EXPERT REVIEW

Stress, microRNAs, and stress-related psychiatric disorders: an overview

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Stress is a major risk factor for psychiatric disorders. During and after exposure to stressors, the stress response may have pro- or maladaptive consequences, depending on several factors related to the individual response and nature of the stressor. However, the mechanisms mediating the long-term effects of exposure to stress, which may ultimately lead to the development of stress-related disorders, are still largely unknown. Epigenetic mechanisms have been shown to mediate the effects of the environment on brain gene expression and behavior. MicroRNAs, small non-coding RNAs estimated to control the expression of about 60% of all genes by post-transcriptional regulation, are a fundamental epigenetic mechanism. Many microRNAs are expressed in the brain, where they work as fine-tuners of gene expression, with a key role in the regulation of homeostatic balance, and a likely influence on pro- or maladaptive brain changes. Here we have selected a number of microRNAs, which have been strongly implicated as mediators of the effects of stress in the brain and in the development of stress-related psychiatric disorders. For all of them recent evidence is reported, obtained from rodent stress models, manipulation of microRNAs levels with related behavioral changes, and clinical studies of stress-related psychiatric disorders. Moreover, we have performed a bioinformatic analysis of the predicted brain-expressed target genes of the microRNAs discussed, and found a central role for mechanisms involved in the regulation of synaptic function. The complex regulatory role of microRNAs has suggested their use as biomarkers for diagnosis and treatment response, as well as possible therapeutic drugs. While, microRNA-based diagnostics have registered advancements, particularly in oncology and other fields, and many biotech companies have launched miRNA therapeutics in their development pipeline, the development of microRNA-based tests and drugs for brain disorders is comparatively slower.

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INTRODUCTION

Stress and stress-related psychiatric disorders

Various adverse life events, generically addressed to as 'stress' have been shown to represent a major risk factor for psychiatric disorders, particularly for those characterized by a lower genetic component, such as major depressive disorder (MDD), anxiety disorders and post-traumatic stress disorder (PTSD). It is fundamental to remember that stress is a physiological response of the brain and body to environmental changes, which may result in efficient adaptation or maladaptive changes possibly triggering the development of pathology. The outcome of this process depends on several factors related to the individual response (genetic background, sex, previous life experiences) and to the nature of the stressor (intensity, duration, perceived control) [1–3]. The mechanisms mediating the long-term effects of exposure to stress, which may ultimately lead to the development of stress-related disorders, are still largely unknown. However, recent compelling evidence has shown that epigenetic mechanisms have a key role in mediating the effects of the environment on gene expression, including the effects of stress on brain and behavior [4, 5]. Epigenetic mechanisms are generally defined as molecular mechanisms leading to changes in gene expression levels that are not due to variations in the DNA sequence, including DNA methylation, histone post-translational modifications, and post-transcriptional regulation by non-coding RNAs such as microRNAs (miRNAs), which are the focus of this article.

miRNAs function in the brain

The miRNAs are a large family of small (20–22 nucleotides) noncoding RNAs, found in a variety of organisms from algae to humans, with a key role in the posttranscriptional regulation of gene expression. The last miRbase (miRbase v22.1 database), the primary online repository for miRNA sequences and annotation, includes 2693 human, 2013 mouse and 768 rat mature miRNAs (https://www.mirbase.org/). Most miRNA genes are expressed under the control of their own promoters and regulatory sequences, while others are arranged in clusters, and may be co-regulated with other members of the cluster. Mature miRNAs are derived from precursor molecules (pri-miRNAs), which are either transcribed from individual miRNA genes or from portions of introns of protein-coding genes [6–8].

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In general, miRNAs exert their posttranscriptional regulation by base-pairing with target mRNAs: protein synthesis is inhibited either by repressing translation or by inducing deadenylation and degradation of target mRNAs. In some cases, miRNAs were also reported to activate translation [9–11]. It has been estimated that in mammals miRNAs may regulate the expression of at least 60% of all protein-coding genes [12]. Individual miRNAs may target up to hundreds of different mRNAs, and a single mRNA may be modulated by several different miRNAs, thus suggesting a coordinated and fine-tuned regulation of protein expression by miRNAs [6, 8]. MiRNAs have been involved in the regulation of nearly every cellular process and therefore it is not surprising that changes in their expression or function are associated with a great number of human pathologies [11, 13, 14].

Many miRNAs are expressed in the brain and some of them are considered as brain specific. Initially, research has identified miRNAs as important developmental switches in neuronal differentiation, which contribute to shape cell-type specificity by targeting master regulatory genes such as transcription factors [15–17]. More recently, it has become clear that miRNAs do not work just as on-off switches but rather as fine-tuners of gene expression. This is possible because often a miRNA reduces translation of the target mRNAs by a small proportion. Therefore, the miRNA system is considered crucial for the regulation of homeostatic balance, and a likely way whereby stress induces pro- or maladaptive changes in the brain. Nearly two decades of research on brain miRNAs have established their role in development, neuronal differentiation, and survival, as well as in the regulation of synaptic homeostasis and plasticity [17–19].

MICRORNAS AS MEDIATORS OF STRESS ACTION AND IN STRESS-RELATED PSYCHIATRIC DISORDERS

MiRNAs represent ideal candidates for the modulation of cellular/molecular mechanisms in the response to environmental changes (Fig. 1). The presence of different sets of miRNAs in distinct neuronal compartments, such as dendrites and neuronal somata, enables the miRNA system to finely regulate synaptic homeostasis and plasticity, in particular by modulating local translation of synaptic proteins [19]. Therefore, the role of this complex, multi-faceted form of regulation has been increasingly investigated to study how stress shapes epigenetic marks for fine-tuning of genes involved in brain plasticity across the lifespan [3, 20–25].

The aim of this review article is to summarize and discuss recent evidence on miRNAs as mediators of the effects of stress in the brain and whether and how these changes are involved in the development of stress-related psychiatric disorders.

In recent years, a great number of reports showed changes in the expression pattern of selected miRNAs, as well as in miRNA profiling, in brain areas of different animal models of chronic or acute stress, in multiple mouse and rat strains. Changes in the expression levels of multiple miRNAs were also reported in studies on post-mortem brains, cerebrospinal fluid (CSF), or peripheral tissues of patients with psychiatric disorders. The main approaches for miRNA analysis are reported in Table 1. In the literature analyzed, miRNAs were mostly studied in the following brain areas: hippocampus, prefrontal cortex (PFC), amygdala, nucleus accumbens. Historically, these are the areas that have been more often connected to the development of stress-related disorders (see [1–3, 26–30]).

Chronic vs acute stress in rodent models and pathophysiology

Most rodent studies on miRNAs use chronic models of stress to induce depressive-like behaviors. Indeed, chronic stress paradigms have been consistently reported to cause impairments in behavior, cognition, and memory, together with atrophy of cortico-limbic brain regions, decrease of hippocampal neurogenesis, alterations in monoaminergic, glutamatergic and GABAergic transmissions, increased neuroinflammation and hypothalamic-pituitary-adrenal (HPA) axis disturbances, all features associated to stress-related disorders in humans [1–3, 31–34]. However, in recent years it has been increasingly appreciated that acute stress protocols may be very informative as to the determinants of resilient vs vulnerable trajectories of the stress response [3]. Indeed, it is well known that even a single exposure to traumatic stress may result into a stress-related disorder, such as MDD, PTSD or anxiety disorders [35, 36]. Accordingly, preclinical studies have shown that acute/subacute stress protocols in rodents may induce long-term changes partly similar to those induced by chronic stress [37–39]. Moreover, a detailed dissection of the short- and long-term response to acute stress has shown that a brief exposure to inescapable stress may trigger both rapid and sustained functional/morphological changes in prefrontal cortex (PFC) [40, 41]. For these reasons in the following section, we report the changes induced in miRNAs by both chronic and acute stress protocols.

We will present preclinical and clinical evidence linking miRNAs with stress response and stress-related psychiatric disorders (Table 2). Rather than listing all the numerous findings (which would exceed the space available for this review), we have selected the miRNAs that most frequently have been associated with stress and psychopathology. We will then discuss the biological functions downstream these miRNAs, which could be involved in their action. Finally, in the last section, we will explore the potential role of miRNAs as biomarkers for diagnosis and drug treatment response (including possible treatments with miRNA mimics and antagonists).

MIRNAS IN RODENT STRESS MODELS AND IN CLINICAL STUDIES

miR-9

MiR-9 is an evolutionarily conserved miRNA highly enriched in both the developing and mature nervous system of vertebrates, where it exerts prominent roles in the regulation of brain development, axonal development, neurogenesis, and neuronal plasticity [42–45]. Its validated targets include transcriptional modulators (both activators and repressors), as well as neuronal structural and synaptic proteins. MiR-9 has been extensively investigated in different brain areas of animal models (mainly chronic stress models) and some evidence is available also in clinical studies on patients with stress-related psychiatric disorders.

Two independent studies used microarray profiling to evaluate miRNAs expression changes in brain areas of rodents exposed to acute or repeated restraint stress (RS) and validated miR-9 as significantly modulated by stress [46, 47]. In the first study, miR-9 was found to be downregulated in central amygdala and hippocampus of rats both after one RS session (4 h) and after 14 days of stress [46]. Instead, in the second study, miR-9 levels were remarkably increased in PFC, but not hippocampus, of CD1 mice exposed to acute RS (2 h), but not after repeated stress (5 days) [47].

