269
hsa-miR-675-5p	1.47	-1.10	0.5352
hsa-miR-487a-3p	737.87	-1.04	0.5388
hsa-miR-345-3p	11.00	-1.12	0.5410
hsa-miR-651-3p	1.90	-1.13	0.5420
hsa-miR-155-5p	75.06	1.04	0.5422
hsa-miR-548z+hsa-miR-548h-3p	18.28	1.10	0.5453
hsa-miR-499b-5p	1.84	1.12	0.5479
hsa-miR-637	1.16	-1.03	0.5502
hsa-miR-374a-5p	3402.05	1.05	0.5512
hsa-miR-340-5p	3310.40	1.08	0.5512
hsa-miR-655-3p	13.84	1.13	0.5529
hsa-miR-3131	1.45	-1.11	0.5547
hsa-miR-1269b	1.10	1.02	0.5555
hsa-miR-1200	3.22	-1.18	0.5569
hsa-miR-580-3p	1.25	1.04	0.5569
hsa-miR-144-3p	835.13	1.15	0.5596
hsa-miR-3150b-3p	1.20	1.05	0.5602
hsa-miR-196a-5p	12.96	1.12	0.5603
hsa-miR-608	7.11	1.13	0.5663
hsa-miR-1204	2.09	1.13	0.5673
hsa-miR-4707-5p	3.00	1.15	0.5692
hsa-miR-1250-5p	28.45	1.11	0.5719
hsa-miR-210-5p	6.71	-1.15	0.5732
hsa-miR-4425	1.41	-1.08	0.5757

hsa-miR-147b	5.22	1.16	0.5774
hsa-miR-1910-5p	10.40	-1.16	0.5795
hsa-miR-99b-5p	2419.02	-1.05	0.5799
hsa-miR-212-3p	9.65	-1.11	0.5816
hsa-miR-146b-5p	208.86	-1.03	0.5831
hsa-miR-412-3p	3.67	-1.14	0.5840
hsa-miR-494-3p	753.51	1.21	0.5866
hsa-miR-1255b-5p	2.83	1.14	0.5878
hsa-miR-1245a	2.01	-1.13	0.5902
hsa-miR-1203	3.71	-1.15	0.5910
hsa-miR-548ar-5p	1.19	1.02	0.5975
hsa-miR-3140-3p	1.09	1.02	0.5975
hsa-miR-548c-5p+hsa-miR-548o-5p+hsa-miR-548am-5p	1.09	1.02	0.5975
hsa-miR-548e-3p	1.09	1.02	0.5975
hsa-miR-548o-3p+hsa-miR-548ah-3p+hsa-miR-548av-3p	1.09	1.02	0.5975
hsa-miR-550a-5p	1.09	1.02	0.5975
hsa-miR-615-5p	1.09	1.02	0.5975
hsa-miR-652-5p	1.09	1.02	0.5975
hsa-miR-767-3p	1.09	1.02	0.5975
hsa-miR-515-3p	1.75	-1.11	0.5993
hsa-miR-1283	433.89	1.08	0.6035
hsa-miR-561-5p	2.04	1.12	0.6049
hsa-miR-301a-3p	568.47	1.04	0.6063
hsa-miR-490-3p	47.83	1.05	0.6063
hsa-miR-4448	1.60	1.13	0.6081
hsa-miR-3916	1.33	1.07	0.6096
hsa-miR-767-5p	18.04	-1.09	0.6126
hsa-miR-512-5p	3.92	1.14	0.6136
hsa-miR-3065-3p	6.88	-1.13	0.6147
hsa-miR-616-3p	2.53	-1.14	0.6174
hsa-miR-769-3p	142.18	1.03	0.6181
hsa-miR-101-3p	82.15	1.06	0.6194
hsa-miR-216b-5p	87.65	1.02	0.6211
hsa-miR-378c	1.66	-1.10	0.6217
hsa-miR-593-3p	70.54	1.04	0.6228
hsa-miR-30b-5p	2999.57	1.05	0.6303
hsa-miR-370-5p	2.68	1.12	0.6307
hsa-miR-548ar-3p	3.20	-1.14	0.6312
hsa-miR-122-5p	49.53	-1.14	0.6346

hsa-miR-1228-3p	3.68	-1.13	0.6356
hsa-miR-1260b	47.49	1.07	0.6378
hsa-miR-1908-3p	1.98	1.11	0.6412
hsa-miR-3613-5p	4.89	1.11	0.6413
hsa-miR-4647	6.07	1.12	0.6445
hsa-miR-33a-5p	55.81	-1.14	0.6453
hsa-miR-873-5p	168.68	-1.04	0.6456
hsa-miR-130a-3p	2867.39	-1.01	0.6460
hsa-miR-376c-5p	7.04	-1.12	0.6461
hsa-miR-1-3p	323.27	-1.04	0.6462
hsa-miR-3158-3p	29.95	1.05	0.6482
hsa-miR-222-3p	956.63	-1.03	0.6514
hsa-miR-579-3p	77.47	1.49	0.6536
hsa-miR-323b-5p	1.10	1.02	0.6550
hsa-miR-509-5p	6.98	1.11	0.6566
hsa-miR-885-5p	1904.56	-1.03	0.6583
hsa-miR-873-3p	99.26	1.03	0.6593
hsa-miR-3613-3p	6.83	-1.10	0.6600
hsa-miR-4792	1.60	1.10	0.6603
hsa-miR-30a-3p	159.71	-1.02	0.6610
hsa-miR-598-3p	1407.54	-1.02	0.6627
hsa-miR-380-3p	4.01	1.11	0.6627
hsa-miR-362-3p	58.66	-1.04	0.6633
hsa-miR-6503-3p	1.54	1.09	0.6663
hsa-miR-1206	4.30	1.12	0.6666
hsa-miR-145-5p	6039.74	-1.04	0.6682
hsa-miR-1244	9.47	1.13	0.6706
hsa-miR-548l	1.10	1.01	0.6711
hsa-miR-2053	1.81	-1.09	0.6722
hsa-miR-27a-3p	36.70	-1.04	0.6749
hsa-miR-190a-3p	20.58	1.08	0.6773
hsa-miR-515-5p	1.91	-1.09	0.6792
hsa-miR-935	1.30	1.06	0.6809
hsa-miR-1247-5p	3.44	-1.12	0.6816
hsa-miR-937-3p	11.02	-1.07	0.6821
hsa-miR-152-5p	1.24	-1.04	0.6850
hsa-miR-298	1.14	1.03	0.6869
hsa-miR-4455	17.65	1.06	0.6881
hsa-miR-302e	2.24	-1.09	0.6917
hsa-miR-92a-1-5p	1.67	-1.08	0.6948
hsa-miR-3130-3p	1.15	1.04	0.6951

