



The Missing Link: How Exosomes and miRNAs can Help in Bridging Psychiatry and Molecular Biology in the Context of Depression, Bipolar Disorder and Schizophrenia

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Abstract

MicroRNAs (miRNAs) only recently have been recognized as promising molecules for both fundamental and clinical neuroscience. We provide a literature review of miRNA biomarker studies in three most prominent psychiatric disorders (depression, bipolar disorder and schizophrenia) with the particular focus on depression due to its social and healthcare importance. Our search resulted in 191 unique miRNAs across 35 human studies measuring miRNA levels in blood, serum or plasma. 30 miRNAs replicated in more than one study. Most miRNAs targeted neuroplasticity and neurodevelopment pathways. Various limitations do not allow us to make firm conclusions on clinical potential of studied miRNAs. Based on our results we discuss the rationale for future research investigations of exosomal mechanisms to overcome methodological caveats both in studying etiology and pathogenesis, and providing an objective back-up for clinical decisions.

Keywords Exosomes · miRNA · Biomarker · Depression · Schizophrenia · Bipolar disorder · Psychiatry

Introduction

Mental disorders are a major concern for healthcare systems worldwide and a significant burden to both an individual and society (Thyloth et al. 2016). Major depressive disorder (MDD) is rated as one of the greatest contributors to global disability, affecting 300 million people worldwide, the main cause of suicide and is not restricted to any particular age

group (Mojtabai et al. 2016; Organization 2017). One of the challenges in the management of depression is the lack of definitive diagnostic tools, with multiple studies suggesting a high rate of misdiagnosis in general practice (Mitchell et al. 2009; Pelletier et al. 2017), which may be related to changes in mood disorders section in DSM-5 (Mojtabai 2013; Park and Kim 2018; Uher et al. 2014). In spite of having a wide range of drugs (Girardi et al. 2009; Pompili et al. 2013) for depression the response rate in patients is rather moderate (Undurraga and Baldessarini 2012). There are high hopes for wide use of the non-pharmacologic treatment (e.g. Transcranial Magnetic Stimulation) (Berlim et al. 2013; Serafini et al. 2015) when pharmacologic treatment fails. A substantial minority experiences more disabling conditions such as schizophrenia or bipolar disorder due to their early-onset, chronicity and severity (Ferrari et al. 2016; Moreno-Kustner et al. 2018). Bipolar disorder often shows predominance of depressive symptoms, which makes it difficult for differentiation and therapy (Miller et al. 2014). Due to the above-mentioned epidemiological relevance of depressive disorders and the fact that this article could not solely cover every existing mental illness, only depression will be discussed in detail hereafter. Bipolar disorder and schizophrenia will be discussed in the context of psychiatric illnesses' biomarkers and in comparison to the biomarker studies in depression.

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The underlying biological mechanisms of depression and other affective disorders have been described from many perspectives, accounting for the role of stress (Young et al. 2016), inflammation (Brites and FeRNAndes 2015), genetic and environmental factors (Palazidou 2012), alterations in monoamine neurotransmission (Liu et al. 2017), neuroplasticity (Dean and Keshavan 2017). These data gave rise to the speculation that depression presents the dysregulations of these pathways (monoamine and glutamate neurotransmission, neuroinflammation, HPA axis and stress response, brain-derived neurotrophic factor—BDNF) that lead to neuroplasticity changes which disturb neurocircuitry involved in affect regulation which in turn shows up clinically as depressive symptoms (Dean and Keshavan 2017). Abundance in potential pathways has led to identification of dozens of biomarkers with various statistical significance: BDNF (Pinto et al. 2017), IL-6 and IL-1 (Carvalho et al. 2016), cortisol (Boiko et al. 2017), etc. (Carvalho et al. 2016). MiRNAs have shown promising results as potential biomarkers in various fields of medicine (Liu and Lu 2015), however, they are underinvestigated in depression (as well as in other psychiatric disorders), although different studies showed their importance in the central nervous system (Aksoy-Aksel et al. 2014; Wang et al. 2012) and that their levels are frequently altered in mental disorders and change during treatment (Kolshus et al. 2014; Liu et al. 2018).

MiRNAs are one of the most abundant subclasses of small non-coding RNAs with an average length of 19–24 nucleotides (Bartel 2004). Their main function is regulating post-transcriptional gene expression through (1) mRNA degradation, (2) inhibition of translation (Bartel 2004). MiRNAs in eukaryotes downregulate gene expression to keep the activity of various biological pathways at optimal level (Vasudevan 2012). Different studies demonstrated that each miRNA can regulate expression of more than one mRNA and even without full complementarity (Mohr and Mott 2015; Thomson et al. 2011). Neuronal miRNAs account for 70% of all miRNAs in our body and are involved in regulating neurogenesis and neuroplasticity (Nowak and Michlewski 2013). Many researchers suggest that miRNAs are transported throughout the body predominantly in the exosomes (Cheng et al. 2014; Soheli 2016; Tian et al. 2017). The exact miRNA profile of exosomes depends on exosomes' origin, suggesting tissue-specific miRNA biogenesis and selective sorting of miRNA (Abels and Breakefield 2016; Ha and Kim 2014; Winter et al. 2009). MiRNAs are considered as key functional element of exosomes which could influence cell in two ways: (1) negative regulation of gene expression (Zhang et al. 2015); (2) interaction with cell receptors as ligands (Fabbri et al. 2012). This with the fact of involvement in regulation of nearly every pathway in cell make miRNAs very promising biomarker for disease progression and treatment response.

Exosomes are derived from inward budding of endosomal membrane of the multi-vesicular bodies/endosomes (MVBs/MVEs) vesicles carrying lipids, proteins and nucleic acids that are secreted into the extracellular environment and could be taken up by other cells (van Niel et al. 2018). Exosomes are bilayer membrane extracellular vesicles (EVs) 30–150 nm in size with varying composition (Colombo et al. 2014). They are released by most types of cells and can be found in almost any biological fluid (blood, urine, cerebrospinal fluid, etc.) (Yanez-Mo et al. 2015). The exact composition of exosomes (tetraspanins, cytoskeletal proteins, transport and binding proteins, etc.) depends on many factors such as origin of cell, cellular release site, physiological or pathological state of the cell (Fiandaca et al. 2015; Yanez-Mo et al. 2015), and as a result defines the exact mechanism of exosome-cell interaction (van Niel et al. 2018). The most up-to-date information regarding proteins, lipids and RNAs in exosomes is available on <http://www.exocarta.org/>, <http://www.microvesicles.org/> and http://student4.postech.ac.kr/evpedia2_xe/xe/. Exosomes also play an important role in CNS physiology and pathology as they are a route of local and distant communication between neurons and glia, as well as cells of other organs and tissues (Janas et al. 2016; Von Bartheld and Altick 2011). Banigan et al. showed that schizophrenia and bipolar disorder have distinct exosomal miRNA content derived from post-mortem brain samples (Banigan et al. 2013; Choi et al. 2017). Proteins related to neuron-derived exosomes also showed potential diagnostic utility as blood biomarkers of MDD (Kuwano et al. 2018). All of this combined shows that exosomes and their cargo (especially miRNAs due to their pleiotropic regulation) are intriguing biomarker candidates potentially containing information of clinical importance as well as information elucidating transcriptional networks underlying mental disorders, which can be missed.