Another study in the same year [48] showed that early life maternal separation increased medial PFC miR-9 levels in adulthood with mechanisms involving Repressor Element-1 Silencing Transcription factor (REST) 4. Interestingly, the authors suggested that these long-lasting molecular changes could promote vulnerability to stress in adulthood.

More recently, different studies asked whether miR-9 levels were altered by a validated model of depression in rodents, the chronic unpredictable mild stress protocol (alternatively reported as CUS, CUMS, CMS, or UCMS). In one study, CUS in adult rats was combined with early-life stress [49]. Both maternal deprivation and CUS decreased miR-9 expression, in the striatum and nucleus accumbens respectively, while prior maternal deprivation further

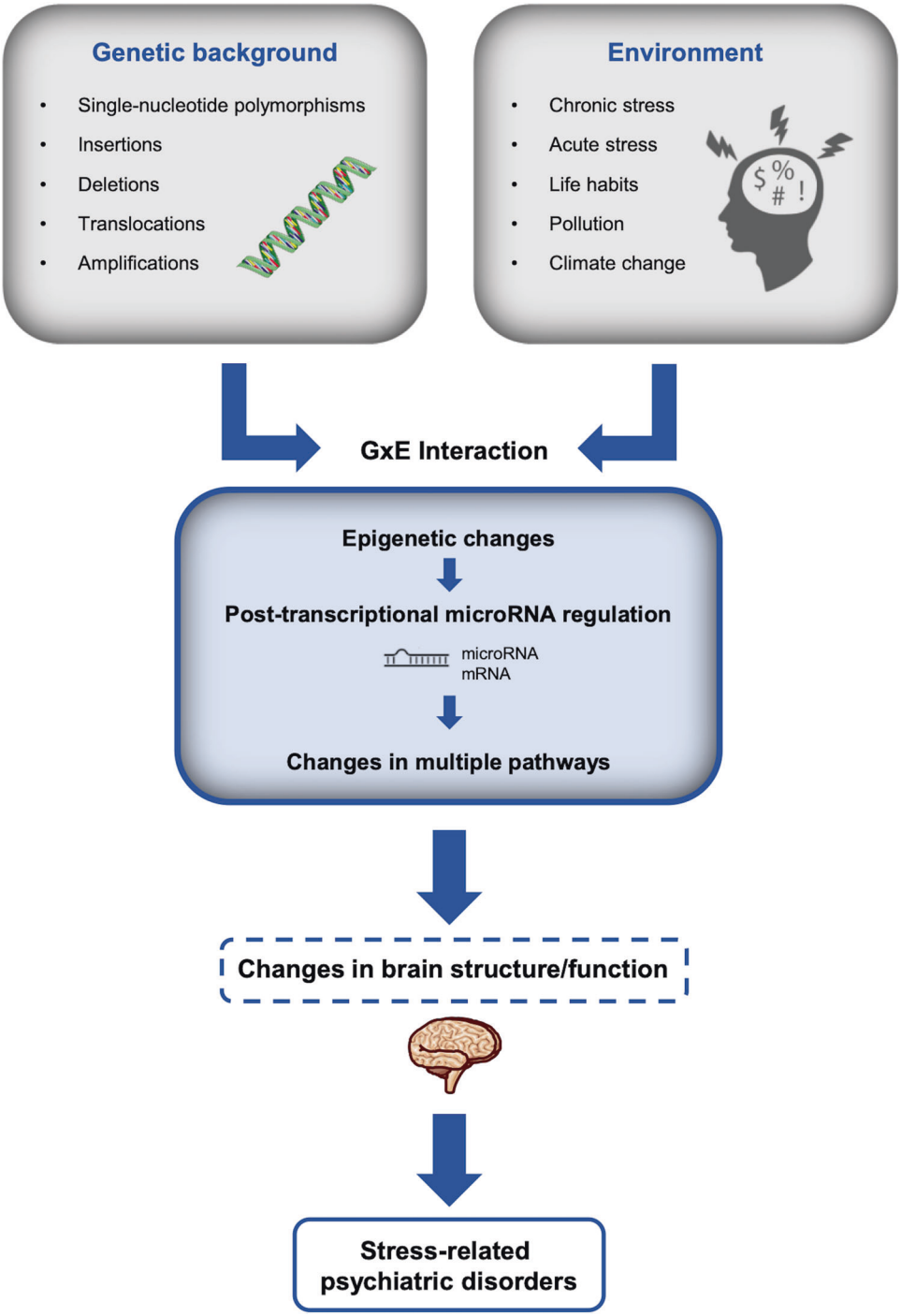

Fig. 1 Stress and microRNAs in the etiology of stress-related disorders. Etiology of stress-related psychiatric disorders is dependent on a continuous interaction between the genetic background of an individual and exposure to environmental stimuli. The genetic background is a combination of genetic factors, including polymorphisms, gene insertions/deletions, translocations and amplifications. Environmental stimuli comprise many different factors, including different forms of stress. In addition to genetic background, the degree of resilience or sensitivity to stress is also moderated by developmental stage, sex and previous life experiences (not shown here). This complex interaction may lead to a predisposition for the development of psychiatric disorders. Various epigenetic mechanisms mediate the effect of the environmental stimuli on gene expression, with a major role played by microRNAs, which regulate the availability of mRNAs for translation. This post-transcriptional regulation induces changes in multiple pathways and, in turn, changes in brain structure and function and triggers the development of stress-related psychiatric disorders. Created with Servier Medical Art (smart.servier.com).

worsened both depressive-like behavior and miR-9 reduction induced by CUS. MiR-9 alterations were found to be inversely correlated with expression changes in dopamine D2 receptor, validated as a target of miR-9. Interestingly, chronic escitalopram treatment, although rescuing depressive-like behavior, did not reverse decreased miR-9 expression in either the nucleus accumbens or striatum.

In BALB/c mice exposed to CMS, miR-9 levels were increased in the PFC and rescued by antidepressant treatments [50]. Conversely, CUMS was reported to increase miR-9 expression in the

Table 1. Main approaches for the study of miRNAs.

Approach	Methodology	Pros	Cons
Assessment of the expression of single miRNAs	- Real-time PCR - Northern blot - In situ hybridization	Inexpensive and sensitive	Low throughput
Genome-wide screening of miRNA expression profiles	- RNA sequencing - miRNA microarrays	High throughput	Expensive
Bioinformatic analysis of miRNA-target mRNA interaction (in silico)	Web-based algorithms	Inexpensive and informative	Subject to error
Assay of miRNA-target mRNA interaction (in vitro)	Luciferase reporter assay	Inexpensive and informative	May produce artifacts
In vivo and in vitro models with altered miRNA expression levels	Up- or down-regulation of expression of specific miRNAs Mutation of miRNA biogenesis genes Virus-mediated manipulation of specific miRNA levels Manipulation of specific miRNA levels by administration of miRNA mimics or inhibitors	Informative	Expensive and time-consuming

In many studies the expression changes of single miRNAs are measured, mostly by using Real-time PCR (or other methods, see Table). In a smaller number of studies a global screening of miRNAs is carried out (in recent years mostly by RNA sequencing). After selection of the miRNAs of interest a bioinformatic analysis is carried out with one or more web-based algorithms, to identify target genes of each miRNA. Then, experiments are carried out to check the miRNA-target mRNA interaction, mostly by using a luciferase reporter assay in cultured cells.
An additional way to investigate the miRNA-target mRNA interaction, but also to study the pathophysiological outcomes of miRNA changes is the manipulation of specific miRNAs in animal models (see Table).

hippocampus of C57BL/6 mice, while lentiviral miR-9 down-regulation in the hippocampus rescued the depressive-like phenotype, as well as the reduction of newborn neurons number and neuronal markers induced by CUMS [51]. Similar results were obtained from the same authors in rats subjected to CUMS and intravenously injected with a synthetic miR-9 inhibitor [52]. Differently, further work found that miR-9 levels were selectively reduced in the hippocampus of rats vulnerable to CMS, while acute subanesthetic ketamine recovered both depressive-like behavior and miR-9 levels to basal condition in just 24 h [53]. Importantly, decreased miR-9 levels were associated with dendritic simplification partly mediated by REST upregulation, while treatment with ketamine completely rescued the changes.

Overall, if the involvement of miR-9 in the stress response seems to be undoubted, more studies are required to define its region-specific roles and downstream effects.

Clinical evidence on patients with stress-related disorders is more consistent, since the three available publications reported increased peripheral blood levels of miR-9 in MDD patients [54–56]. Moreover, neuroimaging analysis of intrinsic amygdala functional connectivity revealed that the connection of amygdala to PFC-limbic circuits could mediate the impact of miR-9 on the severity of depression [55]. Finally, miR-9-containing exosomes derived from MDD serum were shown to induce microglial polarization in vitro and in vivo and to activate inflammatory pathways [56].

miR-16

In early studies, miR-16 has been identified and validated as a miRNA targeting the serotonin transporter gene and was found to increase in serotonergic raphe nuclei while decreasing in noradrenergic locus coeruleus and hippocampus after chronic treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants [57–59]. Interestingly, Brain-Derived Neurotrophic Factor (BDNF) is also a target of miR-16 [58, 59]. Accordingly, miR-16 was implicated in mechanisms underlying hippocampal adult neurogenesis induced by SSRI treatment, and miR-16 silencing in the hippocampus rescued the depressive-like phenotype caused by CUMS in mice [58]. Antidepressant effects were also reported when miR-16 was injected in the raphe of CUMS rats, with mechanisms involving the regulation of apoptosis and autophagy [59]. Conversely, intracerebroventricular injection of anti-miR-16 induced depressive-like behaviors in female rats [60].