hsa-miR-146b-3p	16.00	-1.07	0.6953
hsa-miR-369-5p	1.62	-1.08	0.6991
hsa-miR-3192-5p	1.62	1.08	0.6993
hsa-miR-372-3p	3.80	-1.10	0.7005
hsa-miR-5001-3p	1.11	1.01	0.7005
hsa-miR-545-3p	5.82	-1.14	0.7026
hsa-miR-1270	3.72	1.10	0.7036
hsa-miR-329-5p	1.70	1.08	0.7043
hsa-miR-328-5p	8.07	-1.08	0.7065
hsa-miR-324-5p	1043.53	-1.02	0.7077
hsa-miR-770-5p	52.87	-1.03	0.7092
hsa-miR-1266-5p	1.41	-1.06	0.7099
hsa-miR-564	1.40	-1.06	0.7115
hsa-miR-766-5p	1.25	-1.04	0.7141
hsa-miR-888-5p	21.50	1.04	0.7148
hsa-miR-1302	3.89	-1.11	0.7191
hsa-miR-137	3899.99	-1.03	0.7202
hsa-miR-519b-3p	1.64	1.06	0.7237
hsa-miR-23a-3p	4104.07	1.01	0.7284
hsa-miR-548i	11.59	1.07	0.7295
hsa-miR-6503-5p	1.55	-1.06	0.7316
hsa-miR-548j-3p	1.74	1.07	0.7327
hsa-miR-517c-3p+hsa-miR-519a-3p	40.29	-1.04	0.7334
hsa-miR-3202	1.15	-1.02	0.7334
hsa-miR-494-5p	1.72	1.07	0.7351
hsa-miR-1271-5p	13.05	1.08	0.7355
hsa-miR-513a-3p	6.06	-1.09	0.7377
hsa-miR-491-5p	284.80	1.02	0.7387
hsa-miR-1972	17.49	-1.05	0.7391
hsa-miR-548q	8.31	1.09	0.7392
hsa-miR-190b	4.08	-1.08	0.7420
hsa-miR-1205	1.30	-1.05	0.7437
hsa-miR-523-3p	1.16	-1.02	0.7465
hsa-miR-337-3p	103.14	1.01	0.7500
hsa-miR-548ak	3.82	1.08	0.7519
hsa-miR-449c-5p	1.32	-1.04	0.7559
hsa-miR-579-5p	2.37	-1.07	0.7564
hsa-let-7e-5p	5695.25	1.01	0.7577
hsa-miR-3151-5p	360.40	-1.02	0.7589
hsa-miR-181d-3p	1.98	-1.07	0.7590
hsa-miR-520e	1.25	1.04	0.7603

hsa-miR-138-5p	164.62	1.03	0.7608
hsa-miR-576-5p	6.55	1.08	0.7612
hsa-miR-6511a-5p	1.09	1.01	0.7618
hsa-miR-208b-5p	1.22	1.03	0.7623
hsa-miR-573	1.84	-1.06	0.7630
hsa-miR-3196	1.20	-1.03	0.7647
hsa-miR-4536-5p	18.45	1.05	0.7726
hsa-miR-513c-3p	1.12	1.02	0.7759
hsa-miR-376c-3p	2624.52	-1.03	0.7833
hsa-miR-548j-5p	2.35	-1.07	0.7851
hsa-miR-3185	2.21	1.06	0.7889
hsa-miR-188-3p	1.26	1.03	0.7890
hsa-miR-502-3p	2.11	1.06	0.7891
hsa-miR-142-3p	1232.64	-1.04	0.7916
hsa-miR-542-5p	187.58	1.04	0.7919
hsa-miR-3164	2.26	-1.07	0.7921
hsa-miR-133b	1.38	-1.04	0.7945
hsa-miR-1233-3p	16.28	1.06	0.7952
hsa-miR-139-5p	360.46	-1.02	0.7957
hsa-miR-563	4.23	-1.07	0.7964
hsa-miR-3127-5p	1.86	1.06	0.7966
hsa-miR-518f-3p	29.68	1.02	0.7992
hsa-miR-30e-5p	931.82	1.03	0.7996
hsa-miR-485-5p	11.65	1.06	0.8000
hsa-miR-127-5p	46.57	-1.02	0.8003
hsa-miR-103a-3p	22.40	-1.03	0.8026
hsa-miR-4787-5p	2.45	-1.06	0.8029
hsa-miR-378i	129.48	-1.02	0.8031
hsa-miR-224-5p	1.86	1.05	0.8044
hsa-miR-522-3p	22.56	1.03	0.8045
hsa-miR-125a-3p	17.66	-1.03	0.8050
hsa-miR-1262	7.02	1.05	0.8069
hsa-miR-519c-3p	5.85	-1.06	0.8074
hsa-miR-1278	2.30	-1.06	0.8083
hsa-miR-514a-3p	9.30	-1.04	0.8086
hsa-miR-1304-3p	1.63	1.05	0.8112
hsa-miR-519b-5p+hsa-miR-519c-5p+hsa-miR-523-5p+hsa-miR-518e-5p+hsa-miR-522-5p+hsa-miR-519a-5p	2.56	1.06	0.8129
hsa-miR-30a-5p	1485.79	1.02	0.8142
hsa-miR-302f	1.41	-1.03	0.8147

hsa-miR-520f-3p	42.18	1.03	0.8149
hsa-miR-301a-5p	10.25	-1.05	0.8174
hsa-miR-619-3p	1.79	1.05	0.8174
hsa-miR-183-5p	13.36	1.04	0.8208
hsa-miR-3605-5p	1.48	-1.03	0.8208
hsa-miR-3180-3p	1.80	-1.05	0.8218
hsa-miR-613	2.63	-1.05	0.8227
hsa-miR-1224-5p	1.77	1.05	0.8230
hsa-miR-2278	1.28	1.03	0.8233
hsa-miR-134-3p	4.97	1.05	0.8324
hsa-miR-640	2.42	-1.05	0.8339
hsa-miR-518c-3p	4.52	-1.06	0.8350
hsa-miR-383-5p	105.10	1.02	0.8372
hsa-miR-1277-3p	8.03	1.05	0.8410
hsa-miR-584-5p	15.08	1.04	0.8423
hsa-miR-585-3p	13.51	-1.04	0.8425
hsa-miR-548a-5p	10.19	1.04	0.8454
hsa-miR-32-5p	489.41	-1.04	0.8466
hsa-miR-648	1.14	1.01	0.8473
hsa-miR-105-5p	67.55	-1.03	0.8481
hsa-miR-302a-3p	6.66	1.05	0.8484
hsa-miR-548d-3p	5.49	-1.05	0.8489
hsa-miR-525-3p	4.87	-1.07	0.8505
hsa-miR-190a-5p	261.52	1.02	0.8547
hsa-miR-362-5p	37.07	1.02	0.8548
hsa-miR-3180	6.60	-1.05	0.8558
hsa-miR-1303	1.31	1.03	0.8566
hsa-miR-4524a-5p	1.15	-1.01	0.8576
hsa-miR-760	1.11	-1.01	0.8579
hsa-miR-548g-3p	27.53	-1.02	0.8582
hsa-miR-514b-5p	23.64	1.02	0.8591
hsa-miR-455-3p	34.94	1.02	0.8625
hsa-miR-410-3p	368.94	-1.01	0.8664
hsa-miR-514b-3p	1.46	-1.03	0.8717
hsa-miR-135a-5p	2305.38	-1.01	0.8733
hsa-miR-128-3p	17984.93	1.01	0.8755
hsa-miR-939-5p	15.67	-1.04	0.8766
hsa-miR-766-3p	48.89	-1.01	0.8781
hsa-miR-520h	25.15	1.02	0.8785
hsa-miR-1287-3p	14.03	1.03	0.8836
hsa-miR-570-3p	1.60	-1.03	0.8838