The most recent work regarding the role of exosomes in mental disorders by (Saeedi et al. 2019) gives a broad review of potential role of exosomes in mental disorders supporting our idea that exosomes have a huge potential as biomarkers due to their role in neurobiology and their ability to reflect physiological and pathological changes taking place in the brain. We, in turn, provide an overview of miRNAs in exosomes as potentially the most important cargo that is responsible for changes in normal CNS physiology. Initially, we intended to conduct meta-analysis of peripherally measured (serum, plasma, whole blood) miRNA levels in depression and compare them to the bipolar disorder and schizophrenia. However, our literature search revealed substantial discordance in the expression levels of candidate microRNAs among various studies that made conduction of meta-analysis impossible. Therefore, rather than conducting a meta-analysis of potential candidates, this report provides a qualitative summary of the current state of knowledge on

specific changes in miRNA profiles in depression, bipolar disorder and schizophrenia, assesses the potential for their use as biomarkers in clinical practice and provides the analysis of how exosomes can facilitate miRNA testing. We also provide information on potential or validated targets of analyzed miRNAs that were found either in the analyzed studies or in the additional literature.

Materials and Methods

For our report, we searched PubMed and Google Scholar databases for all published studies in English through October 1, 2018 using search terms “depression”, “bipolar disorder”, and “schizophrenia” together with their abbreviations and derivatives to include all articles examining miRNAs in relation to any form of depression schizophrenia or bipolar disorder. This search yielded in identifying 302 articles. Out of 302 articles 11 review articles (Alural et al. 2017; Dwivedi 2014; Fries et al. 2018; Geaghan and Cairns 2015; He et al. 2017; Kichukova et al. 2015; Maffioletti et al. 2014; Narahari et al. 2017; Sethi 2017; Sun and Shi 2015; Yuan et al. 2018) were manually searched for any additional relevant studies. Our search resulted in 35 studies that met our criteria: 19 for depression, 3 for bipolar-affective disorder, 11 for schizophrenia, 1 for bipolar and depression, 1 for depression, anxiety or stress and adjustment disorder. The most frequently used miRNA sources were whole blood and plasma (both 14 studies). Serum was chosen as a miRNA source in six studies. Only one study analyzed both blood and plasma levels of a miRNA. Inclusion criteria were: (1) human studies; (2) quantitative analysis of miRNA derived from blood, serum or plasma. Exclusion criteria were: (1) animal studies; (2) other meta-analyses without direct miRNA measurement; (3) peripheral blood mononuclear cell (PBMC) studies; (4) comorbid disorders. The references cited in the analyzed papers were manually searched for any additional relevant studies. Attempts were made to obtain more miRNA expression data from some authors of the selected studies; no additional information was received.

Results

Overall, 237 miRNAs were measured across 35 studies with 191 unique miRNAs. All miRNAs included were significantly differentially expressed either between patients and healthy control or before and after a particular intervention in the analyzed studies (Table 1). More specified information on the studies is provided in Supplementary materials. 30 miRNAs replicated in more than one study (Table 2). In Table 2 we additionally provided information on potential miRNA targets contributing to the development

of psychiatric disorder. Intercomparison between studies showed 61 only downregulated, 113 only upregulated and 17 both up- and downregulated miRNAs (Table 3). One miRNA was found differentially expressed in all three disorders, eight were found both in bipolar and depression, one—in bipolar and schizophrenia, and six—in depression and schizophrenia (Table 4). The most popular miRNA level measurement method was quantitative real time PCR (qRT-PCR). Four studies used NGS methods (Gallego et al. 2018; Ma et al. 2018; Wei et al. 2015; Zhang et al. 2018) but only two (Ma et al. 2018; Wei et al. 2015) of them used qRT-PCR as validation method. Only two studies (Gallego et al. 2018; Zhang et al. 2018) thus far measured exosomal miRNA in peripheral specimens.

Diverse study designs, miRNA isolation and quantification protocols have led to not entirely consistent results (see “Methodological Limitations” section below). This fact and inability to look thoroughly through expression data from all studies restricted the possibility of adequate intercomparison, and therefore, we analyzed and compared only readily available data provided in the articles’ texts, i.e., miR-17, miR-17-3p, miR-17-5p were considered three individual cases and therefore analyzed separately. This resulted in identification of 30 miRNAs that were replicated in more than one study (Table 2). More detailed information is available in Supplementary Materials, Tables 1 and 2.

Discussion

Most of the miRNA targets were directly or indirectly involved in different pathologic pathways in depression particularly regarding neuroplasticity and brain development (Table 2). Immune system, inflammation, metabolism of neuromediators, circadian rhythms, other signaling pathways (Wnt, endocytosis, etc.) were also targeted. Same pathway could be targeted by different miRNAs from different disorders as well as the same miRNA could be implicated in several disorders. All three disorders showed overlaps in miRNAs, targeted genes and pathways (Fig. 1 and Tables 2 and 4).

Most of the MDD-related miRNAs targeted pathways or genes related to the neuroplasticity and neurodevelopment (e.g., BDNF). Goldie et al. argued that exosomes with miRNAs are an important component in regulation of neuronal plasticity (Goldie et al. 2014). They proposed that neuronal exosomes facilitate control of synapses. The disruption of this complex mechanism could lead to inadequate control of synaptic plasticity with further suppression or even loss of signal transduction which could be observed in neuropsychiatric pathologies. This suggestion was based on finding of synaptic signal transduction deficit and over-abundance of

Table 1 Details on analyzed studies (extended version in Supplementary Materials)

Disorder	Source	Patients	Controls	Study design	Ref.
MDD (?)	Serum	84	78	DSM-IV depression criteria (no specifications); no antidepressant therapy for new or previous diagnosis of depression within 2 weeks prior to study; all patients were treated with paroxetine; miRNA levels measured at baseline and after 8 weeks of treatment	Kuang et al. (2018)
MDD (?)	Plasma	40	40	CCMD-3 criteria (no specifications); first-time diagnosed, drug-naïve	Li et al. (2013)
MDD (?)	Serum	39	36	DSM-IV depression criteria (no specifications)	Gheysarzadeh et al. (2018)
MDD (?)/anxiety or stress/adjustment disorder	Plasma	169	52	ICD-10 criteria (no specifications); the study compared miRNA levels in a mindfulness-based group therapy program with treatment as usual (mostly individual CBT). Patients received antidepressants (mostly SSRIs) and tranquilizers if necessary	Wang et al. (2015)
MDD (?)	Serum (exosomes)	1	1	No specifications on diagnostic criteria	Zhang et al. (2018)
MDD	Plasma	50	41	DSM-IV criteria; homogenous study group (no comorbid psychiatric or medical conditions; psychotic, melancholic, anxious, seasonal, and atypical subtypes and alcohol users were exclusion criteria)	Camkurt et al. (2015)
MDD	Blood	10	–	ICD-10 or DSM-IV criteria; 8 drug-naïve and 2 went off herbal treatment for at least 2 weeks prior the study; measurements at baseline (T0) and after 12 weeks of escitalopram treatment (T12)	Bocchio-Chiavetto et al. (2013)
MDD	Blood	11	11	No specifications (DSM-IV (?))	Issler et al. (2014)
MDD	Blood	32	18	DSM-IV criteria; all patients were drug-naïve and were treated with citalopram. MiRNA levels were measured at baseline and 8 weeks of treatment	Lopez et al. (2014)
MDD	Blood	18	18	ICD-10 or DSM-IV criteria	Li et al. (2015)
MDD	Plasma	5		DSM-IV-TR criteria of MDD and MDE; the study measured miRNA levels at baseline and 12 weeks after the escitalopram treatment	Enatescu et al. (2016)
MDD	Blood	62	73	DSM-IV criteria; drug-naïve patients	Liu et al. (2016)
MDD	Serum	18	17	DSM-IV criteria; patients were psychotropic drug-free for at least 1 month before blood sampling	Roy et al. (2017a, b)

Table 1 (continued)