As regards direct effects of stress on miR-16 levels, miR-16 expression was reduced in the PFC of mice exposed to CMS [50], and in the raphe and CSF of CUMS rats [61]. Instead, it was increased in the hippocampus of adult rats exposed to early-life maternal separation [62]. In another CMS study in rats, miR-16 was found to be significantly modulated by stress only in resilient animals. MiR-16 was increased in serum and in ventral tegmental area, and decreased in the nucleus accumbens and PFC in a time-dependent manner over the 7 weeks of CMS [63]. Finally, early traumatic adolescent stress was reported to induce a long-lasting increase of miR-16 levels in the hippocampus both during adolescence and in adulthood, while chronic antidepressant treatment restored miR-16 to control levels [64].

Overall, despite some inconsistencies, most of the studies converge in reporting that the reduction of miR-16 in raphe and the increase in hippocampus caused by chronic stress contribute to the induction of depressive-like phenotypes in animal models.

As for clinical evidence, miR-16 was reported to be decreased in CSF [60] and serum [65] of MDD patients. One study found reduced miR-16 blood levels in MDD patients responding to escitalopram treatment compared to non-responders [66]. Interestingly, peripheral blood levels of miR-16 were reported to be increased in students after chronic stress exposure caused by Japanese nationally-administered examination for academic promotion [67, 68].

miR-34

The miR-34 family includes three members (miR-34a, miR-34b, miR-34c), a group of highly conserved miRNAs with important roles in the modulation of physiological and pathological processes in several tissues, including the brain [69, 70]. Intriguingly, the miR-34 family has been consistently implicated in the regulation of the stress response [71]. MiR-34a, was upregulated after auditory fear conditioning in basolateral amygdala (BLA) and its inhibition was shown to suppress fear memory consolidation, with mechanisms involving the Notch pathway [72]. Similarly, miR-34c was remarkably increased after acute and chronic stress challenges in the central amygdala and miR34c overexpression in this brain region induces anxiolytic behavior after stress

Table 2. Preclinical and clinical evidence linking selected miRNAs with stress and stress-related psychiatric disorders.

miR-9					
Preclinical evidence					
Animals	**Stress**	**Tissue**	**Change**	**Method**	**Reference**
Male BALB/c mice, 3-mo.	CMS	PFC	++	RT-qPCR	[50]
Male Sprague-Dawley rats, adult	CMS	HPC	-	RT-qPCR, ISH	[53]
Sprague-Dawley rats, PND2-PND14	MS	mPFC	+	Northern blot, RT-qPCR	[48]
Sprague-Dawley rats, 10 we. (CUS) PND1-PND14 (MD)	MD CUS MD + CUS MD CUS MD + CUS	NAc Striatum	= -- -- -- = --	RT-qPCR	[49]
Male C57BL/6 mice	CUMS	HPC	+	RT-qPCR	[51]
Male rats, adult	RS Chronic RS	AMY HPC AMY HPC	- - - -	Spotted array, RT-qPCR	[46]
Male CD1 mice, 10–12 wks	Acute RS Chronic RS	FC	++ =	Microarray, Northern blot	[47]
Clinical evidence					
Subjects	**Clinical assessment**	**Tissue**	**Change**	**Method**	**Reference**
50 MDD vs. 30 HC	DSM-V, HAM-D	Serum	+	RT-qPCR	[54]
6 MDD vs. 3 HC	HAM-D, MADRS	Serum exosomes	++	RT-qPCR	[56]
40 MDD vs. 34 HC	DSM-V, HAM-D	Serum	+	RT-qPCR	[55]
miR-16					
Preclinical evidence					
Animals	**Stress**	**Tissue**	**Change**	**Method**	**Reference**
Male BALB/c mice, 3-mo.	CMS	PFC	-	RT-qPCR	[50]
Male Wistar rats, 21 d.	6 days of FS	HPC	+	RT-qPCR	[64]
Male Sprague-Dawley rats, PND1-PND14	MD	HPC	+	RT-qPCR	[62]
Sprague Dawley rats, 8 we.	CUMS	CSF RN	-- -	RT-qPCR	[61]
Sprague-Dawley rats	CUMS	RN	+	RT-qPCR	[59]
Male Wistar Han rats	CMS	Serum VTA mPFC NAc	+ + - -	RT-qPCR	[63]
Clinical evidence					
Subjects	**Clinical assessment**	**Tissue**	**Change**	**Method**	**Reference**
36 MDD vs. 30 HC	HAM-D	CSF Blood	- =	RT-qPCR	[60]
55 MDD (31 resp, 24 non-resp) 124 MDD (97 resp, 27 non-resp)	HAM-D, MADRS HAM-D, MADRS	Blood	- =	RT-qPCR Flow cytometry-fluorescence	[66]
39 MDD vs. 36 HC	HAM-D	Serum	-	RT-qPCR	[65]
25 students before vs. after examination	STAI	Blood	+	Microarray, RT-qPCR	[67]
10 students before vs. after examination	STAI	Blood	+	Microarray, RT-qPCR	[68]
miR-34					
Preclinical evidence					
Animals	**Stress**	**Tissue**	**Change**	**Method**	**Reference**
C57BL/6 mice, 11–16 we.	SDS Acute RS	AMY	++ ++	Microarray, RT-qPCR	[71]
Sprague Dawley rats, PND2-PND16	MS	AMY	++	miRNA-seq, RT-qPCR	[149]
Female rats, PND45 F1, F2 (neonatal) F1 (adult male/female) F2 (adult male/female)	CUS EPM+Fear conditioning EPM+Fear conditioning	Oocytes Blood AMY mPFC mPFC mPFC	- - - + =/- -/-	RT-qPCR	[76]

Table 2. continued

Male C57Bl/6 J mice, 2 mo.	Auditory fear conditioning	BLA	+	Microarray, RT-qPCR	[72]
Male mice, 8–9 we.	Acute RS	BLA mPFC	++ +	RT-qPCR	[73]
Male B6 mice, 5 we.	CSDS	BNST	--	miRNA-seq	[148]
Clinical evidence					
Subjects	**Clinical assessment**	**Tissue**	**Change**	**Method**	**Reference**
8 BP vs. 14 HC 15 MDD vs. 14 HC	DSM-IV DSM-IV	AnCg AnCg	- -	RT-qPCR	[79]
15 suicide vs. 16 HC	DSM-IV	PFC	++	RT-qPCR	[78]
6 MDD vs. 6 HC 32 MDD vs. 21 HC	ICD-10, DSM-IV, HAM-D	CSF, Serum Serum	++ ++	RT-qPCR	[80]
32 MDD vs. 32 HC	DSM-IV, SCID-I/P, HAM-D, BSI-CV, LES	Peripheral blood leukocytes	++	RT-qPCR	[82]
10 MDD (before vs. after 12 weeks SSRI	DSM-IV, HAM-D	Blood	--	RT-qPCR	[83]
84 MDD vs. 78 HC 78 HC (before vs. after 8 weeks SSRI)	DSM-IV, HAM-D DSM-IV, HAM-D	Serum	++ --	RT-qPCR	[81]
miR-124					
Preclinical evidence					
Animals	**Stress**	**Tissue**	**Change**	**Method**	**Reference**
Male Wistar rats	SDS	HPC PFC	+ +	RT-qPCR	[96]
C57BL/6 J mice	CUMS	PFC	++	RT-qPCR	[93]
Male Sprague-Dawley rats, 8 we.	CUMS	HPC	+	RT-qPCR	[91]
Sprague-Dawley rats, PND2-PND14	MS	mPFC	+	Northern blot	[48]
Male Wistar rats, 21 d.	CUMS DEX (s.c., 1.5 mg/kg/day)	BLA	+ +	RT-qPCR	[89]
Male Wistar rats, 21 d.	CUMS DEX (s.c., 1.5 mg/kg/day)	PFC HPC PFC HPC	+ + + +	RT-qPCR	[90]
Mice	CSDS	HPC	+	RT-qPCR	[97]
Male Sprague-Dawley rats, 7–8 we.	CUMS (5 we.) CUMS (8 we.)	HPC HPC	+ -	RT-qPCR	[92]
Male BALB/c mice, 8–10 we.	CUMS	HPC	-	RT-qPCR	[94]
Male Sprague-Dawley rats	CORT (50 mg/kg/day)	PFC	++	RT-qPCR	[99]
Male BALB/c mice, 8 we.	CUMS	HPC	-	Northern blot	[95]
Male C57BL/6 mice, 9 we.	CORT (s.c., 40 mg/kg)	HPC	++	RT-qPCR	[101]
Wistar rats, PND2-PND34	ELSS	AMY	-	RT-qPCR	[98]
Male C57BL/6 mice, 5 we.	CORT (s.c., 40 mg/kg)	HPC	++	RT-qPCR	[100]
Male Kunming mice, adult	CUMS	HPC	++	Microarray	[88]
Male C57BL/6 J/Cnrm mice, 13–15 we.	Acute RS	AMY	-	RT-qPCR	[102]
Male rats, adult	Acute RS	HPC	-	Spotted array, RT-qPCR	[46]
Male Wistar rats	FST	HPC	+	RT-qPCR	[103]
Male Sprague-Dawley rats, 8–12 we.	SPS	HPC	-	RNA-seq, RT-qPCR	[104]
Clinical evidence					
Subjects	**Clinical assessment**	**Tissue**	**Change**	**Method**	**Reference**
45 NT MDD vs. 32 HC	HAM-A, HAM-D	Plasma	++	RT-qPCR	[106]
32 MDD vs. 30 HC	DSM-IV, HAM-D	PBMC	++	RT-qPCR	[105]
miR-132					
Preclinical evidence					
Animals	**Stress**	**Tissue**	**Change**	**Method**	**Reference**
Sprague-Dawley rats, PND2-PND14	MS	mPFC	+	RT-qPCR, Northern blot	[48]
Mice, 8–12 we.	Acute multimodal stress Chronic multimodal stress	AMY HPC AMY HPC	++ ++ ++ =	RT-qPCR	[113]