hsa-miR-572	1.71	-1.03	0.8857
hsa-miR-553	1.27	-1.02	0.8873
hsa-miR-591	2.00	1.03	0.8908
hsa-miR-764	3.69	1.04	0.8911
hsa-miR-548n	10.27	1.04	0.8913
hsa-miR-589-5p	1.62	1.02	0.8914
hsa-miR-187-3p	40.46	-1.01	0.8929
hsa-miR-191-5p	3482.02	-1.00	0.8940
hsa-miR-656-3p	743.53	1.01	0.8947
hsa-miR-381-5p	45.69	-1.01	0.8948
hsa-miR-345-5p	66.94	-1.02	0.8949
hsa-miR-548aa+hsa-miR-548t-3p	1.66	1.03	0.8987
hsa-miR-1323	11.60	-1.02	0.9033
hsa-miR-508-3p	1.43	-1.02	0.9075
hsa-miR-450a-1-3p	1.25	-1.01	0.9089
hsa-miR-660-3p	3.99	-1.03	0.9091
hsa-miR-133a-3p	144.99	-1.01	0.9099
hsa-miR-513c-5p	4.62	-1.03	0.9110
hsa-miR-3614-3p	1.15	-1.01	0.9118
hsa-miR-182-5p	2.54	-1.03	0.9121
hsa-miR-649	1.50	1.02	0.9167
hsa-miR-429	2.90	-1.03	0.9174
hsa-miR-4458	1.23	-1.01	0.9209
hsa-miR-922	10.12	1.02	0.9219
hsa-miR-197-3p	295.13	1.01	0.9223
hsa-miR-520d-3p	1.72	1.02	0.9251
hsa-miR-520a-3p	1.21	-1.01	0.9252
hsa-miR-506-5p	2.06	1.02	0.9296
hsa-miR-5010-3p	3.88	1.02	0.9299
hsa-miR-219a-5p	7812.06	1.03	0.9307
hsa-miR-765	1.91	-1.02	0.9318
hsa-miR-595	1.81	-1.02	0.9379
hsa-miR-508-5p	2.35	1.02	0.9397
hsa-miR-34a-5p	1221.04	1.01	0.9434
hsa-miR-6721-5p	92.04	1.01	0.9478
hsa-miR-934	2.29	1.01	0.9482
hsa-miR-3065-5p	66.80	1.01	0.9495
hsa-miR-3179	1.55	-1.01	0.9495
hsa-miR-627-3p	2.56	1.01	0.9545
hsa-miR-1178-3p	1.26	1.01	0.9552
hsa-miR-548e-5p	5.06	-1.01	0.9562

hsa-miR-3147	5.05	1.01	0.9570
hsa-miR-516b-5p	1.55	-1.01	0.9599
hsa-miR-612	28.36	1.01	0.9601
hsa-miR-323b-3p	13.51	-1.01	0.9608
hsa-miR-339-3p	4.73	1.01	0.9614
hsa-miR-4707-3p	1.12	1.00	0.9616
hsa-miR-555	2.61	1.01	0.9622
hsa-miR-1306-3p	3.08	1.01	0.9640
hsa-miR-214-3p	6.62	-1.01	0.9659
hsa-miR-574-5p	49.72	1.00	0.9663
hsa-miR-487b-5p	12.16	-1.01	0.9671
hsa-miR-1537-3p	9.26	1.01	0.9688
hsa-miR-92b-3p	290.93	-1.00	0.9698
hsa-miR-384	2.92	-1.01	0.9711
hsa-miR-367-3p	2.12	-1.01	0.9736
hsa-miR-4461	2.58	1.01	0.9737
hsa-miR-520c-3p	3.04	1.01	0.9770
hsa-miR-3168	8.46	1.01	0.9786
hsa-miR-139-3p	366.91	1.00	0.9802
hsa-miR-18b-5p	14.72	1.00	0.9807
hsa-miR-3190-3p	3.31	1.01	0.9825
hsa-miR-892a	2.12	1.00	0.9835
hsa-miR-1910-3p	2.96	-1.00	0.9851
hsa-miR-1973	21.92	-1.00	0.9856
hsa-miR-511-5p	3.54	1.00	0.9861
hsa-miR-665	3.69	-1.00	0.9881
hsa-miR-320d	2.95	1.00	0.9899
hsa-miR-1255a	11.46	1.00	0.9905
hsa-miR-4536-3p	2.19	-1.00	0.9913
hsa-miR-4451	2.14	1.00	0.9918
hsa-miR-1915-3p	30.61	-1.00	0.9965
hsa-miR-1295a	8.10	-1.00	0.9971
hsa-miR-374a-3p	1.70	1.00	0.9976
hsa-miR-127-3p	1688.28	-1.00	0.9983
hsa-miR-300	4.08	1.00	0.9985
hsa-miR-548d-5p	37.81	1.00	0.9986

Table S5. Taqman mRNA/pri-miRNA/miRNA assay information. Table showing the gene name, species, and assay ID for all Taqman assays used

Gene name	Species	Assay ID
18S rRNA	human	Hs99999901_s1
SERPINA3	human	Hs00153674_m1
C4	human	Hs00246758_m1
GRIN2B	human	Hs01002012_m1
GRIA2	human	Hs00181331_m1
NPTX2	human	Hs00383983_m1
GAD1	human	Hs01065893_m1
DICER1	human	Hs00229023_m1
DGCR8	human	Hs00256062_m1
ADAR1	human	Hs00241666_m1
ADARB1 (ADAR2)	human	Hs00953724_m1
pri-miR-132	human	Hs03303111_pri
pri-miR-223	human	Hs03303017_pri
miR-223-3p	human/mouse	2295
miR-30d-5p	human/mouse	420
let-7e	human/mouse/rat	2406
miR-132	human/mouse/rat	457
miR-193b-3p	human	2367
miR-330-3p	human	544
miR-1260	human	2896
miR-28-3p	human	2446
miR-155	mouse/rat	2571
18S rRNA	mouse/rat	Mm03928990_g1
Gria2	rat	Rn00568514_m1
Grin2b	rat	Rn00680474_m1
Adar1	rat	Rn00508006_m1
Gad1	rat	Rn00690300_m1

Table S6. Correlations between miR-223 expression and OFC demographics. Table showing correlations between relative to Control miR-223 expression in BD and SCZ and various demographic variables. Significant correlations with lifetime alcohol use and psychosis feature are shown in red.

Demographics	Spearman r	95% confidence interval	P (two-tailed)
RIN	-0.2545	-0.504 to 0.03406	0.0744
PMI	-0.0856	-0.3629 to 0.2055	0.5543
Brain pH	-0.1963	-0.4567 to 0.09522	0.1720
Refrigerator Interval	-0.0256	-0.3095 to 0.2624	0.8599
Age	0.1277	-0.1645 to 0.3992	0.3770
Sex	0.1145	-0.1775 to 0.3879	0.4286
Race	-0.1377	-0.4078 to 0.1545	0.3401
Lifetime Antipsychotics	0.1656	-0.1265 to 0.4313	0.2503
Suicide Status	-0.1218	-0.3942 to 0.1702	0.3994
Hemisphere	0.2405	-0.04896 to 0.4927	0.0924
Brain Weight	-0.1634	-0.4294 to 0.1288	0.2569
Age of Onset	0.1607	-0.1315 to 0.4271	0.2651
Duration of Illness	-0.0456	-0.3274 to 0.2438	0.7534
Lifetime Alcohol Use	-0.3592	-0.5873 to -0.07827	0.0113
Lifetime Drug Use	-0.1713	-0.4413 to 0.1271	0.2442
Smoking At TOD	0.3232	-0.0109 to 0.5923	0.0511
Time In Hospital	-0.0643	-0.3469 to 0.229	0.6608
Psychotic Feature	0.4479	0.1793 to 0.6544	0.0014

REFERENCES

Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M., Walker, E. F., Woods, S. W., & Heinssen, R. (2007). North American Prodrome Longitudinal Study: A Collaborative Multisite Approach to Prodromal Schizophrenia Research. *Schizophrenia Bulletin*, *33*(3), 665–672.