Disorder	Source	Patients	Controls	Study design	Ref.
MDD	Blood/plasma	(1) 258; (2) 61; (3) 158	–	ICD-10/DSM-IV criteria; (1) Discovery cohort (MDD in a current MDE), Duloxetine and placebo groups, baseline and 8 weeks after treatment levels; (2) 1st validation cohort (MDE), Escitalopram and Nortriptyline, baseline and 8 weeks after treatment levels; (3) 2nd validation cohort (MDD), Escitalopram for 8 weeks, baseline and 8 weeks after treatment levels; miR-503-5p was significantly changed in responders and nonresponders in both placebo- and duloxetine-treated patients; all validated miRNAs could be biomarkers of antidepressant response	Lopez et al. (2017)
MDD	Blood	(1) 55; (2) 124.	(1) 174; (2) –	No specifications on diagnostic criteria; miRNA levels were measured at baseline and 8 weeks after treatment in both cohorts; 1st cohort: 27 were treated with escitalopram (SSRI) and 28 with desvenlafaxine (SNRI). Later they were subdivided in 31 responders (15—escitalopram, 16—desvenlafaxine) and 24 nonresponders (12—escitalopram, 12—desvenlafaxine); 2nd cohort: all treated with duloxetine (SNRI), 97 responders and 27 nonresponders	Fiori et al. (2017)
MDD	Plasma	77	32	DSM-IV criteria	Fang et al. (2018)
MDD	Blood	30	30	Details of inclusion and exclusion criteria were not specified	Su et al. (2015)
MDD	Serum	(1) 6; (2) 32	(1) 6; (2) 21	ICD-10 or DSM-IV criteria; all patients were antidepressant-free; 2 cohort study (discovery and validation): 1st cohort 6 vs. 6 (CSF and serum); 2nd cohort 32 vs. 21 (serum only)	Wan et al. (2015)
MDD	Blood	40	20	Treatment-resistant depression; 24 patients received ECT and 16 patients received KET; details of MDD criteria were not specified	Gururajan et al. (2016)
MDD	Plasma	(1) 123; (2) 259	(1) 55; (2) 238	DSM-IV criteria; 2nd cohort was the expansion of the first one; all the pathologies had dysregulation of NET	Marques et al. (2017)
BD type 1 and 2, MDD	Blood	40 (20 MDD and 20 BD)	20	BD and MD patients had current major depressive episode (DSM-IV-TR criteria)	Maffioletti et al. (2016)
BD type 1	Blood	34	46	Relatives of patients with BD type 1 (first or second-degree relatives; no personal history of BD; high-risk); affected relatives were diagnosed with SCID	Walker et al. (2015)
BD type 1	Blood	10	–	DSM-5, manic phase, drug-free, treated with two different antipsychotics (both groups received valproate as a mood stabilizer); baseline levels and after 1, 4, and 12 weeks	Lim et al. (2016)

Table 1 (continued)

Disorder	Source	Patients	Controls	Study design	Ref.
BD	Plasma	21	21	BD type I, manic phase (DSM-IV), drug-free, antipsychotic and mood stabilizer combination	Rong et al. (2011)
SCZ	Blood	16	16	DSM-IV-TR criteria; all patients were in active psychotic episode. Three patients were drug-naïve and had first episode, and 13 patients were previously on atypical antipsychotic treatment	Camkurt et al. (2016)
SCZ	Blood	44	44	DSM-IV criteria; all patients were first-onset	Ma et al. (2018)
SCZ	Plasma	40	–	The patients were all treated with risperidone and achieved remission in 1 year. No specifications on diagnosis of schizophrenia.	Liu et al. (2013)
SCZ	Plasma	61	62	DSM-IV schizophrenia criteria; Patients were either drug-naïve or absent of psychotropic medication within at least 3 months. 25 patients received a 6-week atypical antipsychotic treatment (miRNA levels were evaluated before medication, and 3 and 6 weeks after); olanzapine had the strongest effect on plasma miRNA level changes; 10 miRNAs were selected according to the latest information in PubMed database, Springer database and the University of British Columbia library database	Sun et al. (2015a, b)
SCZ	Plasma	25	13	DSM-IV criteria, all patients were selected prior to any antipsychotic treatment, or in the absence of treatment for at least 3 months prior to the study; 9 miRNAs were selected according to the latest information in PubMed database, Springer database and the University of British Columbia library database	Sun et al. (2015a, b)
SCZ	Plasma	37	10	DSM-IV criteria	Alacam et al. (2016)
SCZ	Serum	115	40	Paranoid and undifferentiated schizophrenia (ICD-10). Patients were classified into schizophrenia subtypes, with family history or not. All the patients were treated. 9 miRNAs were chosen according to the literature, Schizophrenia Gene database, and NCBI database	Shi et al. (2012)
SCZ	Plasma	20	20	DSM-IV criteria; Before and after treatment evaluation (4 groups of 5 patients in each); all patients were treated with atypical antipsychotics; 9 miRNAs were selected according to the latest information in PubMed database, Springer database and the University of British Columbia library database	(Song et al. (2014)

Table 1 (continued)

Disorder	Source	Patients	Controls	Study design	Ref.
SCZ	Plasma	726	–	DSM-IV criteria; all participants were divided into two cohorts: (1) test cohort (164 with schizophrenia and 187 controls); (2) validation cohort (400 with schizophrenia, 213 controls, and 162 with nonschizophrenia disorders). 107 patients from validation cohort reached study endpoint, which was 12 months of treatment with atypical antipsychotics (risperidone and aripiprazole)	Wei et al. (2015)
SCZ	Blood	44	44	DSM-IV criteria; all patients were drug-naïve.	Wu et al. (2016)
SSD	Plasma (EVs)	22	17	Patients: 16 (72.7%) had schizophrenia, 5 (22.7%) had schizoaffective disorder and 1 (4.5%) had psychosis not otherwise specified: details or specifications regarding diagnostic criteria were not specified	Gallego et al. (2018)

? means that there are no clear specifications on whether MDD diagnosis was established

SCZ schizophrenia, SSD schizophrenia spectrum disorder, BD bipolar disorder, MDE major depressive episode, MDD major depressive disorder, SCID structured clinical interview for DSM-IV, DSM-IV diagnostic and statistical manual of mental disorders, Fourth edition, DSM-IV-TR diagnostic and statistical manual of mental disorders, Fourth edition, Text revision, CCMD-3 Chinese classification of mental disorders, DSM-5 diagnostic and statistical manual of mental disorders, Fifth edition, ICD-10 international statistical classification of diseases and related health problems 10th revision, CSF cerebrospinal fluid, NET norepinephrine transporter, ECT electroconvulsive therapy, KET ketamine, CBT cognitive behavioral therapy, SSRI selective serotonin reuptake inhibitors, SNRI serotonin–norepinephrine reuptake inhibitors, EVs extracellular vesicles

cortical miRNAs in patients with schizophrenia (Beveridge et al. 2010; Santarelli et al. 2011). MiRNAs in astrocyte-derived exosomes and microglia-derived EVs (exosomes and MVs) were shown to be potential regulators of neuroplasticity (Lafourcade et al. 2016; Prada et al. 2018).