Table 2. continued

Male C57BL/6 mice, 8 we.	Chronic RS	PFC	+	RT-qPCR	[116]
Male Sprague-Dawley rats, 2 mo.	CUS	HPC	++	RT-qPCR	[117]
Wistar rats, PND2-PND34	ELSS	AMY	++	RT-qPCR	[98]
Male Kunming mice, adult	CUMS	HPC	--	Microarray	[88]
Male rats, adult	Chronic RS	HPC	+	Spotted array, RT-qPCR	[46]
Male C57Bl/6 J mice, 9 we.	PSE FS	HPC HPC	++ +	RT-qPCR	[111]
Male Sprague–Dawley rats, 3–4 mo.	SPS	HPC	+	RT-qPCR	[114]
Male Sprague-Dawley rats, 3–4 mo.	SPS	PFC	+	RT-qPCR	[115]
Clinical evidence					
Subjects	**Clinical assessment**	**Tissue**	**Change**	**Method**	**Reference**
45 MDD vs. 32 HC	HAM-A, HAM-D	Plasma	++	RT-qPCR	[106]
81 MDD vs. 123 HC	DSM-IV, HAM-D	Blood	+	RT-qPCR	[118]
62 MDD vs. 73 HC	DSM-IV, HAM-D, HAM-A	Blood	+	RT-qPCR	[119]
30 MDD vs. 30 HC	-	Blood	++	RT-qPCR	[117]
40 MDD vs. 40 HC	CCMD-3, SDS	Serum	+	RT-qPCR	[120]
8 BP vs. 14 HC 15 MDD vs. 14 HC	DSM-IV DSM-IV	AnCg AnCg	- =	RT-qPCR	[79]
miR-134					
Preclinical evidence					
Animals	**Stress**	**Tissue**	**Change**	**Method**	**Reference**
Male Wistar rats	CUMS	BLA	++	RT-qPCR	[125]
Male Sprague-Dawley rats	CUMS	HPC	++	RT-qPCR	[123]
Male Sprague-Dawley rats	CUMS	HPC	++	RT-qPCR	[122]
Male Sprague-Dawley rats, 3–4 mo.	CUMS	HPC PFC OB Plasma	- - = -	RT-qPCR	[130]
Male/female Wistar rats, GD9-D20 Fetal female offspring Adult female offspring (PW10)	DEX (s.c., 0.2 mg/kg/day) Ice water swimming	HPC	+ ++ ++	Microarray, RT-qPCR	[127]
Male Kunming mice, adult	CUMS	HPC	++	Microarray	[88]
Male ICR mice, 5 we.	CUMS	HPC	++	RT-qPCR	[129]
Male Wistar rats	UCMS	vmPFC	++	RT-qPCR	[124]
Male rats, adult	Acute RS Chronic RS	AMY AMY HPC	+ - -	Spotted array, RT-qPCR	[46]
Male Sprague-Dawley rats, adult	Chronic RS	HPC	=	RT-qPCR	[126]
Clinical evidence					
Subjects	**Clinical assessment**	**Tissue**	**Change**	**Method**	**Reference**
100 MDD vs. 100 HC 50 BD vs. 100 HC	DSM-IV, HAM-D, BDI, MAS, PANSS	Plasma	--	RT-qPCR	[130]
miR-135					
Preclinical evidence					
Animals	**Stress**	**Tissue**	**Change**	**Method**	**Reference**
Male Wistar rats, 21 d.	6 days of FS	PFC	-	RT-qPCR	[64]
Male C57BL/6 mice, 8–10 we.	CUMS	Blood HPC	- -	RT-qPCR	[134]
Male C57BL/6 J/Cnrm mice, 13–15 we.	Acute RS	AMY	-	RT-qPCR	[102]
Adult C57BL/6 mice, 8–10-we.	SEFL	BLC	+	RNA-seq, RT-qPCR	[136]
Clinical evidence					
Subjects	**Clinical assessment**	**Tissue**	**Change**	**Method**	**Reference**
50 MDD vs. 50 HC	-	Blood	-	RT-qPCR	[134]
11 MDD vs. 12 HC 4–9 suicide vs. 4–9 HC 6–11 suicide vs. 6–11 HC	HAM-D HAM-D HAM-D	Blood RN RM	- - -	RT-qPCR	[135]
39 MDD vs. 36 HC	HAM-D	Serum	-	RT-qPCR	[65]

Table 2. continued

8 PTSD-sus vs. 8 PTSD-res vs. 8 HC	SRIP	Serum	+ (PTSD-sus vs. PTSD-res/HC)	RNA-seq	[136]
55 MDD (31 resp, 24 non-resp) 124 MDD (97 resp, 27 non-resp)	HAM-D, MADRS HAM-D, MADRS	Blood	= -	RT-qPCR Flow cytometry-fluorescence	[66]
miR-218					
Preclinical evidence					
Animals	**Stress**	**Tissue**	**Change**	**Method**	**Reference**
Male Sprague-Dawley rats	CORT (s.c., 4.76 mg/day)	PFC	+	RT-qPCR	[137]
Male C57BL/6 mice, PND75 ± 15	CSDS	mPFC	-	RT-qPCR	[139]
Male C57BL/6 mice, PND75 ± 15	CSDS	Blood	-	RT-qPCR	[140]
Male C57BL/6 mice	CSDS	Blood	-	RT-qPCR	[138]
Male Sprague-Dawley rats	CORT (s.c., 50 mg/kg/day)	PFC	++	TLDA, RT-qPCR	[99]
Clinical evidence					
Subjects	**Clinical assessment**	**Tissue**	**Change**	**Method**	**Reference**
24 MDD suicide vs. 35 HC sudden-death	DSM-IV	mPFC	-	RT-qPCR	[139]
miR-1202					
Clinical evidence					
Subjects	**Clinical assessment**	**Tissue**	**Change**	**Method**	**Reference**
39 MDD vs. 36 HC	HAM-D	Serum	-	RT-qPCR	[65]
55 MDD (31 resp, 24 non-resp) 124 MDD (97 resp, 27 non-resp)	HAM-D, MADRS HAM-D, MADRS	Blood	- -	RT-qPCR Flow cytometry-fluorescence	[66]
14 MDD vs. 11 HC 32 MDD vs. 18 HC	DSM-IV	PFC Blood	- -	Microarray, RT-qPCR	[141]

For each miRNA listed in the table, studies analyzing genes, precursors, and mature miRNA have been included. MiRNAs expression changes are reported as follows: 1 "+" or "-" for differences up to 1-fold changes and 2 "++" or "--" for changes >1-fold. "=" means no changes.
CMS Chronic Mild Stress, *CUMS* Chronic Unpredictable Mild Stress, *CUS* Chronic Unpredictable Stress, *MS* Maternal Separation, *MD* Maternal Deprivation, *RS* Restraint Stress, *SDS* Social Defeat Stress, *FS* Footshock Stress, *ELSS* Early Life Social Stress, *SPS* Single Prolonged Stress, *SEFL* Stress-Enhanced Fear Learning, *SPE* Scent Predator Exposure, *EPM* Elevated plus-maze.
HAM-D Hamilton Depression Rating Scale, *HAM-A* Hamilton Anxiety Rating Scale, *MADRS* Montgomery–Åsberg Depression Rating Scale, *PANSS* Positive and Negative Syndrome Scale, *SRIP* Self-Rating Inventory for PTSD, *STAI* State-Trait Anxiety Inventory, *ICD-10* International Classification of Diseases, *DSM-(IV or V)* Diagnostic and Statistical Manual of Mental Disorders, version IV or V, *CCMD-3* Chinese Classification of Mental Disorders, *SCID* Structured Clinical Interview for DSM, *BDI* Beck's Depression Inventory, *MAS* Bech–Rafaelsen Mania Scale, *SDS* Self-Rating Depression Scale, *BSI-CV* Beck Scale for Suicide Ideation-Chinese Version, *LES* Life events scale.

paradigms [71]. A number of stress-related proteins, including corticotropin releasing factor receptor type 1 (CRFR1) have been validated as miR-34c targets [73, 74].

Targeted deletion of the three members of miR-34 family (triple knockout: TKO) has been used to study the role of miR-34 in stress response. miR-34 TKO mice were found to lack stress-induced serotonin and GABA release in the medial PFC and BLA, and to be resilient to stress-induced anxiety [73, 74]. Furthermore, it has been hypothesized that the miR-34 family is implicated in the antidepressant effects of chronic fluoxetine with mechanisms involving the upregulation of serotonin 5-HT-2c receptor in dorsal raphe [75].

