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miRNAs in NMDA receptor-dependent synaptic plasticity and psychiatric disorders

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Abstract

The identification and functional delineation of miRNAs (a class of small non-coding RNAs) have added a new layer of complexity to our understanding of the molecular mechanisms underlying synaptic plasticity. Genome-wide association studies in conjunction with investigations in cellular and animal models, moreover, provide evidence that miRNAs are involved in psychiatric disorders. In the present review, we examine the current knowledge about the roles played by miRNAs in NMDA (*N*-methyl-D-aspartate) receptor-dependent synaptic plasticity and psychiatric disorders.

Keywords

miRNA; NMDA receptor; psychiatric disorders; synaptic plasticity

INTRODUCTION

miRNAs are non-coding RNAs that fine-tune the expression of their target genes [1, 2]. More than 2500 miRNAs have been annotated in the human genome, and more than 60% of human protein-coding genes are predicted miRNA targets [3]. Hundreds of miRNAs are expressed specifically in mammalian brains and participate in a variety of functions, including cell differentiation, neural development, learning, memory and behaviour [4, 5]. In addition to globally modulating gene expression, miRNAs can be localized to synaptic sites where they are regulated by neuronal activity and influence synaptic function locally [6–13]. In line with the importance of miRNAs for brains and synapses, miRNAs have been implicated in the aetiology and pathophysiology of neurodegenerative and psychiatric diseases [14–16]. For example, genetic variants in the *MIR137* gene are associated with the risk of schizophrenia [14]. In the present review, we focus on recent progress in interrogating the functions of miRNAs in synaptic plasticity, especially NMDA (*N*-methyl-D-aspartate) receptor-dependent long-term synaptic potentiation and depression, and the genetic association of miRNAs with psychiatric disorders.

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miRNA BIOGENESIS AND FUNCTION

miRNA biogenesis consists of three major steps, each of which produces a characteristic type of RNA (Figure 1). The first step is the transcription of miRNA genes by RNA polymerase II into pri-miRNAs (primary miRNAs), which usually are several kilobases long. The nuclear RNase III Drosha then recognizes the stem-loop structure of pri-miRNAs and cleaves them into pre-miRNAs (precursor miRNAs) which have 70–80 nt, a 2-nt 3′ overhang and a stem–loop structure [17]. Specific and effective cleavage of pri-miRNAs by Drosha requires DGCR8 (DiGeorge syndrome critical region 8), a double-stranded-RNA-binding protein that forms the pri-miRNA microprocessor complex with Drosha [18, 19]. Pre-miRNAs are transported from the nucleus to the cytoplasm by exportin-5 in a Ran/GTP-dependent manner [17]. The last step of miRNA biogenesis is the processing of pre-miRNAs by the RNase III Dicer, which recognizes the double-stranded region of the pre-miRNA hairpin and cleaves it into ~22 (15–34)-nt mature miRNAs [20, 21]. FMRP (fragile X mental retardation protein) interacts with miRNAs and Dicer [21].

Mature miRNAs primarily function as post-transcriptional inhibitors of protein synthesis by inhibiting translation or destabilizing mRNAs. In some cell types or conditions, however, miRNAs can also promote translation [22, 23]. Translational inhibition by miRNAs occurs in RISC (mRNA-induced silencing complex) (Figure 1), a ribonuclear protein complex consisting of AGO (Argonaut) 1, AGO2, Pumilio 2, MOV10 (Moloney leukaemia virus 10) and FMRP [21, 24–26]. Mature miRNAs are loaded into RISC where they serve as a guide for recognizing target mRNAs through imperfect base pairing with the MRE (miRNA-response element) in the 3′-UTR, 5′-UTR or coding region of the mRNAs [27–32]. The binding of miRNAs and target mRNAs can induce mRNA deadenylation and recapping, thereby repressing translation [33–36].

SUBCELLULAR LOCALIZATION OF miRNAs IN NEURONS

Neurons have elaborative dendrites and axons which can extend a great distance from the soma. The maintenance and modulation of synapses, many of which located on distal neurites, are dependent on *de novo* protein synthesis [6]. Both mRNAs and the translational machinery are present in dendrites and axons, and local translation plays important roles in a variety of neuronal activities, including axon outgrowth, synaptic plasticity and dendritic spine remodelling [6–13]. In addition to regulating global translation, miRNAs also take part in local protein synthesis as implicated by the presence of a subset of pri-, pre-and mature miRNAs in dendrites, axons and synaptic fractions [6–13]. Proteins in the miRNA biogenesis pathway, such as Drosha, DGCR8 and Dicer, are also present in the PSD (postsynaptic density) fraction [37, 38]. Dicer in PSD is regulated by synaptic activity. NMDA stimulation of hippocampal slices or calcium treatment of synaptoneurosomes (a subcellular preparation enriched in pre- and post-synaptic components) causes the release of Dicer from PSD and enhancement of its RNase activity [37]. These observations suggest that miRNA production can be locally regulated by synaptic activity. This regulation serves as a post-transcriptional means of modulating protein synthesis in active synapses. This notion is supported by the findings that miRNAs (such as *miR-26a*, *miR-191*, *miR-135* and *miR-501-3p*) are located in dendrites, and their expression can be regulated by synaptic