Other popular targets were related to glutamatergic system (GRM4, SLC17A7). Alterations in it contribute to development of neuropsychiatric disorders (Niciu et al. 2012) particularly GRM4 to depression risk (Dadkhah et al. 2017). Serotonergic system was also targeted by miRNAs (SERT, 5HT1A, 5HT1D). MiRNAs regulating different signaling pathways associated with depression (MAPK and Wnt signaling) were consistently altered. Interestingly, the same miRNAs were altered in BD. To a lesser extent, components of immune system and circadian rhythm were targets of miRNAs although disruption in circadian clock can contribute to the development of psychiatric disorders (Karatsoreos 2014). MDD shared similarities with schizophrenia in same miRNAs targeting BDNF, signaling pathways, glutamatergic system and ATXN1. Although ATXN1 showed to be implicated in all disorders (Liu and Su 2018), miRNAs regulating this gene were altered only in MDD and schizophrenia. There were also miRNAs that were altered only in depression (miR-451a, miR-1202, miR-135a, miR-425-3p, miR-34a-5p, miR-335, miR-26a, miR-24-3p, miR-221-3p,

miR-182, let-7d), but one miRNA (miR-451a) showed discordance in expression levels (Camkurt et al. 2015; Kuang et al. 2018; Wan et al. 2015). This could be due to different sources of miRNA (downregulation was observed in serum in contrast to upregulation in plasma) or due to different approach in sampling (pointed out by Camkurt et al. 2015).

Our analysis showed that there are miRNAs exclusively altered in schizophrenia (miR-30e, miR-7, miR-195, miR-34a, and miR-346). They control neuron survival, neuroinflammation, components of glutamatergic system and various psychiatry-related genes. However, schizophrenia showed overlaps with two other disorders.

Therefore, MDD shows similarities predominantly with BD in pathways related to Wnt and MAPK signaling, axon guidance, endocytosis, BDNF, regulation of immune system, synaptic plasticity, circadian rhythm, hippocampal neurogenesis and also in targets associated with BD, schizophrenia and schizoaffective disorder (GABA receptor subunits, 5-HT1D, DISC1 and Reelin signaling). MDD shared pathways and targets with schizophrenia in Wnt/ β -catenin, cancer, endocytosis, MAPK, PTEN signaling pathways, calcium-sensor proteins (VSNL1), BDNF, HTR2A, glutamate signaling (SLC38A2, GRM7, GRIA2), neurodevelopment-related genes (RUNX3, ITGB1, FMR1, STAT3) and schizophrenia susceptibility genes (PDGFRA, PPARG). Different

Table 2 Frequently assessed miRNAs and their potential targets and mechanisms in psychiatric disorder pathogenesis (extended version is available in Supplementary Materials)

miRNA	Number of studies	Disorder	Source	Expression	Potential target/mechanism	Target ref.
miR-132	8	BD type 1	Blood	↑	BDNF; inflammation, immune functions	Wanet et al. (2012), Yuan et al. (2018)
		SCZ	Plasma	↓		
		SCZ	Plasma	↑		
		MDD	Plasma	↑		
		MDD	Blood	↑		
		MDD	Plasma	↑		
		MDD	Blood	↑		
		MDD	Blood	↑		
miR-181b	4	SCZ	Serum	↑	VSNL1, GRIA2; Signaling pathways: Wnt/ β -catenin, cancer, endocytosis, MAPK	Beveridge et al. (2008), Enatescu et al. (2016)
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		MDD	Plasma	↓		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
miR-30e	3	SCZ	Plasma	↑	Neuronal survival, neuroinflammation; Signaling pathways: Wnt/ β -catenin, Axon guidance, IGF1, NGF	Labouesse et al. (2018), Li et al. (2018a, b), Lu et al. (2017), Wang et al. (2013)
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
miR-7	3	SCZ	Plasma	↑	SHANK3, targets interacting with SHANK3 in actin-regulatory pathway. Neuroprotection; inflammation; PTEN pathway; neurite outgrowth, synapse formation, brain development	Chakrabarti et al. (2016), Choib et al. (2015), Garbett et al. (2015), Prata et al. (2017)
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
		SCZ	Plasma	↑		
miR-451a	3	MDD	Plasma	↑	SLC17A7	Our target prediction.
		MDD	Serum	↓		
		MDD	Serum	↓		
		SCZ	Serum	↓		
		SCZ	Plasma	↓		
		SCZ	Plasma	↑		
		BD type 1	Blood	↓		
		MDD	Plasma	↓		
miR-195	3	SCZ	Serum	↓	BDNF, RELN, VSNL1, HTR2A, HTR4, GPRIN3	Beveridge et al. (2010), Butler et al. (2016), Guo et al. (2010)
		SCZ	Plasma	↓		
		SCZ	Plasma	↑		
		BD type 1	Blood	↓		
		MDD	Plasma	↓		
		MDD	Blood/plasma	↓		
		MDD	Blood/plasma	↓		
		MDD	Blood/plasma	↓		
miR-146b-5p	3	BD type 1	Blood	↓	Signaling pathways (MAPK and Wnt), BDNF	Enatescu et al. (2016), Hsu et al. (2015), Lopez et al. (2017)
		MDD	Plasma	↓		
		MDD	Blood/plasma	↓		
		MDD	Blood/plasma	↓		
		MDD	Blood/plasma	↓		
		MDD	Blood/plasma	↓		
		MDD	Blood/plasma	↓		
		MDD	Blood/plasma	↓		
miR-1202	3	MDD	Blood	↓	GRM4	Fiori et al. (2017)
		MDD	Blood	↓		
		MDD	Serum	↓		
		MDD	Blood	↓		
		MDD	Serum	↓		
		MDD	Blood	↓		
		MDD	Blood	↓		
		MDD	Serum	↓		
miR-135a	3	MDD	Blood	↓	SERT, HTR1A, Cplx1, Cplx2	Issler et al. (2014), Mammironi et al. (2018)
		MDD	Blood	↓		
		MDD	Serum	↓		
		MDD	Blood	↓		
		MDD	Blood	↓		
		MDD	Blood	↓		
		MDD	Blood	↓		
		MDD	Serum	↓		

(1) ↓ in both placebo and duloxetine-treated patients;
(2) ↓ only in response group;
(3) ↓ only in response group.

Table 2 (continued)

MiRNA	Number of studies	Disorder	Source	Expression	Potential target/mechanism	Target ref.
miR-652	2	BD type 1 MDD	Blood Plasma	↑ ↓	Signaling pathways (Wnt, axon guidance, and endocytosis); pathways and targets associated with BD, schizophrenia and schizoaffective disorder (GABA receptor subunits, 5-HT1D, DISC1 and Reelin signaling); immune system and oxidative stress pathways	Enatescu et al. (2016), Hsu et al. (2015), Liguori et al. (2018), Walker et al. (2015)
miR-425-3p	2	MDD	Blood	↑	MAPK/Wnt signaling pathways	Lopez et al. (2017)
		MDD	Blood/plasma	(1) ↓ in both placebo and duloxetine-treated patients; (2) ↓ only in response group;		
miR-375	2	MDD	Plasma	↑	BDNF	Wan et al. (2015)
		SSD	Plasma (EYs)	↑		
miR-34a-5p	2	MDD	Serum	↑	BDNF, SHANK3 and potentially other targets interacting with SHANK3 in actin-regulatory pathway	Bavamian et al. (2015), Choi et al. (2015), Dwivedi, (2011), Wan et al. (2015)
		MDD	Serum	↑		
miR-34a	2	SCZ	Plasma	↑	BDNF, SHANK3 and potentially other targets interacting with Shank3 in actin-regulatory pathway.	Bavamian et al. (2015), Choi et al. (2015), Dwivedi, (2011), Wan et al. (2015)
		SCZ	Plasma	↑		
miR-346	2	SCZ	Serum	↑	GRID1, circadian rhythm	Bavamian et al. (2015), Figueredo et al. (2013)
		SCZ	Plasma	↑		
miR-335	2	MDD	Blood	↑	GRM4, synaptic plasticity	Capitano et al. (2017), Li et al. (2015)
		MDD	Blood	↓		
miR-26a	2	MDD	Blood	↑	BDNF, signaling pathways (Wnt signaling, Cancer, Endocytosis, Axon guidance and MAPK signaling)	Caputo et al. (2011), Enatescu et al. (2016)
		MDD	Plasma	↓		
miR-24-3p	2	MDD	Blood	↑	SERT, Wnt signaling, Cancer, Endocytosis, Axon guidance, MAPK signaling.	Enatescu et al. (2016), Liao et al. (2016), Lopez et al. (2017)
		MDD	Blood/plasma	(1) ↓ in placebo and duloxetine-treated patients; (2) ↓ only in response group; (3) ↓ only in response group.		
miR-221-3p	2	MDD	Serum	↑	Gja1 (Cnx43)	Shen et al. (2018)
		MDD	Serum	↑		
miR-182	2	MDD	Plasma	↑	BDNF, circadian rhythms	Li et al. (2016a, b), Li et al. (2013), Saus et al. (2010)
		MDD	Blood	↑		
miR-17-5p	2	BD type 1 MDD	Blood Plasma	↑ ↑	CREB1, CHRM2, NTRK3, NPAS3, immune system, circadian rhythm, hippocampal neurogenesis	Chen et al. (2018), Cox et al. (2010), Gao et al. (2016), Jin et al. (2016), Roy et al. (2017a, b), Wong et al. (2013)
miR-144-5p	2	MDD/Anxiety or stress/ Adjustment disorder SSD	Plasma Plasma (EYs)	↓ ↑	PKC, Wnt/β-catenin, PTEN pathways, ATXN1	Dwivedi (2014), Liu and Su (2018)