Of note, alterations of miR-34 expression were also reported in trans-generational stress effects [76]. Pre-reproductive stress in adolescent female rats was found to induce anxiogenic behavior in the first and second-generation offspring, with mechanisms involving miR-34a, miR-34c, and CRFR1 modulation [76, 77].

As for clinical evidence, significant upregulation of miR-34c was observed in the PFC of suicide victims [78], while miR-34a was found reduced in postmortem brains of both MDD and bipolar depression patients (although not surviving to multiple correction testing) [79]. Conversely, other studies reported the upregulation of miR-34a in CSF and serum [80, 81] and of miR-34b and miR-34c in peripheral blood mononuclear cells (PBMC) [82] of depressed patients. Accordingly, antidepressant treatments in MDD patients reduced the blood level of both miR-34a and miR-34c [81, 83]. Interestingly, a negative correlation between the level of miR-34c expression and cognitive functions was reported in patients with MDD [84].

miR-124

MiR-124 is one of the most abundant miRNAs, estimated between 25–48% of the total miRNA content in the whole brain [85], with important functions in the regulation of adult neurogenesis [86, 87].

A number of studies have assessed the changes of miR-124 expression in rodents subjected to CUMS, which increased miR-124 levels in mouse frontal lobe and hippocampus, along with induction of anhedonic depressive-like behavior. Duloxetine administration in the last 3 weeks of CUMS reversed both anhedonic behavior and miR-124 increase [88]. In a different approach, the outcomes of CUMS or administration for three weeks of dexamethasone, a synthetic glucocorticoid, were

investigated in adult and adolescent rats. Both CUMS and dexamethasone induced depressive-like behavior, cognitive impairment and increase of miR-124 and FK506 binding protein 5 (FKBP5) (a co-chaperone protein of glucocorticoid receptor) in BLA, PFC, and hippocampus. Depressive-like behaviors were positively correlated with the level of miR-124a whereas glucocorticoid receptor levels were negatively correlated [89, 90]. Similarly, CUMS induced depressive-like behaviors and at the same time increased expression of miR-124 and reduced cAMP response element-binding protein 1 (CREB1) and BDNF in rat hippocampus. The injection of miR-124 antagomir rescued depressive-like behaviors, as well as the altered expression of miR-124, CREB1, and BDNF [91]. Moreover, other studies in line with the above showed increased expression of miR-124 after CUMS of variable lengths [92, 93]. In the latter work, CUMS reduced sirtuin 1 (SIRT1) expression in PFC. Furthermore, lentiviral-mediated miR-124 overexpression exacerbated depressive-like behaviors and resulted in down-regulation of SIRT1, while miR-124 inhibition up-regulated SIRT1 expression, showing that this protein is a functional target of miR-124 and suggesting its involvement in pathogenesis of depression.

By contrast, a few additional studies found down-regulation of miR-124 with CUMS. In one of them, restoration of miR-124 expression attenuated depressive-like behaviors, by targeting the signal transducer and activator of transcription 3 (STAT3). In another one, CUMS-induced depressive-like behaviors and reduced hippocampal expression of miR-124 were rescued by antidepressant treatment, while neither viral-mediated hippocampal overexpression nor intrahippocampal infusion of a miR-124 inhibitor affected depressive-like behaviors in non-stressed mice. However, miR-124 overexpression in hippocampal neurons conferred behavioral resilience to CUMS, with histone deacetylase 4 (HDAC4), HDAC5, and glycogen synthase kinase 3b (GSK3b) identified as targets for miR-124 [94, 95].

A different stress protocol, chronic social defeat stress (CSDS), also induced depressive-like behaviors and up-regulation of miR-124 in the rat and mouse hippocampus, accompanied by down-regulation of BDNF (another target of miR-124) [96, 97]. Overexpression of miR-124 exacerbated depressive-like behaviors while intra-hippocampal injection of BDNF or miR124 silencers resulted in an antidepressant effect. Early-life stress also has been shown to affect miR-124, with maternal separation increasing and early-life social stress reducing its expression level in medial PFC and amygdala, respectively [48, 98].

A few studies investigating the outcomes of chronic treatment with corticosterone (the major stress hormone) found variable effects, including depressive-like phenotype, up-regulation of miR-124, down-regulation of miR-124 targets (glucocorticoid receptor), and rescue of the phenotype by miR-124 antagomir [99–101].

MiR-124 was also investigated in relation to acute stress of various nature. Down-regulation of miR-124 was found in the amygdala, along with up-regulation of mineralocorticoid receptor, one of its targets [102]. Instead, increased expression of miR-124 was found in the hippocampus, correlated with a decrease of glucocorticoid receptor [103]. In a third work, the level of miR-124 in the hippocampus was down-regulated and lentiviral-mediated increase of miR-124 alleviated a PTSD-like behavior, with concomitant reduction of TNF receptor-associated Factor 6 and NF-κB [104].

In clinical studies, the level of miR-124 was found significantly higher in PBMC of MDD patients and either down-regulated or up-regulated after prolonged treatment with antidepressants [105, 106]. An interaction effect between miR-124 precursor gene 1 and polymorphisms of its target Regulator of G-Protein Signaling-4 (RGS4) was found, which could play a role in MDD development, with RGS4 polymorphisms possibly associated with antidepressant response [107]. In a further work, methylation levels of the three miR-124 precursor genes (miR124-1/2/3) were investigated in treated and untreated MDD patients. Mean methylation score was lower in MDD patients, with no changes in methylation induced by antidepressant treatment, suggesting that miR-124 methylation could be a diagnostic marker for MDD [108].

Overall, most studies have shown increased miR-124 with chronic stress rodent models or MDD. A number of prominent targets of miR-124 that could be involved in pathogenesis of depression have been identified, in particular the glucocorticoid receptor. Consequently, miR-124 has been suggested as a potential biomarker and therapeutic target for depression [109].

miR-132

The gene expressing miR-132 is an activity-regulated early response gene, regulated by the CREB protein pathway, and highly expressed in neurons where it increases spine density by translational inhibition of its target protein p250GAP, a GTPase-activating protein of the Rho family [110].

Different paradigms have been used to investigate whether miR-132 levels are modulated by acute and chronic stressors in different brain regions. Acute stress has been shown to induce a long-lasting increase of miR-132 expression. Exposure to predator scent and acute footshock increased miR-132 levels in the hippocampus and enhanced anxiety-like and cognitive impairments in mice up to 7 days after stress exposure [111]. Moreover, hippocampal miR-132 levels were increased 30 min after fear conditioning and returned to baseline levels after 120 min. Downregulation of miR-132 in the hippocampus impaired fear acquisition in trace memory in mice [112]. Acute multimodal stress paradigm increased miR-132 expression in both hippocampus and amygdala [113]. Single prolonged RS, a putative model for PTSD, increased miR-132 levels in the hippocampus [114] and PFC [115] of rats seven days after stress exposure. The injection of a lentiviral-mediated miR-132 inhibitor into lateral ventricle prevented the stress-induced behavioral changes and downregulation of fragile X-related protein 1, BDNF, tropomyosin receptor kinase B, synapsin-I, postsynaptic density protein 95 (PSD95) in the hippocampus [114] and PFC [115]. In addition, miR-132 reduction also prevented the decrease in the number of spine densities and the increase in apoptosis in PFC of single prolonged stressed animals [115].

As for effects of chronic stress, it was reported that adult rats exposed to early-life maternal separation showed an anxiety-like phenotype associated with increased miR-132 levels in the amygdala [98]. Remarkably, Lactobacillus supplementation reversed behavioral and molecular changes [98]. Similarly, miR-132 levels were increased also in the medial PFC of both young and adult rats exposed to maternal separation [48]. 14 days of chronic RS increased miR-132 levels in the amygdala but not in the hippocampus [113]. Moreover, in a recent paper increased levels of miR-132 in the PFC were found to play a key role in the induction of depressive-like behavior induced by chronic RS in mice, while the administration of miR-132 antagomir resulted in antidepressant-like effects [116]. Interestingly, prophylactic treatment with R-ketamine protected against the behavioral consequences of stress through mechanisms implying the prevention of miR-132 increase in the PFC.

Differently, CUMS reduced miR-132 levels in the hippocampus of mice, whereas no changes were observed in the frontal lobe [88]. Treatment with duloxetine was able to reverse both the behavioral changes and the reduction of miR-132 in the hippocampus [88]. In contrast, in another study miR-132 levels were found increased in the hippocampus of CUS-exposed mice, whereas BDNF and methyl-CpG binding protein 2 (MeCP2) levels decreased [117]. The downregulation of MeCP2 in primary hippocampal neurons enhanced miR-132 expression and reduced BDNF levels [117].

Remarkably, both the down- and upregulation of miR-132 in forebrain excitatory neurons affected basal anxiety and

differentially altered the expression of phosphatase and tensin homolog (PTEN) and Sirt1, two targets of miR-132, in the hippocampus and amygdala of mice [113].