Akbarian, S., Kim, J. J., Potkin, S. G., Hagman, J. O., Tafazzoli, A., Bunney, W. E., & Jones, E. G. (1995). Gene Expression for Glutamic Acid Decarboxylase Is Reduced Without Loss of Neurons in Prefrontal Cortex of Schizophrenics. *Archives of General Psychiatry*, *52*(4), 258–266.

Al-Amin, M. M., Nasir Uddin, M. M., & Mahmud Reza, H. (2013). Effects of Antipsychotics on the Inflammatory Response System of Patients with Schizophrenia in Peripheral Blood Mononuclear Cell Cultures. *Clinical Psychopharmacology and Neuroscience*, *11*(3), 144–151.

Alexander, M., Ramstead, A. G., Bauer, K. M., Lee, S.-H., Runtsch, M. C., Wallace, J., Huffaker, T. B., Larsen, D. K., Tolmachova, T., Seabra, M. C., Round, J. L., Ward, D. M., & O'Connell, R. M. (2017). Rab27-Dependent Exosome Production Inhibits Chronic Inflammation and Enables Acute Responses to Inflammatory Stimuli. *The Journal of Immunology*, *199*(10), 3559–3570.

Anderson, I. M., Haddad, P. M., & Scott, J. (2012). Bipolar disorder. *BMJ*, *345*, e8508

Andreazza, A. C., & Young, L. T. (2014). The neurobiology of bipolar disorder: Identifying targets for specific agents and synergies for combination treatment. *The International Journal of Neuropsychopharmacology*, *17*(7), 1039–1052.

Arion, D., Unger, T., Lewis, D. A., Levitt, P., & Mirnics, K. (2007). Molecular evidence for increased expression of genes related to immune and chaperone function in the prefrontal cortex in schizophrenia. *Biological Psychiatry*, *62*(7), 711–721.

Batinić, B., Santrač, A., Divović, B., Timić, T., Stanković, T., Obradović, A. L., Joksimović, S., & Savić, M. M. (2016). Lipopolysaccharide exposure during late embryogenesis results in diminished locomotor activity and amphetamine response in females and spatial cognition impairment in males in adult, but not adolescent rat offspring. *Behavioural Brain Research*, *299*, 72–80.

Bavamian, S., Mellios, N., Lalonde, J., Fass, D. M., Wang, J., Sheridan, S. D., Madison, J. M., Zhou, F., Rueckert, E. H., Barker, D., Perlis, R. H., Sur, M., & Haggarty, S. J. (2015). Dysregulation of miR-34a links neuronal development to genetic risk factors for bipolar disorder. *Molecular Psychiatry*, *20*(5), 573–584.

Beentjes, T. A. A., Goossens, P. J. J., & Poslawsky, I. E. (2012). Caregiver Burden in Bipolar Hypomania and Mania: A Systematic Review. *Perspectives in Psychiatric Care*, *48*(4), 187–197.

Berridge, M. J. (2014). Calcium signalling and psychiatric disease: Bipolar disorder and schizophrenia. *Cell and Tissue Research*, *357*(2), 477–492.
Beveridge, N. J., Gardiner, E., Carroll, A. P., Tooney, P. A., & Cairns, M. J. (2010). Schizophrenia is associated with an increase in cortical microRNA biogenesis. *Molecular Psychiatry*, *15*(12), 1176–1189.
Beveridge, Natalie J., & Cairns, M. J. (2012). MicroRNA dysregulation in schizophrenia. *Neurobiology of Disease*, *46*(2), 263–271.
Canetta, S. E., & Brown, A. S. (2012). Prenatal infection, maternal immune activation, and risk for schizophrenia. *Translational Neuroscience*, *3*(4), 320–327.
Canfrán-Duque, A., Pastor, O., Reina, M., Lerma, M., Cruz-Jentoft, A. J., Lasunción, M. A., & Busto, R. (2015). Curcumin Mitigates the Intracellular Lipid Deposit Induced by Antipsychotics In Vitro. *PLOS ONE*, *10*(10), e0141829.
Cantoni, C., Cignarella, F., Ghezzi, L., Mikesell, B., Bollman, B., Berrien-Elliott, M. M., Ireland, A. R., Fehniger, T. A., Wu, G. F., & Piccio, L. (2017). Mir-223 regulates the number and function of myeloid-derived suppressor cells in multiple sclerosis and experimental autoimmune encephalomyelitis. *Acta Neuropathologica*, *133*(1), 61–77.
Cava, C., Manna, I., Gambardella, A., Bertoli, G., & Castiglioni, I. (2018). Potential Role of miRNAs as Theranostic Biomarkers of Epilepsy. *Molecular Therapy. Nucleic Acids*, *13*, 275–290.
Chai, X. J., Whitfield-Gabrieli, S., Shinn, A. K., Gabrieli, J. D. E., Nieto Castañón, A., McCarthy, J. M., Cohen, B. M., & Öngür, D. (2011). Abnormal Medial Prefrontal Cortex Resting-State Connectivity in Bipolar Disorder and Schizophrenia. *Neuropsychopharmacology*, *36*(10), 2009–2017.
Chan, B. D., Wong, W.-Y., Lee, M. M.-L., Cho, W. C.-S., Yee, B. K., Kwan, Y. W., & Tai, W. C.-S. (2019). Exosomes in Inflammation and Inflammatory Disease. *Proteomics*, *19*(8), e1800149.
Chen, Q., Wang, H., Liu, Y., Song, Y., Lai, L., Han, Q., Cao, X., & Wang, Q. (2012). Inducible microRNA-223 down-regulation promotes TLR-triggered IL-6 and IL-1β production in macrophages by targeting STAT3. *PloS One*, *7*(8), e42971.
Chen, Y., Song, Y., Huang, J., Qu, M., Zhang, Y., Geng, J., Zhang, Z., Liu, J., & Yang, G.-Y. (2017). Increased Circulating Exosomal miRNA-223 Is Associated with Acute Ischemic Stroke. *Frontiers in Neurology*, *8*, 57.
Cho, K. H. T., Xu, B., Blenkiron, C., & Fraser, M. (2019). Emerging Roles of miRNAs in Brain Development and Perinatal Brain Injury. *Frontiers in Physiology*, *10*.
Cirillo, M. A., & Seidman, L. J. (2003). Verbal Declarative Memory Dysfunction in Schizophrenia: From Clinical Assessment to Genetics and Brain Mechanisms. *Neuropsychology Review*, *13*(2), 43–77.
Clark, L., & Sahakian, B. J. (2008). Cognitive neuroscience and brain imaging in bipolar disorder. *Dialogues in Clinical Neuroscience*, *10*(2), 153–165.

Colombo, M., Raposo, G., & Théry, C. (2014). Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. *Annual Review of Cell and Developmental Biology*, *30*, 255–289.

Correll, C. U., Sheridan, E. M., & DelBello, M. P. (2010). Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: A comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar Disorders*, *12*(2), 116–141.

Coyle, J. T. (2006). Glutamate and schizophrenia: Beyond the dopamine hypothesis. *Cellular and Molecular Neurobiology*, *26*(4–6), 365–384.

Davis, K. L., Kahn, R. S., Ko, G., & Davidson, M. (1991). Dopamine in schizophrenia: A review and reconceptualization. *The American Journal of Psychiatry*, *148*(11), 1474–1486.

DeLisi, L. E., Szulc, K. U., Bertisch, H. C., Majcher, M., & Brown, K. (2006). Understanding structural brain changes in schizophrenia. *Dialogues in Clinical Neuroscience*, *8*(1), 71–78.