Table 2 (continued)

miRNA	Number of studies	Disorder	Source	Expression	Potential target/mechanism	Target ref.
miR-140-3p	2	BD type 1 & 2 MDD	Blood Blood	↑ ↑	Synaptic plasticity, immune system	Cirigliano et al. (2017)
miR-130b	2	SCZ MDD	Plasma Blood	↑ ↑	Schizophrenia susceptibility genes (PDGFRA, PPARG), neurodevelopment-related genes (RUNX3, ITGB1, FMRI, STAT3), PTEN, Wnt/β-catenin pathways	Gu et al. (2018), Li et al. (2016a, b), Wei et al. (2015)
miR-106b-5p	2	BD type 1 SCZ	Blood Blood	↑ ↑	Neurogenesis, PTEN, Wnt/β-catenin	Brett et al. (2011), Li et al. (2017), Lu et al. (2017)
let-7g	2	SCZ	Serum	↑	Glutamate signaling (SLC38A2, GRM7)	Roy et al. (2017a, b)
let-7d	2	MDD MDD MDD	Blood Blood Plasma	↑ ↑ ↓	Dopamine metabolism, synapse maturation, growth, and dendritic arborization, neurogenesis, Wnt, cancer, MAPK signaling, endocytosis, actin cytoskeleton pathways	Chandrasekar and Dreyer (2011), Enatescu et al. (2016), Mendes-Silva et al. (2016), Wu et al. (2015), Zhao et al. (2013)
miR-210-3p	2	MDD	Serum (exosomes)	↓	Target miRNA gene (BNIP3) involved in cell death/survival, autophagy, antistress reaction factor, depression, potential role in maintenance and/or reformation of synapses; angiogenesis and neurogenesis in brain tissue repair and remodeling after brain injury	Ivan et al. (2014), Tohda et al. (2010), Zeng et al. (2014)
miR-16	2	MDD MDD	Whole blood Serum	↑ ↓	Regulates SERT via raphe nuclei and hippocampal responses to antidepressants; regulation of apoptosis and autophagy	Bai et al. (2012), Shao et al. (2018), Yang et al. (2017)
miR-195-5p	2	MDD Schizophrenia	Serum (exosomes) Plasma	↑	HTR2A, BDNF; DRD1 ^a , GRIA3 ^a , VEGFA ^a , FASN ^a , APP ^a , GSK3B ^a	Alacam et al. (2016), Beveridge et al. (2010), Zhang et al. (2018)

SCZ schizophrenia, SSD schizophrenia spectrum disorder, BD bipolar disorder, MDD major depressive disorder, EYs extracellular vesicles, BDNF brain-derived neurotrophic factor, MAOA monoamine oxidase A, SLC6A3 solute carrier family 6 member 3, CLOCK clock circadian regulator, GRM3 glutamate metabotropic receptor 3, SYN2 synapsin II, VSNLI visinin like 1 protein, GRIA2 glutamate ionotropic receptor AMPA type subunit 2, MAPK mitogen-activated protein kinase, SHANK3 SH3 and multiple ankyrin repeat domains 3, SLC17A7 solute carrier family 17 member 7, RELN reelin, HTR2A 5-hydroxytryptamine receptor 2A, HTR4 5-hydroxytryptamine receptor 4, GPRIN3 GPRIN family member 3, GRM4 glutamate metabotropic receptor 4, SERT serotonin transporter, 5-HT1a 5-hydroxytryptamine receptor 1A, 5-HT1D 5-hydroxytryptamine receptor 1D, GRIDI1 glutamate ionotropic receptor delta type subunit 1, CREB1 cAMP responsive element binding protein 1, CHRM2 cholinergic receptor muscarinic 2, NTRK3 neurotrophic receptor tyrosine kinase 3, NPAS3 neuronal PAS domain protein 3, PKC protein kinase C, PTEN phosphatase and tensin homolog, ATXN1 ataxin 1, PDGFRA platelet derived growth factor receptor alpha, PPARG peroxisome proliferator activated receptor gamma, RUNX3 runt related transcription factor 3, ITGB1 integrin subunit beta 1, FMRI fragile X mental retardation 1, STAT3 signal transducer and activator of transcription 3, SLC38A2 solute carrier family 38 member 2, GRM7 glutamate metabotropic receptor 7, IGF1 insulin growth factor 1, NGF nerve growth factor, Cplx1 complexin-1, Cplx2 complexin-2, DISC1 DISC1 scaffold protein, Gjal (Cnx43) gap junction protein, alpha 1 (connexin 43), BNIP3 BCL2/adenovirus E1B 19 kDa protein-interacting protein 3, DRD1 dopamine receptor D1, GRIA3 glutamate ionotropic receptor AMPA type subunit 3, VEGFA vascular endothelial growth factor A, FASN fatty acid synthase, APP amyloid beta precursor protein, GSK3B glycogen synthase kinase 3 beta

^aWe have not found evidences of these miRNA targets in provided references in Zhang et al. (2018)

miRNAs were altered in different disorders and regulated different targets nevertheless they were involved in the same pathways shared between all three disorders. The overlap between all three disorders was shown in miR-652: although, it was altered only in BD and MDD studies, it regulates pathways and targets associated with BD, schizophrenia and schizoaffective disorder (Walker et al. 2015).

We acquired interesting results regarding miR-34a and miR-34a-5p. These miRNAs showed similar behavior in two different disorders: it was upregulated compared to controls in two schizophrenia studies (Song et al. 2014; Sun et al. 2015a, b) and showed tendency to downregulation after treatment (Song et al. 2014) and the same was shown for depression (Kuang et al. 2018; Wan et al. 2015) [but with significant downregulation after treatment (Kuang et al. 2018)]. Although the results are promising there is a difference between these groups: in depression studies the mature product of miRNA was measured (miR-34a-5p) but not in schizophrenia studies (miR-34).