Human studies consistently reported an increase of miR-132 levels in the blood of MDD patients [106, 117–120] while one work on post-mortem brain samples of bipolar and MDD patients found reduced or unchanged miR-132 expression compared to healthy controls, respectively [79].

miR-134

miR-134 is a brain-specific microRNA mainly expressed in the synaptic-dendritic compartment of neurons, where it negatively affects the density of dendritic spines by regulating synaptic LIM Domain Kinase 1 (Limk1) levels [121]. CUMS has been used to investigate the relationship between behavioral changes (depression-like and cognitive impairment) and miR-134 levels. CUMS specifically increased miR-134 levels in the hippocampus [88, 122, 123], ventro-medial PFC [124], and in the amygdala [125]. However, changes in miR-134 may be stress-related since two weeks of RS, although inducing a depressive-like behavior and a reduction of apical dendritic spines number in the CA1 hippocampal region, had no effect on miR-134 levels [126]. In another study, changes in hippocampal miR-134 levels were assessed in prenatal dexamethasone-exposed female offspring [127]. In this model, pregnant rats are injected with dexamethasone in the last week of gestation and the female offspring is exposed to chronic stress in adulthood (5 min swimming in ice water once a day for 2 weeks). Prenatally stressed rats displayed a depressive-like phenotype and increased miR-134 levels; these changes were higher in female rats exposed to chronic stress during the postnatal period. Interestingly, the H3K9 acetylation level on the miR-134 promoter was significantly increased in the fetal hippocampus of prenatally stressed rats, as well as in adult offspring before and after chronic stress.

The role of miR-134 is also demonstrated by the evidence that specific miR-134 knockdown in the hippocampus of mice prevented depression-like phenotypes and changes in spinal morphology after CUMS exposure [128, 129]. Furthermore, downregulation of miR-134 regulated autophagy in dendrites, improved mitochondrial deficit and induced autophagosome formation in the hippocampus of CUMS mice. These changes are partly due to miR-134 ability to directly reduce the expression of protein kinase AMP-activated catalytic subunit alpha 2 [129] and BDNF in the hippocampus [128]. Remarkably, overexpression of miR-134 in the hippocampus [128] or in the medial PFC [124] recapitulates behavioral, morphological, and molecular changes induced by CUMS [128]. Furthermore, overexpression of an adeno-associated virus miR-134 sponge in the medial PFC of UCMS stressed rats improved depressive-like behaviors, neuronal reduction in spine density, and rescued the reduction in Limk1 and p-cofilin in stressed rats [124]. Interestingly, treatment with duloxetine [88], ginsenoside [125] or exposure to an enriched environment [122] were able to restore miR-134 levels and behavioral changes in CUMS rodents.

Interestingly, miR-134 levels were found to be reduced not only in brain areas, but also in plasma of rats exposed to CUMS [130].

Clinical studies have also been conducted to investigate changes in plasma levels of miR-134 in depressed patients. MiR-134 plasma levels were found significantly lower in MDD patients than in control groups but, after 8 weeks of antidepressant therapy, mean miR-134 plasma levels increased in responders and partially responders, but not in non-responders [130].

miR-135

In the brain, miR-135 has been shown to play key roles in the control of neuronal morphology and dendritic spine remodeling ultimately controlling synaptic plasticity [131, 132]. miR-135 has two subtypes “a” and “b”. Acute RS in mice has been shown to decrease miR-135a levels in amygdala [102]. Accordingly, in vivo downregulation of miR-135a in the BLA of mice significantly altered glutamate transmission and increased anxiety-like behaviors [133]. Complexin 1 and 2, proteins involved in synaptic vesicle fusion, were identified as targets of miR-135a.

Other works adopted different protocols, obtaining converging evidence of reduced miR-135a expression after stress exposure. Adult mice subjected to CUMS had significantly reduced levels of miR-135a in the hippocampus and in the blood [134]. Importantly, both the intraperitoneal injection of miR-135a mimic and 3 week-treatment with fluoxetine rescued depressive-like behavior, hippocampal cell apoptosis, and inflammatory response induced by CUMS. Other authors, using repeated footshock on adolescent rats, found a strong decrease of miR-135a in the PFC of stressed rats, accompanied by an increase in depressive- and anxiety-like behavior, impaired learning ability and spatial memory [64]. Interestingly, the same trend was conserved in adulthood suggesting a role of miR-135 in the long-lasting effect of early exposure to stress.

One of the most striking pieces of evidence of miR-135a involvement in stress response has been produced by a study that investigated the role of miR-135a in regulating the serotonergic system activity [135]. Knockdown of miR-135 in the raphe nuclei increased anxiety-like behavior induced by CSDS and decreased the response to imipramine, while overexpression exerted opposite effects. These changes reflected alteration in the expression of serotonergic targets.

Conversely miR-135b was reported to be increased in the BLA complex of mice exposed to acute RS and auditory fear conditioning [136].

As regards clinical studies, there is general agreement on decreased levels of miR-135a in the blood of MDD patients compared to healthy controls [65, 134, 135]. Moreover, miR135a was found to be reduced also in raphe nuclei of post-mortem brain samples of depressed suicide victims [135]. MiR-135b was also increased in the serum of PTSD patients compared to healthy controls [136].

miR-218

Several studies linked miR-218 with stress and depression, although with some inconsistencies. Chronic administration of the stress hormone corticosterone to rats, together with inducing depressive-like behavior, was reported to increase miR-218 (and other miRNAs, including miR-124) expression in the PFC with mechanisms downstream the glucocorticoid receptor [99, 137]. Interestingly, high levels of circulating miR-218 in adolescent mice were associated with higher vulnerability to CSDS in adulthood, while miR-218 downregulation in medial PFC during adolescence promoted resilience to stress in adulthood, suggesting that miR-218 in adolescence could be considered as a peripheral marker of stress vulnerability in adulthood [138].

Conversely, in other studies a reduction of miR-218 levels has been associated with both stress vulnerability and MDD. MiR-218 was reduced in the PFC and blood of mice susceptible to CSDS [139, 140]. Interestingly, miR-218 downregulation in medial PFC increased stress susceptibility, whereas its overexpression promoted stress resilience [140]. Moreover, miR-218 was found to be reduced also post-mortem in the PFC of MDD patients compared to healthy controls [139].

miR-1202

According to miRbase, miR-1202 is a primate specific miRNA and is specifically enriched in the brain [141]. The expression level was found significantly downregulated in the PFC of depressed suicide patients [141]. Interestingly, miR-1202 was also found reduced in the blood of depressed subjects [65, 141], while antidepressants rescued these changes in responders [66, 142], suggesting that miR-1202 could be considered as a marker of antidepressant response efficacy in MDD.

GRM4, encoding the metabotropic glutamate receptor subtype 4, is a validated gene target of miR-1202 and the levels of miR-1202 were inversely correlated to the level of GRM4 expression in the PFC of patients [141].

Interestingly, using functional nuclear magnetic resonance of depressed subjects in combination with the analysis of miR-1202 before and after antidepressant treatment, it has been reported that miR-1202 expression variations correlate with activity in brain regions linked to depression [142].

General considerations and limitations on stress-related miRNAs and putative downstream biological processes

Although the miRNAs listed above are the most intensely studied in the context of stress response and stress-related psychiatric disorders, other miRNAs could also play relevant roles. As an example, it has been shown that miR-144-3p overexpression in mice BLA rescued impaired fear extinction and protected against fear renewal. Moreover, CUS significantly reduced levels of miR-144-3p in the mouse hippocampus while circulating miR-144-3p was also reported as a candidate biomarker for depression diagnosis and for ketamine treatment response. Also, miR-29c has been suggested to serve as a blood biomarker for stress-induced neuronal alterations [143–146].

On the other hand, genome-wide studies highlighted complex tissue- and stress-specific patterns of miRNA changes induced by stress in animal models [104, 136, 147–149] or associated with mood disorders in patients [136, 145, 150]. In general, studies that test single miRNAs involve an upstream choice that may represent an early bias; under this respect genome-wide studies may be more informative.

It must also be acknowledged that, even though converging preclinical and clinical evidence strongly support the involvement of miRNAs in both stress response and depressive behavior, the reported results are often inconsistent, and the same miRNA can be found up- or down-regulated depending on the experimental condition. This is particularly evident for preclinical studies, in which conflicting results may depend on the type and length of different stress protocols, species (rat/mouse), strains, sex, brain area or other tissues, time elapsed since the last stress session, stage of life when stress is administered (early life vs adulthood), method used for miRNA measurement (Northern blot, qPCR), and miRNA species analyzed (pri-miRNA, mature miRNA, -3p, -5p). Moreover, if in animal models behavioral changes can be easily associated with the measurement of miRNA levels in selected brain areas, human data are largely from peripheral tissues (mainly, blood or serum) and only rarely from post-mortem brains (with relevant preservation limits particularly for labile molecules such as small RNAs). Altogether, these differences make the translation of preclinical evidence to clinical level highly challenging and, instead of suggesting a main role for specific changes in individual miRNAs, support the involvement of a more complex modulatory pattern of several miRNAs in the etiopathogenesis of stress-related disorders.

Nevertheless, miRNAs remain appealing tools for the development of novel diagnostic and therapeutic approaches (see the following section). On the other hand, the study of molecular pathways and biological processes modulated by miRNAs involved in the stress response and stress-related psychiatric disorders could help in the identification of key pathophysiological mechanisms and novel pharmacological targets. With this idea, we have performed a bioinformatic analysis of the validated brain-enriched target genes (in humans) of the 9 miRNAs discussed in the previous section [see Supplementary Information for details]. The network analysis of the first 20 biological process terms highlights a central role for synaptic mechanisms, in particular synapse assembly (Fig. 2). Overall, our analysis suggests that the biological processes downstream of different stress-related miRNAs converge on the regulation of synaptic structure and function, thus confirming the key role of these mechanisms in both the neuronal response to stress and psychiatric disorders.