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activity [6, 7, 10–12, 38, 39]. For instance, NMDA receptor activation inhibits *miR-191* expression locally in dendrites, which in turn leads to elevation of its target tropomodulin-2 [11].

miRNAs and RISC are also in axons [40]. Natera-Naranjo et al. [41] detected ~130 mature miRNAs in the axons of superior cervical ganglia neurons, and showed that several of them, including *miR-16*, *miR-204*, *miR-221* and *miR-15b*, are highly enriched in distal axons. *miR-338* is found in axons, where it regulates the translation of cytochrome *c* oxidase IV mRNAs [42]. In addition to mature miRNAs, a subset of pre-miRNAs, whose mature forms are enriched in the axons of sympathetic neurons, are also present in axons [43]. It is likely that the close proximity of miRNAs to synapses facilitates the spatial and temporal precision of synaptic protein regulation, thereby ensuring efficient and individualized modulation of synapses in response to synaptic excitation.

NMDA RECEPTOR-DEPENDENT SYNAPTIC PLASTICITY

The strength of synaptic transmission can be modulated by neural activity. Synaptic plasticity is the ability of synapses to increase or decrease their efficacies [44]. The change in synaptic strength can last from milliseconds to weeks [45]. Long-term synaptic plasticity, including LTP (long-term potentiation) and LTD (long-term depression) of synapses, is an important cellular mechanism underlying information storage in the brain [46–49]. Long-term synaptic plasticity can be classified by its primary site of expression (such as presynaptic plasticity and postsynaptic plasticity), or by the type of neurotransmitter receptor that is required for induction such as NMDA receptor-dependent, mGluR (metabotropic glutamate receptor)-dependent or muscarinic receptor-dependent plasticity [50–54]. The present review focuses on NMDA receptor-dependent LTP and LTD.

NMDA receptors are ionotropic glutamate receptors which are ubiquitously expressed in the nervous system. They are blocked by Mg^{2+} at resting membrane potentials and are activated by both glutamate binding and membrane depolarization (for the removal of Mg^{2+} blockade) [55]. A number of induction protocols are used to induce NMDA receptor-dependent synaptic plasticity, such as high-frequency (100 Hz) stimulation, theta burst stimulation, pairing of pre- and post-synaptic spiking, and low-frequency (1 Hz) stimulation [56–59]. In hippocampal slices, NMDA receptor activation results in Ca^{2+} influx which engages signalling cascades that regulate AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptor trafficking [60]. The modulation of AMPA receptor trafficking results in insertion or removal of AMPA receptors from synapses, the primary mechanism underlying the expression of NMDA receptor-dependent synaptic plasticity [61–64]. The duration and exact mechanism of NMDA receptor-dependent synaptic plasticity are dependent on the stimulation intensity [63]. Strong stimulation induces long-lasting LTP or LTD that requires translation, whereas weak stimulation-induced synaptic modification persists for no more than 2 h and is independent of protein synthesis [64–67].

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REGULATION OF NMDA RECEPTOR-DEPENDENT SYNAPTIC PLASTICITY BY miRNAs

miRNAs play multifaceted roles in NMDA receptor-dependent synaptic plasticity. They determine the capacity of neurons to modulate synaptic strength by controlling the expression level of NMDA receptors, AMPA receptors and signalling molecules in the synaptic plasticity pathway [43, 68–71]. They also modulate the translation of selective proteins in response to synaptic activation to maintain synaptic potentiation or depression for prolonged periods of time [72].

NMDA receptors are heterotetramers, containing two GluN1 subunits and two GluN2A–GluN2D or GluN3A/GluN3B sub-units [73]. The expression of GluN2A and GluN2B is developmentally regulated in the hippocampus, with GluN2A increasing and GluN2B decreasing during brain maturation [74]. NMDA receptors are miRNA targets [75, 76]. The 3′-UTRs of *GluN2A* and *GluN2B* mRNAs contain numerous computationally predicted miRNA-binding sites [71], and several of them have been experimentally validated. Corbel et al. [71] showed that *GluN2B* is targeted by *miR-539* and *GluN2A* is targeted by *miR-19a*. Moreover, the same group showed that *miR-539* and *miR-19a* are inversely correlated with GluN2B and GluN2A expression during development, and therefore appear to influence the temporal pattern of NMDA receptor expression [71]. Other researchers reported that the *miR-223*-binding site controls GluN2B expression in response to excitotoxicity [77], and the *miR-125b*–binding site in the *GluN2A* 3′-UTR confers the regulation by FMRP [78].

miRNAs also control the synaptic expression of AMPA receptors. Using the 3′-UTR of *GluA1* mRNAs as bait, we pulled down their binding miRNAs and identified *miR-501-3p* as a regulator of GluA1 expression [12]. *miR-501-3p* not only determines the basal level of GluA1 expression, but also is responsible for NMDA receptor-dependent reduction in GluA1 in rat hippocampal neurons [12]. Moreover, *miR-501-3p* is up-regulated locally in dendrites following NMDA receptor activation, indicative of its contribution to local protein synthesis [12]. Other validated miRNAs targeting *GluA1* mRNAs include *miR-92a* [79]. Letellier et al. [79] showed that *miR-92* mediates the down-regulation of GluA1 in response to activity blockade by tetrodotoxin and AP5 (2R–amino-5-phosphonovaleric acid), a selective NMDA receptor antagonist [79]. The GluA2 subunit of AMPA receptors is regulated by *miR-124, miR-223* and *miR-181* [77, 80, 81].