MiR-132 is the most replicated miRNA (8 studies) but showed varied expression. This data is consistent with the results of Yuan et al. (2018). They explain such reproducibility due to miR-132 regulation of BDNF via methyl CpG-binding protein 2 (MECP2) gene (Su et al. 2015). BDNF is essential for neuronal growth and survival (Tapia-Arancibia et al. 2004). However, we need to mention that proposed explanation for the role of miR-132/BDNF interaction in MDD is very hazy. MiR-132 has been shown to be involved in regulating many genes and processes (Liu et al. 2015; Salta and De Strooper 2017; Wang and Liang 2015). On our side, we analyzed miR-132 targets using online databases for miRNA targets miRDB (<http://mirdb.org/>) and genes affiliated with all three disorders using the MalaCards human disease database (<http://www.malacards.org/>). The analysis showed that at least two genes (MAO A and SLC6A3) are targets of miR-132 and associated with all three disorders. This was also true for other genes (CLOCK in depression and BD; GRM3 and SYN2 in schizophrenia and BD).

Therefore, various potential targets of different miRNAs (including our results) should be very carefully interpreted as most of these targets have not been validated via four step protocol involving (1) *in silico* target prediction; (2) miRNA–target interaction screening; (3) verification of direct interaction (4) *in vivo* gene expression measurement (Varendi et al. 2015). Thus, there is a chance that some miRNA interactions could be false positive. Most notably is that Varendi et al. showed controversies in miRNA-BDNF (including miR-26a, miR-132, miR-182 and miR-195) relationships which makes us cautious in our conclusions.

There are also problems regarding BDNF itself. Several studies have shown that difference in BDNF peripheral levels exist between depressed compared to healthy and that

BDNF levels change after treatment with antidepressants (Jiang et al. 2017; Molendijk et al. 2014; Polyakova et al. 2015). However, most of BDNF studies have methodologic flaws and BDNF plasma levels alterations were found in other psychiatric disorders as well (FeRNAndes et al. 2015a, b; Molendijk et al. 2012; Polyakova et al. 2015; Suliman et al. 2013) as well as in other diseases (Pichler et al. 2017; Salta and De Strooper 2017; Walker et al. 2015; Weber et al. 2017; Yu et al. 2015). Table 2 contains information regarding other replicated miRNAs and their targets.

The only study provided information regarding exosomal miRNAs was (Zhang et al. 2018).

Methodological Limitations

Recent data warns us that currently available techniques and protocols are unable to precisely differentiate between sub-populations of exosomes, and therefore, we are unable to say what is responsible for any given effect (van Niel et al. 2018; Willms et al. 2016). The purity of exosome pellet directly affects the number of false-positive results in functional analyses (van Niel et al. 2018). There is also a lot to clarify in miRNA-EVs (including exosomes) relationships: (a) whether response in a cell is mediated by induction of endogenous miRNA expression or by the miRNA brought by EVs; (b) how EVs unload their RNA cargo inside the cell; (c) in what form miRNAs are delivered; (d) whether all the EVs contain miRNAs or particular sub-population; etc. (for more information about EVs-RNA relationship look up at (Chevillet et al. 2014; Mateescu et al. 2017, Tkach and Thery 2016 and references therein).

There is a problem regarding exosome identification as previously considered “exosome markers” are present in all types of extracellular vesicles which opens up a discussion about validity of different findings in ‘exosomes’ (Kowal et al. 2016). Therefore, we should consider using guidelines proposed by Kowal et al. as well as the recommendations of International Society for Extracellular Vesicles (ISEV) for precise interpretation of data regarding biology of exosomes (Clayton et al. 2018; Kowal et al. 2016; Mateescu et al. 2017).

Another confusion in miRNA-EV relationship is that miRNAs could be transported by other means (Miller and Raison 2016; Scott 2017; Vickers et al. 2011, Zhang et al. 2015). This in couple with the fact that low-density lipoproteins mimic exosomes (Sodar et al. 2016) is a serious obstacle in isolating pure exosomes and important miRNAs could potentially be missed. Tosar et al. also showed that miRNAs represent a minor fraction of RNAs inside different EVs (including exosomes) (Tosar et al. 2015), and different other types of nucleic acids were identified inside exosomes: mRNA, rRNA, tRNA, DNA, etc., (Lazaro-Ibanez et al. 2014; Li et al. 2014; Tamkovich et al. 2016). These conflicting

Table 3 Different expression levels of miRNAs in analyzed studies

Expression	Up and down	Down	Up
miRNAs	miR-195	miR-134	miR-720
	miR-132	miR-1915-5p	miR-125b-3p
	miR-335	miR-1972	miR-2278
	miR-451a	miR-4793-3p	miR-3150a-3p
	miR-144-5p	miR-4440	miR-137
	miR-181b	miR-1915-3p	miR-22-3p
	miR-26a	let-7a-5p	miR-92a-3p
	let-7d	let-7d-5p	miR-937
	miR-652	let-7f-5p	miR-676*
	miR-24-3p	miR-92b-5p	miR-489
	miR-425-3p	miR-1343-5p	miR-637
	miR-210-3p	miR-664b-5p	miR-608
	miR-16	miR-6778-5p	miR-4263
	miR-135a	miR-146b-5p	miR-382
	miR-195-5p*	miR-17	miR-199a-5p
	miR-181b-5p*	miR-365	miR-664
	miR-301a-3p*	miR-520c-3p	miR-494
		miR-432	miR-29c-5p
		miR-770-5p	miR-494
		miR-34c-5p	miR-29c-5p
		miR-1202	miR-330-3p
		miR-320a	let-7e
		miR-583	miR-375
		miR-650	miR-433
		miR-708	miR-1298
		miR-654	miR-1909
		miR-151-5p	miR-1471
		miR-99b	miR-124-3p
		miR-223	miR-204-5p
		miR-744	miR-942-5p
		miR-301b	miR-6734-5p
		miR-27a	miR-423-5p
		miR-24	miR-124
		miR-146a	miR-1255a
		miR-126	miR-3161
		miR-151-3p	miR-183
		miR-221	miR-106a-5p
		miR-125a-5p	miR-20a-5p
		let-7b	miR-574-3p
		let-7c	miR-361-5p
			miR-223-3p
			miR-1308
			let-7g
			miR-644
			miR-450b
			miR-328
			miR-328
			miR-221-3p
			miR-664a-3p
			let-7c-5p
			miR-92a
			miR-34a-5p
			let-7d-3p
			miR-197-3p
			miR-30e
			miR-34a
			miR-1193
			miR-7
			miR-3173-3p
			miR-130b
			miR-3154
			miR-193a-3p
			miR-129-5p
			miR-9-5p
			miR-3661
			miR-29a-3p
			miR-1287
			miR-125a-3p
			miR-532-3p
Total	17	61	113

*Differentially expressed in one study

data shows that our emphasis on miRNAs as principal gene expression regulators is speculative and oversimplification at this time due to a huge number of various non-coding RNAs (ncRNAs) such as PIWI-interacting RNAs (piRNAs), small nucleolar ncRNAs, transcribed ultraconserved

region (T-UCRs), and large intergenic ncRNAs which are also involved in regulating cellular pathways (Hombach and Kretz 2016). As we also mentioned before, potential targets of different miRNA (including our results) should be validated which can help understand what particular pathways