It is worth mentioning that previous studies have implicated some of these same miRNAs in other psychiatric disorders, such as schizophrenia and autism [151–154]. This is quite comprehensible, in view of a theoretical framework looking at mental illness as a continuum.

THE PROMISE OF MIRNA-BASED DIAGNOSIS AND THERAPY

Potential of miRNAs as biomarkers for diagnosis and drug treatment response

The pleiotropic properties of miRNAs, which may target multiple mRNAs and downstream pathways at the same time, have suggested their use both as biomarkers for diagnosis and as treatment drugs. Indeed, many non-communicable diseases have a multifactorial origin and the perspective of using the pleiotropic properties of miRNAs has greatly stimulated research and development in the last decade. The brain has a more complex regulation than other organs, which makes it more difficult to obtain efficient drugs by targeting single effectors in psychiatric disorders. Therefore, the opportunity offered by miRNAs to regulate multiple pathways could be in principle a potential solution to the problems of diagnosis and therapy in psychiatry (Fig. 3A). This opportunity has started to show some results in the last few years for diseases related to peripheral organs/systems. In particular, miRNA-based diagnostics have registered multiple advancements in oncology, where diagnostic tests for different forms of cancer, based on detection of miRNA panels in biopsies or body fluids, have been developed [155]. The development of miRNA-based tests for brain disorders is comparatively slower, with the only exception represented by CogniMIR, an assay for monitoring brain aging based on quantitative analysis of brain-enriched and inflammation-associated miRNAs in plasma. The test, still under development, should be used for detection of Alzheimer's disease at presymptomatic, mild cognitive impairment, and dementia stages [155]. However, assessment of peripheral biomarkers for brain disorders is limited by the possible lack of correspondence between peripheral and central measurements. A recent study analyzed the correspondence between miRNA expression in PBMC and 14 brain areas in baboons, using paired (within subject) samples [156]. They observed significant correlations between PBMC and the brain areas for tissue-wide patterns in miRNA expression. Co-expression between miRNAs among the different tissue types revealed major clusters of up- and downregulated miRNAs in the blood-based samples, with enrichment of miRNAs expressed in immune cell types. The results provided preliminary evidence of blood-brain correlation for miRNA expression, with particular emphasis on inflammation.

Although very promising, therapeutic applications are still lagging behind diagnostic ones, with the first approval of a small interfering RNA-related drug in 2018 paving the way for miRNA-related drugs [157]. However, many biotech companies have launched miRNA therapeutics in their development pipeline, and several candidate miRNA-related drugs are in clinical development or in phase 1 and 2 clinical trials for cancer, hepatitis C, cardiac failure, and others [158]. To our knowledge, none has entered clinical development yet for MDD, PTSD, or other psychiatric disorders. The major problems posed by the use of miRNA-related drugs are: (1) Efficient and targeted delivery; (2) Possible on- and off-target side-effects; (3) Poor stability [158–160]. Efficient and targeted delivery is essential for obtaining therapeutic effect and avoiding unwanted side effects. With the brain this is further complicated because only lipid-soluble small molecules (<400 daltons) may cross the blood-brain barrier (BBB). MiRNAs have hydrophilic nature, negative charge, and relatively high molecular weight, rendering them poorly permeable across biological membranes. Both non-viral (such as micelle, liposome,

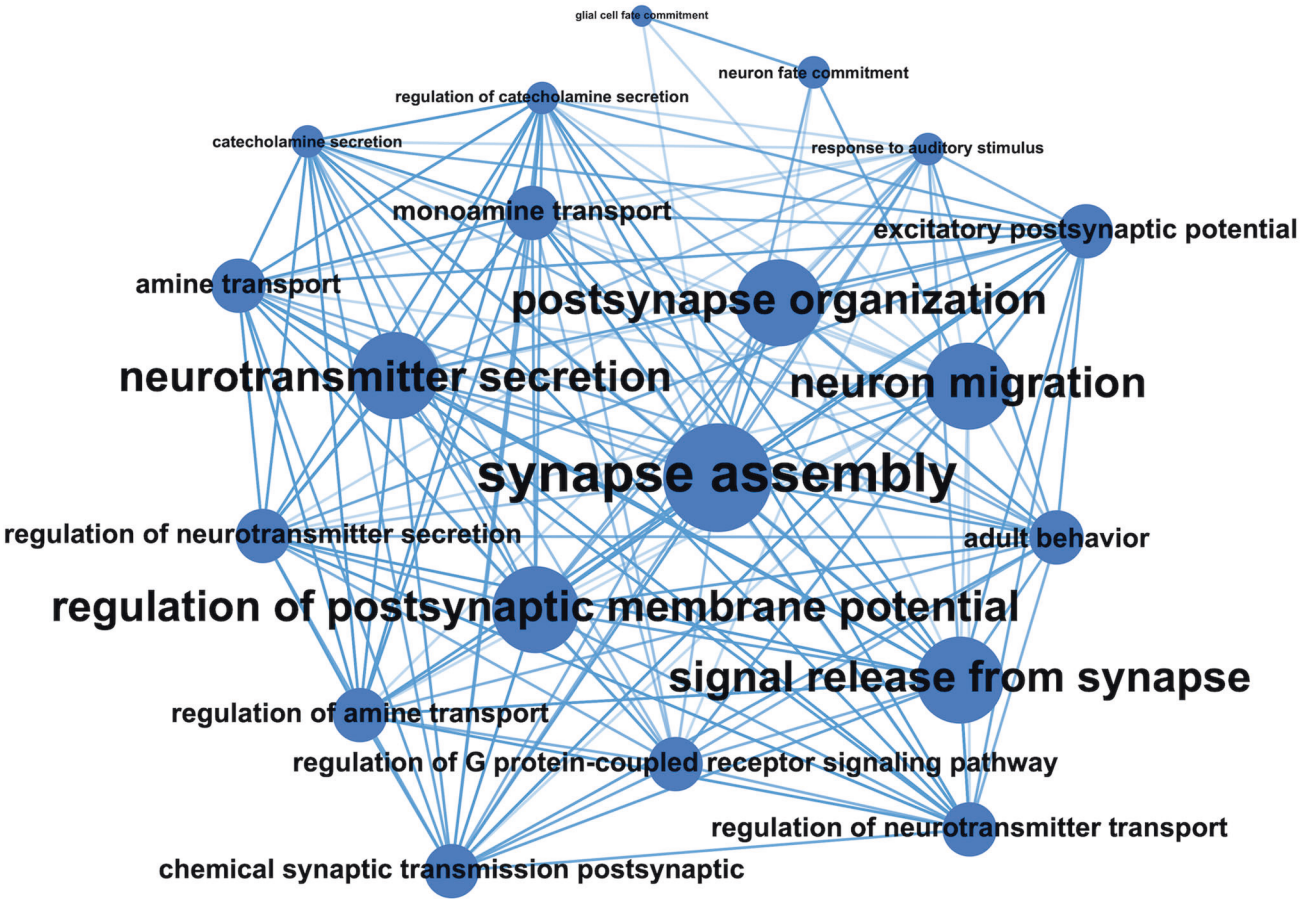

Fig. 2 Network analysis of the first 20 biological processes containing target genes of the nine stress-related microRNAs. The software Gephi was used to perform network analysis on the first 20 GO Biological Processes enriched in target genes of the 9 selected miRNAs (for more details, see Supplementary Information). Nodes represent GO Biological Processes and the size gradient represents Gene Ratio. The edges represent genes that are shared between GO categories and the color gradient of the edge is directly proportional to the number of genes shared.

nanoparticle, and others) and viral-mediated delivery (particularly adeno-associated viruses-based systems) are actively tested for the central nervous system [161, 162] (Fig. 3B). Indeed, crossing the BBB is still a major problem for miRNA-related drugs, and different tools are currently investigated, including intranasal delivery, far less invasive compared to other brain delivery routes, and exosomes (see below) [161].

On- and off-target side effects are a major challenge for the development of miRNA-therapeutics in the clinic. In general, miRNA-based therapeutics comprise synthetic miRNAs used to restore endogenous miRNA levels (miRNA mimics), antisense inhibitor oligonucleotides to prevent the interaction of an endogenous miRNA with its target mRNA (antimiRs or antagomiRs), or miRNA sponges containing multiple miRNA binding sites to trap and sequester miRNAs (Fig. 3B). In turn, the multi-targeting mode of miRNA action may cause problems. For instance, a miRNA can target mRNAs that exert opposing effects within the same molecular pathway, with on-target side effects [163]. Furthermore, a miRNA may affect targets in different molecular pathways, with off-target unwanted side effects. This requires careful target identification, based on the use of target prediction algorithms and cellular/molecular validation methods (see above). Editing of miRNA binding sites by using CRISPR/Cas9 systems is a promising approach for a more precise functional target validation [164]. Finally, poor stability inside the cellular milieu is another major challenge towards successful clinical development. Native miRNAs may encounter rapid intracellular degradation due to cell nucleases and this results in a short half-life in vivo [165].

These problems represent major limitations for the use of miRNAs for therapy of brain disorders and have greatly delayed so far the development of miRNA-related drugs. Future developments will show if the use of miRNAs can be implemented in spite of these difficulties. In the context of miRNA-based diagnosis and therapy exosomes have raised special interest (below).