Desdín-Micó, G., & Mittelbrunn, M. (2016). Role of exosomes in the protection of cellular homeostasis. *Cell Adhesion & Migration*, *11*(2), 127–134.

Durrenberger, P. F., Fernando, S., Kashefi, S. N., Ferrer, I., Hauw, J.-J., Seilhean, D., Smith, C., Walker, R., Al-Sarraj, S., Troakes, C., Palkovits, M., Kasztner, M., Huitinga, I., Arzberger, T., Dexter, D. T., Kretzschmar, H., & Reynolds, R. (2010). Effects of Antemortem and Postmortem Variables on Human Brain mRNA Quality: A BrainNet Europe Study. *Journal of Neuropathology & Experimental Neurology*, *69*(1), 70–81.

Egan, M. F., & Weinberger, D. R. (1997). Neurobiology of schizophrenia. *Current Opinion in Neurobiology*, *7*(5), 701–707.

Fatemi, S. H., Hossein Fatemi, S., Stary, J. M., Earle, J. A., Araghi-Niknam, M., & Eagan, E. (2005). GABAergic dysfunction in schizophrenia and mood disorders as reflected by decreased levels of glutamic acid decarboxylase 65 and 67 kDa and Reelin proteins in cerebellum. *Schizophrenia Research*, *72*(2–3), 109–122.

Faour-Nmarne, C. & Azab, A. N. (2016). Effects of olanzapine on LPS-induced inflammation in rat primary glia cells. *Innate immunity* 22, 40–50

Fazi, F., Racanicchi, S., Zardo, G., Starnes, L. M., Mancini, M., Travaglini, L., Diverio, D., Ammatuna, E., Cimino, G., Lo-Coco, F., Grignani, F., & Nervi, C. (2007). Epigenetic silencing of the myelopoiesis regulator microRNA-223 by the AML1/ETO oncoprotein. *Cancer Cell*, *12*(5), 457–466.

Feigenson, K. A., Kusnecov, A. W., & Silverstein, S. M. (2014). Inflammation and the two-hit hypothesis of schizophrenia. *Neuroscience and Biobehavioral Reviews*, *38*, 72–93.

Fillman, S. G., Cloonan, N., Catts, V. S., Miller, L. C., Wong, J., McCrossin, T., Cairns, M., & Weickert, C. S. (2013). Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia. *Molecular Psychiatry*, *18*(2), 206–214.

Fillman, S. G., Sinclair, D., Fung, S. J., Webster, M. J., & Shannon Weickert, C. (2014). Markers of inflammation and stress distinguish subsets of

individuals with schizophrenia and bipolar disorder. *Translational Psychiatry*, *4*, e365.
Follert, P., Cremer, H., & Beclin, C. (2014). MicroRNAs in brain development and function: A matter of flexibility and stability. *Frontiers in Molecular Neuroscience*, *7*.
Fornito, A., Yücel, M., Dean, B., Wood, S. J., & Pantelis, C. (2009). Anatomical Abnormalities of the Anterior Cingulate Cortex in Schizophrenia: Bridging the Gap Between Neuroimaging and Neuropathology. *Schizophrenia Bulletin*, *35*(5), 973–993.
Frey, B. N., Andreazza, A. C., Nery, F. G., Martins, M. R., Quevedo, J., Soares, J. C., & Kapczinski, F. (2007). The role of hippocampus in the pathophysiology of bipolar disorder. *Behavioural Pharmacology*, *18*(5–6), 419–430.
Fries, G. R., Carvalho, A. F., & Quevedo, J. (2018). The miRNome of bipolar disorder. *Journal of Affective Disorders*, *233*, 110–116.
Gardiner, E., Carroll, A., Tooney, P. A., & Cairns, M. J. (2014). Antipsychotic drug-associated gene–miRNA interaction in T-lymphocytes. *International Journal of Neuropsychopharmacology*, *17*(6), 929–943.
Gilicze, A. B., Wiener, Z., Tóth, S., Buzás, E., Pállinger, É., Falcone, F. H., & Falus, A. (2014). *Myeloid-Derived microRNAs, miR-223, miR27a, and miR-652, Are Dominant Players in Myeloid Regulation* [Review Article]. BioMed Research International.
Glasgow, S. M., Laug, D., Brawley, V. S., Zhang, Z., Corder, A., Yin, Z., Wong, S. T. C., Li, X.-N., Foster, A. E., Ahmed, N., & Deneen, B. (2013). The miR-223/Nuclear Factor I-A Axis Regulates Glial Precursor Proliferation and Tumorigenesis in the CNS. *The Journal of Neuroscience*, *33*(33), 13560–13568.
Goldberg, T. E., Keefe, R. S. E., Goldman, R. S., Robinson, D. G., & Harvey, P. D. (2010). Circumstances Under Which Practice Does Not Make Perfect: A Review of the Practice Effect Literature in Schizophrenia and Its Relevance to Clinical Treatment Studies. *Neuropsychopharmacology*, *35*(5), 1053–1062.
Guidotti, A., Auta, J., Davis, J. M., Di-Giorgi-Gerevini, V., Dwivedi, Y., Grayson, D. R., Impagnatiello, F., Pandey, G., Pesold, C., Sharma, R., Uzunov, D., Costa, E., & DiGiorgi Gerevini, V. (2000). Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: A postmortem brain study. *Archives of General Psychiatry*, *57*(11), 1061–1069.
Ha, M., & Kim, V. N. (2014). Regulation of microRNA biogenesis. *Nature Reviews Molecular Cell Biology*, *15*(8), 509–524.
Haneklaus, M., Gerlic, M., O'Neill, L. a. J., & Masters, S. L. (2013). miR-223: Infection, inflammation and cancer. *Journal of Internal Medicine*, *274*(3), 215–226.
Harraz, M. M., Eacker, S. M., Wang, X., Dawson, T. M., & Dawson, V. L. (2012). MicroRNA-223 is neuroprotective by targeting glutamate receptors.