Table 4 Overlaps in miRNAs between disorders

Disorders	BD and MDD and SCZ	BD and MDD	BD and SCZ	MDD and SCZ	BD	MDD			SCZ
miRNAs	miR-132	miR-140-3p miR-146b-5p miR-17-5p miR-210-3p miR-29c-5p miR-330-3p miR-345-5p miR-652	miR-106b-5p	miR-195-5p miR-181b miR-144-5p let-7g miR-130b miR-375	miR-134 miR-720 miR-1973 miR-3158-3p miR-4521 miR-330-5p miR-378a-5p miR-30d-5p miR-21-3p miR-1915-5p miR-1972 miR-4793-3p miR-4440 miR-15b miR-18a-5p miR-19b-3p miR-145-5p miR-27a-3p miR-148b-3p miR-17-3p miR-30b-5p miR-339-5p miR-106a-5p miR-20a-5p miR-15a-5p miR-92b-5p miR-1343-5p miR-664b-5p miR-6778-5p	miR-1915-3p let-7a-5p let-7d-5p let-7f-5p miR-24-3p miR-425-3p miR-199a-5p miR-182 miR-770-5p miR-34c-5p miR-505 miR-29b-2 miR-26b miR-22 miR-26a miR-664 miR-494 let-7d let-7e let-7f miR-629 miR-106b miR-103 miR-191 miR-128 miR-502-3p miR-374b miR-30d miR-500 miR-589 miR-183 miR-574-3p miR-335 miR-361-5p miR-135a miR-1202 miR-320a miR-451a miR-223-3p miR-583	miR-650 miR-708 miR-654 miR-644 miR-450b miR-328 miR-221-3p miR-34a-5p let-7d-3p miR-1193 miR-3173-3p miR-3154 miR-129-5p miR-3661 miR-1287 miR-532-3p miR-2278 miR-3150a-3p miR-3909 miR-937 miR-676* miR-489 miR-637 miR-608 miR-4263 miR-382 miR-3691-5p miR-433 miR-1298 miR-1909 miR-1471 miR-151-5p miR-99b miR-223 miR-744 miR-301b miR-27a miR-24 miR-146a miR-126	miR-151-3p miR-221 miR-125a-5p let-7b let-7c miR-19a-3p miR-124-3p miR-146a-5p miR-3074-5p miR-16 miR-124 miR-1255a miR-3161 miR-99a-3p miR-205-5p miR-26a-1-3p miR-139-5p miR-7849-3p miR-125b-2-3p miR-664a-3p let-7c-5p miR-197-3p miR-499a-5p miR-4732-3p miR-222-5p miR-1291 miR-668-3p miR-6511a-3p miR-145-3p miR-200a-3p miR-143-3p miR-196b-5p miR-99a-5p miR-144-3p miR-584-5p miR-183-5p miR-107 miR-130b-5p miR-589-5p miR-1910-5p	miR-1308 miR-219-2-3p miR-346 miR-92a miR-195 miR-17 miR-30e miR-34a miR-7 miR-193a-3p miR-9-5p miR-29a-3p miR-125a-3p miR-125b-3p miR-92a-3p miR-365 miR-520c-3p miR-432 miR-204-5p miR-942-5p miR-6734-5p miR-423-5p miR-181b-5p miR-301a-3p
Total	1	8	1	6	29			120	27

BD bipolar disorder, *MDD* major depressive disorder, *SCZ* schizophrenia

are altered and how they correlate with clinical symptoms. Nevertheless, ncRNAs fall outside the scope of this study although this controversy should be clarified acknowledged and clarified in future studies.

There are different issues in miRNA studies in psychiatry that does not allow making unambiguous conclusions: (1)

small proportion of analyzed miRNAs, significant miRNAs could potentially be missed; (2) possible influence of previous psychotropic drug intake; (3) inability to tell whether peripheral miRNAs reflect changes in the brain or peripheral miRNA mediate changes within the brain (Maffioletti et al. 2016; Wan et al. 2015); (4) different quantification

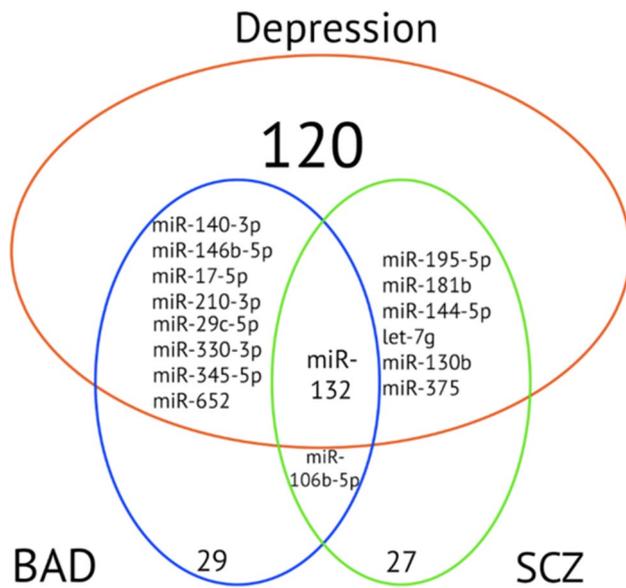


Fig. 1 Overlaps between disorders in miRNAs replicated in more than one study. *BD* bipolar disorder, *MDD* major depressive disorder, *SCZ* schizophrenia

techniques' limitations; (5) small and heterogeneous sample sizes (Yuan et al. 2018); (6) lack of studies comparing psychiatric disorders; (7) potential contamination with blood cells' miRNAs when analyzing whole blood samples; (8) lack of genome-wide screening studies (Cairns 2015); (9) different clinical scales (Yuan et al. 2018); (10) lack of measurement of individual mature miRNA sequences.

As we mentioned earlier, chronic stress and subsequent HPA-axis upregulation contribute to the development of mental disorders and as it was shown miRNAs are frequently altered during stress conditions and potentially could be one of the molecules leading to the disease progression (Issler and Chen 2015; Luoni and Riva 2016; Zucchi et al. 2013). Although other factors (nicotine, alcohol, illicit drugs, etc.) were shown to alter miRNA expression (Kaur et al. 2012), information regarding association and psychiatric disorders is insufficient. This is an important area that requires further research.

Another obstacle in identifying psychiatry-specific miRNAs is comorbidity of somatic disorders and psychiatric disorders: MDD and ovarian cancer (Wu et al. 2018), schizophrenia and cancer (Rizos et al. 2015), etc. (Dieset et al. 2016) Although, data regarding comorbidity is inconsistent (Chou et al. 2016) and further researchers are indicated. Such comorbidity partially could be explained by pleiotropic action of miRNAs. Nevertheless, this does not mean that these diseases with 100% confidence could mimic depression in lab results of miRNAs analysis as it was performed on different specimens as well as miRNAs showed different patterns of expressions. That brings us to the idea that

combination of miRNAs with structured clinical interviews could be more accurate compared to both methods used separately.

Analysis of miRNAs has its own difficulties (discordance between different techniques, dependence on sample collection and RNA extraction methods, etc.) (Gustafson et al. 2016; Tam et al. 2014; Zampetaki and Mayr 2012). Most of studies we analyzed used qRT-PCR as the main miRNA quantification method. This technique is cost-effective, has high sensitivity and specificity but unable to detect novel miRNAs and dependent on reference molecules for data normalization. To our knowledge only one study identified reference genes for qPCR analysis in neuropsychiatric disorders thus far (Liu et al. 2014). The problem of identifying novel miRNAs using qRT-PCR has resulted in very few researchers using large-scale panels in favor of small set of mostly already validated miRNAs. This could be due to the fact that despite the larger amount of post-mortem brain miRNA studies the transition of the results to peripheral specimens is troublesome because of the commonly observed inconsistency between brain-periphery expression levels of miRNA (Sun et al. 2015a, b). This statement is indirectly supported by the fact that miRNAs from CSF poorly correlated with the miRNA from plasma/serum (Gallego et al. 2018; Wan et al. 2015). There is even discordance between different peripheral specimens (plasma vs. PBMC) (Sun et al. 2015a, b).

Marco et al. in their article have shown that different mature products from the same precursor miRNA have different targeting properties and differs in their function (Marco et al. 2012). This could have a very important meaning in fundamental understanding miRNAs' role in psychiatric disorders and therefore individual mature sequences should be identified and validated before considering any miRNA as a biomarker. All of the above together with our data showing that only 191 unique miRNAs were analyzed in 35 study leads us to consider using more sophisticated technologies like Next Generation Sequencing (NGS) in identifying both novel and already known circulating miRNAs, although, it has its own limitations which should be acknowledged.