The potential of exosomes for diagnosis and therapy

miRNAs not only modulate the function of the cells in which they are produced but can also be released into the extracellular space bound to proteins and lipids or incorporated into microvesicles, including exosomes.

Exosomes are bilayered extracellular vesicles with lipid structure and a diameter of 40 to 160 nm. They originate as intraluminal vesicles and are released into the extracellular space. Exosomes are secreted by almost all cell types and are present in almost all body fluids, including cerebrospinal fluid, saliva, breast milk, urine, and blood. As carriers of various signaling molecules such as DNAs, mRNAs, miRNAs, and proteins, they play an important role in cell-to-cell communication in both physiological and pathological processes. After fusion with recipient cell, they transfer their contents into the cell and modulate recipient cell functions [166]. Although the exact mechanisms for the specific targeting of exosomes to recipient cells are not well understood, it is known that various proteins and lipids in their membranes may play an

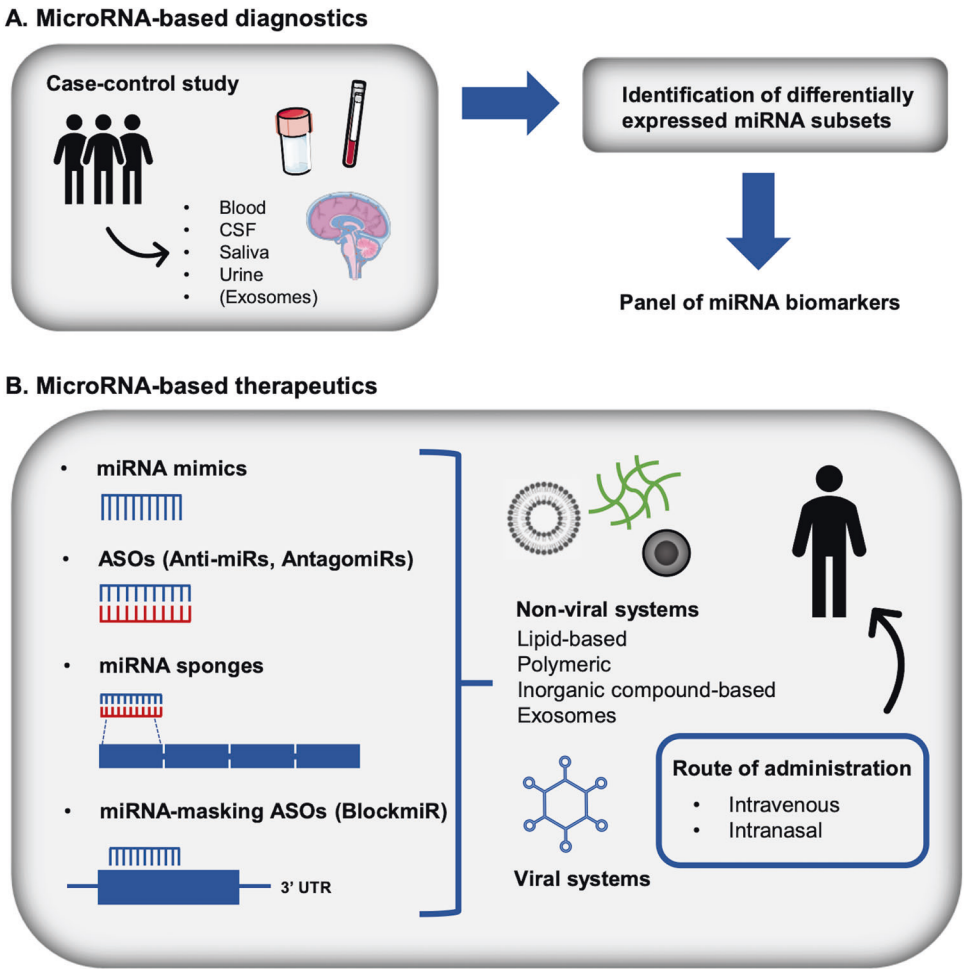

Fig. 3 The potential of microRNAs for diagnosis and therapy of stress-related psychiatric disorders. A MicroRNA-based diagnostics. The analysis of microRNAs (see Table 1 for methods) is increasingly used to identify panels of microRNAs as biomarkers for different disorders. MicroRNA analysis is performed in samples from peripheral tissues, including blood, CSF, saliva and urine. In addition, microRNA-containing exosomes may be obtained from the tissues. The assessment of differentially expressed microRNA subsets in case-control studies allows the identification of biomarkers for pathology. In principle, these biomarkers may also be used to monitor the response to treatment. **B** MicroRNA-based therapeutics. The manipulation of specific microRNA levels may be used for the treatment of psychiatric disorders. The agents that may be used include miRNA mimics (to obviate the demonstrated lack of a microRNA in a psychiatric disorder), antimiRs, miRNA sponges (to block the interaction of pathology-related miRNAs with their target mRNAs), or miRNA-masking antisense oligonucleotides (ASOs). Different forms of delivery may be used, including non-viral systems (lipid-based, polymeric, inorganic compound-based, exosomes), or viral-mediated administration. In the latter case viral vectors, such as adeno-associated viruses, could be used to overexpress or knock down a specific microRNA. The potential routes of administration suitable for targeting the central nervous system are intravenous and intranasal administrations. Created with Servier Medical Art (smart.servier.com).

important role in mediating this process. The composition of exosome membranes can vary depending on the cell origin as well as the physiological or pathological state of the parent cell during exosome biogenesis. Exosome membranes can be composed of various transmembrane proteins such as tetraspanins (e.g., CD81, CD82, CD37, CD63), antigen-presenting molecules (e.g., MHC-I, MHC-II), glycoproteins (e.g., beta-galactosidases, O-linked glycans, N-linked glycans), adhesion molecules (e.g., integrins, p-selectin), and signaling receptors (TNF receptor, FasL) that can interact with the receptor/ligand on the surface of target cells. In addition, lipids such as sphingomyelin, cholesterol, and ceramides are also components of exosome membranes that can also influence the response of target cells [167, 168].

Exosomes have great potential as a diagnostic tool in brain disorders because they can easily cross the BBB and provide information about the state of the brain [166].

As an example, it was recently reported that the number of circulating brain-enriched exosomes enriched for L1CAM+ (a marker predominantly expressed in the brain) was higher in MDD patients [169]. In addition, serum exosomes from MDD patients have higher expression levels of insulin receptor substrate-1, miR-9, and miR-139 compared with healthy controls [56, 169, 170]. Remarkably, injection of exosomes from the blood of MDD patients into the tail vein promoted a depressed-like phenotype in wild-type mice, suggesting a possible role of exosomes in the development of depression [170]. Similar results have also been described in preclinical rodent models. The expression patterns of miRNAs were altered in neuronal enriched exosomes isolated from the serum of mice exposed to footshock, 7 days after the end of stress exposure. Specifically, 13 miRNAs were upregulated and 11 downregulated [171]. Exosomes from stressed mice were enriched in ceramide, and injection of ceramide-enriched exosomes promoted depression-like phenotypes in non-stressed mice [172].

Exosomes are being actively investigated not only as diagnostic biomarkers but also as potential therapeutic tools, also as vehicles for drug delivery. Indeed, exosomes efficiently fuse with other cells and release their contents upon minimal immune response

following exogenous injection, at least in animal models [173]. As an example, bone marrow mesenchymal stem cell-derived exosomes upregulated miR-26a to promote neurogenesis in the hippocampus and block neuronal cell death in rats with depressed-like phenotype [174], and NK cell-derived exosomes were able to transport miR-207 and alleviate depression-like symptoms in mice [175].

Although exosomes are attractive as potential carriers for therapeutic drug delivery, the target specificity of native exosomes is low. Indeed, some approaches have recently been developed to modify exosome membrane proteins to promote site-specific delivery and limit the fraction lost to nonspecific excretion mechanisms [176]. For example, native exosome proteins have been chemically conjugated to the c(RGDyK) peptide (a specific ligand for the integrin αvβ3 expressed on cerebral vascular endothelial cells in response to ischemia) to selectively deliver drugs to the brain after intravenous administration [177]. Remarkably, c(RGDyK)-modified exosomes loaded with curcumin were shown to reduce neuroinflammation and cellular apoptosis in a mouse model of transient middle cerebral artery occlusion [177]. Recombinant DNA has also been used to produce cell lines that secrete modified exosomes that selectively target the brain. Specifically, exosomes expressing the membrane protein Lamb2 fused to the neuron-specific viral rabies glycoprotein (RVG) were produced. They were then purified, loaded with specific siRNAs, and administered intravenously to mice. Notably, the exosomes expressing RVG proteins were delivered to neurons, microglia, and oligodendrocytes of mice, resulting in selective downregulation of specific genes [178, 179].

CONCLUSION

Here we have given a comprehensive overview of the available evidence showing that miRNAs represent a key epigenetic system mediating the effects of stress in the brain, through changes in neuronal structure/function and behavior that may trigger stress-related psychiatric disorders. The pleiotropic properties of miRNAs seem well-suited for the regulation of complex brain processes, such as the stress response, and offer unprecedented opportunities for novel means of diagnosis and therapy in psychiatric disorders. However, the complexity of the brain miRNA system is such that the task of translating its potential into effective diagnostic tests and clinical treatments remains a considerable challenge.

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