Proceedings of the National Academy of Sciences of the United States of America, *109*(46), 18962–18967.
Harraz, M. M., Xu, J.-C., Guiberson, N., Dawson, T. M., & Dawson, V. L. (2014). MiR-223 regulates the differentiation of immature neurons. *Molecular and Cellular Therapies*, *2*(18).
Harrison, P. J. (1999). The neuropathology of schizophreniaA critical review of the data and their interpretation. *Brain*, *122*(4), 593–624.
Hashimoto, T., Volk, D. W., Eggan, S. M., Mirnics, K., Pierri, J. N., Sun, Z., Sampson, A. R., & Lewis, D. A. (2003). Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *23*(15), 6315–6326.
Hauberg, M. E., Roussos, P., Grove, J., Børglum, A. D., & Mattheisen, M. (2016). Analyzing the Role of MicroRNAs in Schizophrenia in the Context of Common Genetic Risk Variants. *JAMA Psychiatry*, *73*(4), 369–377.
He, K., Guo, C., He, L., & Shi, Y. (2017). MiRNAs of peripheral blood as the biomarker of schizophrenia. *Hereditas*, *155*.
Holm, M. M., Kaiser, J., & Schwab, M. E. (2018). Extracellular Vesicles: Multimodal Envoys in Neural Maintenance and Repair. *Trends in Neurosciences*, *41*(6), 360–372.
Horváth, S., & Mirnics, K. (2014). Immune system disturbances in schizophrenia. *Biological Psychiatry*, *75*(4), 316–323.
Hwang, Y., Kim, J., Shin, J. Y., Kim, J. I., Seo, J. S., Webster, M. J., Lee, D., & Kim, S. (2013). Gene expression profiling by mRNA sequencing reveals increased expression of immune/inflammation-related genes in the hippocampus of individuals with schizophrenia. *Translational Psychiatry*, *3*, e321.
Jackowski, A. P., Araújo Filho, G. M. de, Almeida, A. G. de, Araújo, C. M. de, Reis, M., Nery, F., Batista, I. R., Silva, I., & Lacerda, A. L. T. (2012). The involvement of the orbitofrontal cortex in psychiatric disorders: An update of neuroimaging findings. *Revista Brasileira De Psiquiatria (Sao Paulo, Brazil: 1999)*, *34*(2), 207–212.
Javadapour, A., Malhi, G. S., Ivanovski, B., Chen, X., Wen, W., & Sachdev, P. (2007). Increased anterior cingulate cortex volume in bipolar I disorder. *The Australian and New Zealand Journal of Psychiatry*, *41*(11), 910–916.
Ji, Q., Ji, Y., Peng, J., Zhou, X., Chen, X., Zhao, H., Xu, T., Chen, L., & Xu, Y. (2016). Increased Brain-Specific MiR-9 and MiR-124 in the Serum Exosomes of Acute Ischemic Stroke Patients. *PloS One*, *11*(9), e0163645.
Johnnidis, J. B., Harris, M. H., Wheeler, R. T., Stehling-Sun, S., Lam, M. H., Kirak, O., Brummelkamp, T. R., Fleming, M. D., & Camargo, F. D. (2008). Regulation of progenitor cell proliferation and granulocyte function by microRNA-223. *Nature*, *451*(7182), 1125–1129.
Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 617–627.

Khoshnam, S. E., Winlow, W., Farbood, Y., Moghaddam, H. F., & Farzaneh, M. (2017). Emerging Roles of microRNAs in Ischemic Stroke: As Possible Therapeutic Agents. *Journal of Stroke*, *19*(2), 166–187.

Kimoto, S., Zaki, M. M., Bazmi, H. H., & Lewis, D. A. (2015). Altered Markers of Cortical γ-Aminobutyric Acid Neuronal Activity in Schizophrenia: Role of the NARP Gene. *JAMA Psychiatry*, *72*(8), 747–756.

Krol, J., Loedige, I., & Filipowicz, W. (2010). The widespread regulation of microRNA biogenesis, function and decay. *Nature Reviews Genetics*, *11*(9), 597–610.

Kurtz, M. M., Moberg, P. J., Gur, R. C., & Gur, R. E. (2001). Approaches to Cognitive Remediation of Neuropsychological Deficits in Schizophrenia: A Review and Meta-Analysis. *Neuropsychology Review*, *11*(4), 197–210.

Lafourcade, C., Ramírez, J. P., Luarte, A., Fernández, A., & Wyneken, U. (2016). MiRNAs in Astrocyte-Derived Exosomes as Possible Mediators of Neuronal Plasticity. *Journal of Experimental Neuroscience*, *10*(Suppl 1), 1–9.

Lawrence, R. E., First, M. B., & Lieberman, J. A. (2015). Schizophrenia and Other Psychoses. In *Psychiatry* (pp. 791–856). John Wiley & Sons, Ltd.

Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., & Davis, J. M. (2012). Maintenance treatment with antipsychotic drugs for schizophrenia. *The Cochrane Database of Systematic Reviews*, *5*, CD008016.

Lin, J.-R., Cai, Y., Zhang, Q., Zhang, W., Nogales-Cadenas, R., & Zhang, Z. D. (2016). Integrated Post-GWAS Analysis Sheds New Light on the Disease Mechanisms of Schizophrenia. *Genetics*, *204*(4), 1587–1600.

Liu, Q., Zhang, M., Jiang, X., Zhang, Z., Dai, L., Min, S., Wu, X., He, Q., Liu, J., Zhang, Y., Zhang, Z., & Yang, R. (2011). MiR-223 suppresses differentiation of tumor-induced $CD11b^+$ $Gr1^+$ myeloid-derived suppressor cells from bone marrow cells. *International Journal of Cancer*, *129*(11), 2662–2673.

Maffioletti, E., Cattaneo, A., Rosso, G., Maina, G., Maj, C., Gennarelli, M., Tardito, D., & Bocchio-Chiavetto, L. (2016). Peripheral whole blood microRNA alterations in major depression and bipolar disorder. *Journal of Affective Disorders*, *200*, 250–258.

Maia, J., Caja, S., Strano Moraes, M. C., Couto, N., & Costa-Silva, B. (2018). Exosome-Based Cell-Cell Communication in the Tumor Microenvironment. *Frontiers in Cell and Developmental Biology*, *6*.

Mattei, D., Schweibold, R., & Wolf, S. A. (2015). Brain in flames – animal models of psychosis: Utility and limitations. *Neuropsychiatric Disease and Treatment*, *11*, 1313–1329. https://doi.org/10.2147/NDT.S65564

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews*, *30*, 67–76.

McNeill, E., & Van Vactor, D. (2012). MicroRNAs Shape the Neuronal Landscape. *Neuron*, *75*(3), 363–379.

Meinhard, N., Kessing, L. V., & Vinberg, M. (2014). The role of estrogen in bipolar disorder, a review. *Nordic Journal of Psychiatry*, *68*(2), 81–87.

Mellios, N., Feldman, D. A., Sheridan, S. D., Ip, J. P. K., Kwok, S., Amoah, S. K., Rosen, B., Rodriguez, B. A., Crawford, B., Swaminathan, R., Chou, S., Li, Y., Ziats, M., Ernst, C., Jaenisch, R., Haggarty, S. J., & Sur, M. (2018). MeCP2-regulated miRNAs control early human neurogenesis through differential effects on ERK and AKT signaling. *Molecular Psychiatry*, *23*(4), 1051–1065.

Mellios, N, Huang, H.-S., Baker, S. P., Galdzicka, M., Ginns, E., & Akbarian, S. (2009). Molecular determinants of dysregulated GABAergic gene expression in the prefrontal cortex of subjects with schizophrenia. *Biological Psychiatry*, *65*(12), 1006–1014.

Mellios, N, Sugihara, H., Castro, J., Banerjee, A., Le, C., Kumar, A., Crawford, B., Strathmann, J., Tropea, D., Levine, S. S., Edbauer, D., & Sur, M. (2011). MiR-132, an experience-dependent microRNA, is essential for visual cortex plasticity. *Nature Neuroscience*, *14*(10), 1240–1242.

Mellios, N, & Sur, M. (2012). The Emerging Role of microRNAs in Schizophrenia and Autism Spectrum Disorders. *Frontiers in Psychiatry*, *3*.

Mellios, N, Woodson, J., Garcia, R. I., Crawford, B., Sharma, J., Sheridan, S. D., Haggarty, S. J., & Sur, M. (2014). B2-Adrenergic receptor agonist ameliorates phenotypes and corrects microRNA-mediated IGF1 deficits in a mouse model of Rett syndrome. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(27), 9947–9952.

Merikangas, K. R., Akiskal, H. S., Angst, J., Greenberg, P. E., Hirschfeld, R. M. A., Petukhova, M., & Kessler, R. C. (2007). Lifetime and 12-Month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *64*(5), 543–552.

Miller, B. H., Zeier, Z., Xi, L., Lanz, T. A., Deng, S., Strathmann, J., Willoughby, D., Kenny, P. J., Elsworth, J. D., Lawrence, M. S., Roth, R. H., Edbauer, D., Kleiman, R. J., & Wahlestedt, C. (2012). MicroRNA-132 dysregulation in schizophrenia has implications for both neurodevelopment and adult brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(8), 3125–3130.