Psychiatry has its own problems due to the body of interest: the heterogeneity of presented symptoms of individual disorder as well as huge overlap in both symptoms and underlying biology between different disorders (Doherty and Owen 2014) as we mentioned. This lead to developing of Research Domain Criteria (RDoC) project by National Institute of Mental Health in order for more adequate representation of different behavioral traits presented in psychiatric disorders with regard to underlying changes in neurobiology (Owen 2014). There is a variety of flaws in depression studies themselves: use of different clinical scales and cut-off values that make comparison even between similar studies

very difficult (Yuan et al. 2018), lack of reliability and validity of MDD DSM-5 criteria diagnosis (Fried 2017). A symptom-based approach in depression with RDoC framework could potentially improve quality of not only biomarker studies in psychiatry but also could allow us to look inside fundamental neurobiology of disorders which could be clinically relevant (Fried 2015, 2017). Most of the biomarker studies we analyzed were cross-sectional, mostly patient vs. control studies, rare cross-diagnose comparison, focus on statistical significance rather than clinical relevance, lack of replication. This also prevents their use in routine psychiatric practice as diagnostic or prognostic tools, and therefore, we still rely on phenomenology-based approach (DSM) and not on objective biomarkers.

Therefore, due to huge overlaps between candidate genes and pathways and different disorders, an enormous number of targets for the single miRNA, small number of studies identifying valid targets of miRNAs in psychiatric disorders, shared symptoms in different disorders as well as heterogeneity of presentation of single disorder and other methodological limitations mentioned above makes it impossible to point out the exact mechanism of how miRNAs contribute to the pathogenesis in each particular disorder. This in turn prevents their use in clinic both as diagnostic tool and potential therapy.

The limitations of our study include: (1) analysis of only three disorders; (2) exclusion of SNPs in miRNAs and genes analysis; (3) exclusion of miRNA target analysis; (4) absence of direct comparison between studies due to discordant study designs and absence of unified protocol for conducting biomarker researches in psychiatry (different isolation techniques, quantification and analysis methods, sample sizes, inclusion/exclusion criteria, etc.); (5) exclusion of analysis of genes involved in miRNA biogenesis and function regulation.

Future Directions

All the information regarding exosomes, miRNA, psychiatric disorders and their relations as well as results obtained during our analysis have led us to several important conclusions. First, we confirmed our assumption that miRNAs in exosomes are far more suitable candidate for biomarker search based on the available literature regarding exosomes and miRNAs. This is only our hypothesis based on the available literature data as direct comparison between studies is impossible due to the aforementioned reasons. Second, we suggest that exosomes act as integration links between different pathophysiological pathways of depression mentioned in (Dean and Keshavan 2017) and extend it to psychiatric disorders in general. They act as a ‘Fed-Ex’ in our organism transferring information via biomolecules between systems that are not directly connected. Exosomes, therefore, allow

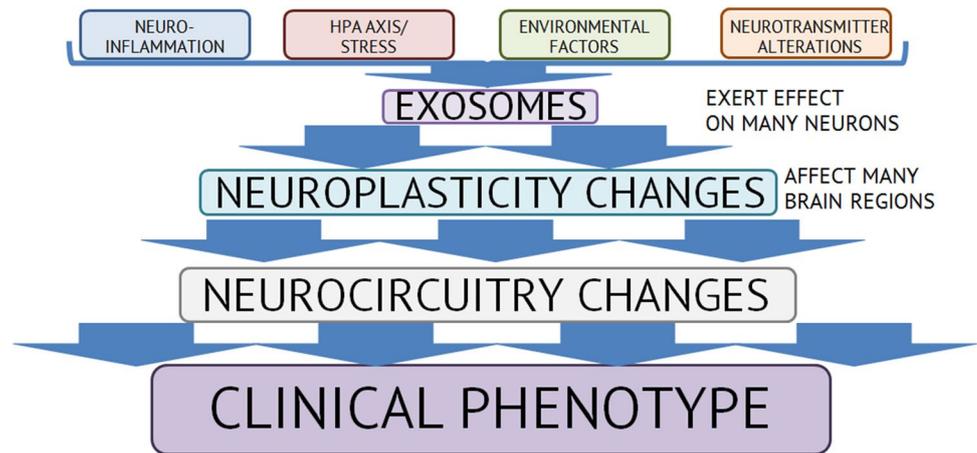
this network to act as a whole as well as provide both horizontal and vertical connections between various levels of this network (e.g., immune system and CNS). This step-by-step interaction via exosomes (and most importantly miRNAs) partly explains how biological signals (e.g., stress, inflammation) are transformed into alterations in neuroplasticity which leads to changes in particular brain areas and to alterations in cognitive processes, emotional sphere, etc. That is why exosome could help us tracking down disruption in normal functioning and potentially identify more precisely what brain regions are affected in particular psychiatric disorder, how it contributes to the clinical presentation and how it correlates with other methods (e.g., MRI) which are often used as guides to where to look for altered miRNAs in post-mortem studies (Dean and Keshavan 2017; Santarelli et al. 2011). This notion is supported also by the recent review (Saeedi et al. 2019) where the authors emphasize that due to the properties of exosomes from CNS (mediators of intercellular communication, ability to cross BBB, main reservoirs of miRNAs (nervous system contributes to approximately 70% of all miRNAs), role in neuroplasticity, neurogenesis, neuroinflammation) are promising biomarker candidates as they could reflect physiologic and pathologic changes in CNS.

Our hypothesis is that exosomes could be a ‘transformer’ of biological signals into behavioral phenotypes seen in depression as well as in psychiatric disorders in general, therefore, serving as a missing link between biology and psychology (Fig. 2). They are able to act very far from their cell of origin therefore enabling effect on distant cells, tissues and organs which may account for systemic changes in mental disorders.

Our hypothesis is supported by the facts that (1) exosomes could be secreted and captured by many cells (both immune and non-immune); (2) exosomes are able to cross BBB (or even change permeability of it); (3) exosomes are main transporters of miRNAs which were shown to regulate various pathways; (4) significant amount of miRNAs replicated in more than one study were shown to regulate BDNF expression which is one of the key players in neuroplasticity; (5) exosomes are flexible in terms of secretion and transport of biomolecules in response to various stimuli. The role of serum-derived exosomes has already been established in autism spectrum disorder: study has shown that they stimulated cultured human microglia to secrete significantly more of the pro-inflammatory IL-1 β (Tsiloni and Theoharides 2018). This in concordance with other studies showing role of exosomes in neuroinflammation which in turn associated with psychiatric disorders.

All of the information above shows an intriguing potential of exosomes in both clinical and fundamental psychiatry.

Fig. 2 Schematic representation of our hypothesis regarding potential function of exosomes in pathogenesis of psychiatric disorders



Conclusions

The field of biomarker research in psychiatry grows rapidly. Nearly two hundred significantly differentially expressed miRNAs were identified in 35 studies of three major psychiatric disorders. But closer look shows that this increase was in expense of quality. Despite the availability of new technologies, we still show high rates of discordance and measure already validated miRNAs thus repeating the errors of previous studies. All these limitations and mistakes should be acknowledged and corrected. Our position is that exosomes could help in overcoming them thus providing deeper understanding the molecular biology of psychiatric disorders and eventually physiological explanation of psychological changes which can become an objective back-up for clinical decisions. We also demonstrated that diagnostic potential of miRNAs in psychiatry is not their strongest side and probably emphasis should be made on risk assessment, disease severity evaluation and treatment response but before that large-scale, prospective, cross-disorder, multi-centered studies are warranted.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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