Morquette, B., Juźwik, C. A., Drake, S. S., Charabati, M., Zhang, Y., Lécuyer, M.-A., Galloway, D. A., Dumas, A., de Faria Junior, O., Paradis-Isler, N., Bueno, M., Rambaldi, I., Zandee, S., Moore, C., Bar-Or, A., Vallières, L., Prat, A., & Fournier, A. E. (2019). MicroRNA-223 protects neurons from degeneration in experimental autoimmune encephalomyelitis. *Brain: A Journal of Neurology*, *142*(10), 2979–2995.

Muneer, A. (2013). Treatment of the depressive phase of bipolar affective disorder: A review. *JPMA. The Journal of the Pakistan Medical Association*, *63*(6), 763–769.

Muneer, A. (2017). Wnt and GSK3 Signaling Pathways in Bipolar Disorder: Clinical and Therapeutic Implications. *Clinical Psychopharmacology and Neuroscience: The Official Scientific Journal of the Korean College of Neuropsychopharmacology*, *15*(2), 100–114.

Neudecker, V., Haneklaus, M., Jensen, O., Khailova, L., Masterson, J. C., Tye, H., Biette, K., Jedlicka, P., Brodsky, K. S., Gerich, M. E., Mack, M.,

Robertson, A. A. B., Cooper, M. A., Furuta, G. T., Dinarello, C. A., O'Neill, L. A., Eltzschig, H. K., Masters, S. L., & McNamee, E. N. (2017). Myeloid-derived miR-223 regulates intestinal inflammation via repression of the NLRP3 inflammasome. *The Journal of Experimental Medicine*, *214*(6), 1737–1752.

NIMH » Bipolar Disorder. (2020, January 31). https://www.nimh.nih.gov/health/topics/bipolar-disorder/index.shtml

NIMH » Schizophrenia. (2016, November 25). https://web.archive.org/web/20161125145206/https://www.nimh.nih.gov/health/topics/schizophrenia/index.shtml

Novick, D. M., Swartz, H. A., & Frank, E. (2010). Suicide attempts in bipolar I and bipolar II disorder: A review and meta-analysis of the evidence. *Bipolar Disorders*, *12*(1), 1–9.

Obuchowicz, E., Bielecka-Wajdman, A. M., Paul-Samojedny, M., & Nowacka, M. (2017). Different influence of antipsychotics on the balance between pro- and anti-inflammatory cytokines depends on glia activation: An in vitro study. *Cytokine*, *94*, 37–44.

Ochoa, S., Usall, J., Cobo, J., Labad, X., & Kulkarni, J. (2012). *Gender Differences in Schizophrenia and First-Episode Psychosis: A Comprehensive Literature Review* [Review Article]. Schizophrenia Research and Treatment.

Pomarol-Clotet, E., Oh, T. M. S. S., Laws, K. R., & McKenna, P. J. (2008). Semantic priming in schizophrenia: Systematic review and meta-analysis. *The British Journal of Psychiatry*, *192*(2), 92–97.

Ponomarev, E. D., Veremeyko, T., Barteneva, N., Krichevsky, A. M., & Weiner, H. L. (2011). MicroRNA-124 promotes microglia quiescence and suppresses EAE by deactivating macrophages via the C/EBP-α–PU.1 pathway. *Nature Medicine*, *17*(1), 64–70.

Prada, I., Gabrielli, M., Turola, E., Iorio, A., D'Arrigo, G., Parolisi, R., De Luca, M., Pacifici, M., Bastoni, M., Lombardi, M., Legname, G., Cojoc, D., Buffo, A., Furlan, R., Peruzzi, F., & Verderio, C. (2018). Glia-to-neuron transfer of miRNAs via extracellular vesicles: A new mechanism underlying inflammation-induced synaptic alterations. *Acta Neuropathologica*, *135*(4), 529–550.

Psychiatric GWAS Consortium Bipolar Disorder Working Group. (2011). Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nature Genetics*, *43*(10), 977–983.

Rajman, M., & Schratt, G. (2017). MicroRNAs in neural development: From master regulators to fine-tuners. *Development*, *144*(13), 2310–2322.

Reemst, K., Noctor, S. C., Lucassen, P. J., & Hol, E. M. (2016). The Indispensable Roles of Microglia and Astrocytes during Brain Development. *Frontiers in Human Neuroscience*, *10*.

Reisinger, S., Khan, D., Kong, E., Berger, A., Pollak, A., & Pollak, D. D. (2015). The poly(I:C)-induced maternal immune activation model in preclinical neuropsychiatric drug discovery. *Pharmacology & Therapeutics*, *149*, 213–226.

Ruby, J. G., Jan, C. H., & Bartel, D. P. (2007). Intronic microRNA precursors that bypass Drosha processing. *Nature*, *448*(7149), 83–86.
Saetre, P., Emilsson, L., Axelsson, E., Kreuger, J., Lindholm, E., & Jazin, E. (2007). Inflammation-related genes up-regulated in schizophrenia brains. *BMC Psychiatry*, *7*, 46.
Santarelli, D. M., Beveridge, N. J., Tooney, P. A., & Cairns, M. J. (2011). Upregulation of dicer and microRNA expression in the dorsolateral prefrontal cortex Brodmann area 46 in schizophrenia. *Biological Psychiatry*, *69*(2), 180–187.
Santarelli, D. M., Liu, B., Duncan, C. E., Beveridge, N. J., Tooney, P. A., Schofield, P. R., & Cairns, M. J. (2013). Gene-microRNA interactions associated with antipsychotic mechanisms and the metabolic side effects of olanzapine. *Psychopharmacology*, *227*(1), 67–78.
Schildge, S., Bohrer, C., Beck, K., & Schachtrup, C. (2013). Isolation and culture of mouse cortical astrocytes. *Journal of Visualized Experiments: JoVE*, *71*.
Sekar, A., Bialas, A. R., de Rivera, H., Davis, A., Hammond, T. R., Kamitaki, N., Tooley, K., Presumey, J., Baum, M., Van Doren, V., Genovese, G., Rose, S. A., Handsaker, R. E., Schizophrenia Working Group of the Psychiatric Genomics Consortium, Daly, M. J., Carroll, M. C., Stevens, B., & McCarroll, S. A. (2016). Schizophrenia risk from complex variation of complement component 4. *Nature*, *530*(7589), 177–183.
Sellgren, C. M., Sheridan, S. D., Gracias, J., Xuan, D., Fu, T., & Perlis, R. H. (2017). Patient-specific models of microglia-mediated engulfment of synapses and neural progenitors. *Molecular Psychiatry*, *22*(2), 170–177.
Shi, Y., Zhao, X., Hsieh, J., Wichterle, H., Impey, S., Banerjee, S., Neveu, P., & Kosik, K. S. (2010). MicroRNA Regulation of Neural Stem Cells and Neurogenesis. *Journal of Neuroscience*, *30*(45), 14931–14936.
Shin, J. H., Park, Y. M., Kim, D. H., Moon, G. J., Bang, O. Y., Ohn, T., & Kim, H. H. (2014). Ischemic brain extract increases SDF-1 expression in astrocytes through the CXCR2/miR-223/miR-27b pathway. *Biochimica Et Biophysica Acta*, *1839*(9), 826–836.
Shurtleff, M. J., Temoche-Diaz, M. M., Karfilis, K. V., Ri, S., & Schekman, R. (2016). Y-box protein 1 is required to sort microRNAs into exosomes in cells and in a cell-free reaction. *ELife*, *5*.
Singh, K. K. (2013). An emerging role for Wnt and GSK3 signaling pathways in schizophrenia. *Clinical Genetics*, *83*(6), 511–517.
Siomi, H., & Siomi, M. C. (2010). Posttranscriptional Regulation of MicroRNA Biogenesis in Animals. *Molecular Cell*, *38*(3), 323–332.
Slezak-Prochazka, I., Durmus, S., Kroesen, B.-J., & van den Berg, A. (2010). MicroRNAs, macrocontrol: Regulation of miRNA processing. *RNA (New York, N.Y.)*, *16*(6), 1087–1095.
Ślusarczyk, J., Trojan, E., Głombik, K., Budziszewska, B., Kubera, M., Lasoń, W., Popiołek-Barczyk, K., Mika, J., Wędzony, K., & Basta-Kaim, A. (2015). Prenatal stress is a vulnerability factor for altered morphology and biological activity of microglia cells. *Frontiers in Cellular Neuroscience*, *9*.

Sørensen, H. J., Mortensen, E. L., Reinisch, J. M., & Mednick, S. A. (2009). Association Between Prenatal Exposure to Bacterial Infection and Risk of Schizophrenia. *Schizophrenia Bulletin*, *35*(3), 631–637.

Swann, A. C., Lafer, B., Perugi, G., Frye, M. A., Bauer, M., Bahk, W.-M., Scott, J., Ha, K., & Suppes, T. (2013). Bipolar Mixed States: An International Society for Bipolar Disorders Task Force Report of Symptom Structure, Course of Illness, and Diagnosis. *American Journal of Psychiatry*, *170*(1), 31–42.

Swathy, B., & Banerjee, M. (2017). Haloperidol induces pharmacoepigenetic response by modulating miRNA expression, global DNA methylation and expression profiles of methylation maintenance genes and genes involved in neurotransmission in neuronal cells. *PLOS ONE*, *12*(9), e0184209.

Tan, B. L. (2009). Profile of cognitive problems in schizophrenia and implications for vocational functioning. *Australian Occupational Therapy Journal*, *56*(4), 220–228.

Tanahashi S., Yamamura S., Nakagawa M., Motomura E. and Okada M. (2012a) Clozapine, but not haloperidol, enhances glial D-serine and L-glutamate release in rat frontal cortex and primary cultured astrocytes. Br. J. Pharmacol. 165, 1543– 1555.

Tanaka, T., Matsuda, T., Hayes, L. N., Yang, S., Rodriguez, K., Severance, E. G., Yolken, R. H., Sawa, A., & Eaton, W. W. (2017). Infection and inflammation in schizophrenia and bipolar disorder. *Neuroscience Research*, *115*, 59–63.

Torrey, E. F., Webster, M., Knable, M., Johnston, N., & Yolken, R. H. (2000). The stanley foundation brain collection and neuropathology consortium. *Schizophrenia Research*, *44*(2), 151–155.

Trépanier, M. O., Hopperton, K. E., Mizrahi, R., Mechawar, N., & Bazinet, R. P. (2016). Postmortem evidence of cerebral inflammation in schizophrenia: A systematic review. *Molecular Psychiatry*, *21*(8), 1009–1026.

Udeochu, J. C., Sanchez-Diaz, C., Cai, A., Jovicic, A., & Villeda, S. A. (2018). Exosome Release Promotes Inflammatory Resolution in Activated and Aged Microglia. *BioRxiv*, 423558.

van Os, J., & Kapur, S. (2009). Schizophrenia. *The Lancet*, *374*(9690), 635–645. https://doi.org/10.1016/S0140-6736(09)60995-8

Vasistha, N. A., Pardo-Navarro, M., Gasthaus, J., Weijers, D., Müller, M. K., García-González, D., Malwade, S., Korshunova, I., Pfisterer, U., Engelhardt, J. von, Hougaard, K. S., & Khodosevich, K. (2019). Maternal inflammation has a profound effect on cortical interneuron development in a stage and subtype-specific manner. *Molecular Psychiatry*, 1–17.

Volk, D. W., Austin, M. C., Pierri, J. N., Sampson, A. R., & Lewis, D. A. (2000). Decreased glutamic acid decarboxylase67 messenger RNA expression in a subset of prefrontal cortical gamma-aminobutyric acid neurons in subjects with schizophrenia. *Archives of General Psychiatry*, *57*(3), 237–245.

Wei, H., Yuan, Y., Liu, S., Wang, C., Yang, F., Lu, Z., Wang, C., Deng, H., Zhao, J., Shen, Y., Zhang, C., Yu, X., & Xu, Q. (2015). Detection of circulating

miRNA levels in schizophrenia. *The American Journal of Psychiatry*, *172*(11), 1141–1147.
Weick, J. P., Groth, R. D., Isaksen, A. L., & Mermelstein, P. G. (2003). Interactions with PDZ proteins are required for L-type calcium channels to activate cAMP response element-binding protein-dependent gene expression. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *23*(8), 3446–3456.
Weick, J. P., Held, D. L., Bonadurer, G. F., Doers, M. E., Liu, Y., Maguire, C., Clark, A., Knackert, J. A., Molinarolo, K., Musser, M., Yao, L., Yin, Y., Lu, J., Zhang, X., Zhang, S.-C., & Bhattacharyya, A. (2013). Deficits in human trisomy 21 iPSCs and neurons. *Proceedings of the National Academy of Sciences*, *110*(24), 9962–9967. https://doi.org/10.1073/pnas.1216575110
Wischhof, L., Irrsack, E., Osorio, C., & Koch, M. (2015). Prenatal LPS-exposure—A neurodevelopmental rat model of schizophrenia—Differentially affects cognitive functions, myelination and parvalbumin expression in male and female offspring. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *57*, 17–30. https://doi.org/10.1016/j.pnpbp.2014.10.004
Wortzel, I., Dror, S., Kenific, C. M., & Lyden, D. (2019). Exosome-Mediated Metastasis: Communication from a Distance. *Developmental Cell*, *49*(3), 347–360.
Xu, B., Zhang, Y., Du, X.-F., Li, J., Zi, H.-X., Bu, J.-W., Yan, Y., Han, H., & Du, J.-L. (2017). Neurons secrete miR-132-containing exosomes to regulate brain vascular integrity. *Cell Research*, *27*(7), 882–897.
Xu, Y., Zhuo, C., Qin, W., Zhu, J., & Yu, C. (2015). Altered Spontaneous Brain Activity in Schizophrenia: A Meta-Analysis and a Large-Sample Study. *BioMed Research International*, *2015*, 204628.
Yang, W., Chendrimada, T. P., Wang, Q., Higuchi, M., Seeburg, P. H., Shiekhattar, R., & Nishikura, K. (2006). Modulation of microRNA processing and expression through RNA editing by ADAR deaminases. *Nature Structural & Molecular Biology*, *13*(1), 13–21.
Yang, Z., Zhong, L., Xian, R., & Yuan, B. (2015). MicroRNA-223 regulates inflammation and brain injury via feedback to NLRP3 inflammasome after intracerebral hemorrhage. *Molecular Immunology*, *65*(2), 267–276.
Zhang, Y., Catts, V. S., Sheedy, D., McCrossin, T., Kril, J. J., & Shannon Weickert, C. (2016). Cortical grey matter volume reduction in people with schizophrenia is associated with neuro-inflammation. *Translational Psychiatry*, *6*(12), e982.