Perturbation of miRNA biogenesis causes a global decrease in miRNA expression and an enhancement of synaptic plasticity. In the hippocampal CA1 region of heterozygous DGCR8-knockout mice, LTP is changed in an age-dependent manner, increasing in 16–20-week-old mice, but remaining intact in 8–10-week-old animals [82]. A 60 % loss of Dicer in adult mice has no effect on LTP, but increases post-tetanic potentiation [83]. Since most mRNAs can be targeted by many different miRNAs, and each miRNA regulates the translation of many different mRNAs that have the same MRE sequence [84], the global change in miRNA transcriptomes in DGCR8 and Dicer mutant mice hampers the extrapolation of each miRNA's specific function. Individual miRNAs therefore need to be manipulated to address this issue.

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Since it is a daunting task to investigate the synaptic functions of the hundreds of miRNAs expressed in mammalian brains one by one, several groups have used large-scale systematic approaches to identify candidate plasticity miRNAs. Park and Tang [85] induced chemical LTP with TEA (tetraethylammonium), a K^+channel blocker, and mGluR-LTD in mouse hippocampal slices, and then extracted RNAs for miRNA microarray [85]. They detected 62 miRNAs in hippocampal slices [85]. With a few exceptions, the majority of them were up-regulated: 55 by LTP and 59 by mGluR-LTD induction [85]. The Bramham laboratory analysed miRNA expression using microarray in the rat dentate gyrus after *in vivo* LTP induction [86]. They showed that, of the 237 probes on the chip, ten miRNAs increased and 11 miRNAs decreased expression at 2 h after stimulation of the medial perforant pathway [86]. Using real-time PCR, they were able to validate the expression change in *miR-132, miR-212* and *miR-219*, and detected alteration of mature and pri-miRNAs by NMDA receptor activation [86].

We recently combined the NGS (next-generation sequencing) platform and bioinformatic analysis to interrogate the functions of miRNAs in NMDA receptor-dependent LTP and LTD [11, 13]. The hippocampal slices were stimulated at the Schaffer collateral pathway with high-frequency stimulation for LTP induction or treated with NMDA for LTD induction. At 90 min after stimulation, the CA1 region was removed for RNA analysis with NGS. We detected a total of 438 miRNAs in the hippocampal CA1 area, with 70 of them changed in LTD (34 up-regulated and 36 down-regulated) and 12 changed in LTP (six down-regulated and six up-regulated) [11, 13]. It is interesting that all miRNAs up-regulated in LTP belong to the *let-7* family [13]. We confirmed the NGS result using real-time PCR and tested the functional significance of miRNA expression change. We found that the alteration of *miR-26a* and *miR-384-5p* is required for protein-synthesis-dependent maintenance, but not induction, of LTP [13]. We identified RSK3 (ribosomal S6 kinase 3),a protein kinase that regulates translation, as a target gene that mediates the functions of *miR-26a* and *miR-384-5p* in LTP [13].

Of the miRNAs changed in LTD, we selected *miR-191* and *miR-135* for functional analysis and revealed that they are required for LTD induction [11]. In addition, both *miR-191* and *miR-135* are required for maintenance, but not induction, of spine remodelling accompanying LTD [11]. The reduction in *miR-191* in LTD leads to an increase in tropomodulin-2 (an actin cytoskeleton regulator), whereas complexin-1/2, which regulates AMPA receptor exocytosis, confers the function of *miR-135* in spine remodelling [11].

We examined the concerted effect of the miRNA transcriptome change on gene expression and cellular activities using bioinformatics. This approach shows that the target genes of miRNAs altered in LTP or LTD are enriched in cellular pathways related to synaptic functions and dendritic spines, such as 'synaptic transmission', 'actin filament-based process', 'cytoskeletal protein binding', 'regulation of phosphorylation', and 'small GTPase-mediated signal transduction' [11, 13]. These miRNAs therefore function as hubs that orchestrate the structural and functional modification of synapses.

The changes in miRNAs following NMDA receptor activation vary in direction and magnitude, indicative of the heterogeneity of the underlying induction mechanisms. NMDA

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receptor activity is both necessary and sufficient to alter miRNA expression, whereas GluN2A–containing and GluN2B–containing NMDA receptors play different roles [87]. In LTD, GluN2A activity is required for the increases in *miR-135* and *miR-501-3p* [11, 12], whereas the decrease in *miR-191* is caused by GluN2B activation [11]. Both transcriptional and post-transcriptional regulation of miRNAs is engaged in by GluN2A and GluN2B in LTD. By contrast, GluN2A is responsible for the decreases in *miR-26a* and *miR-384-5p* at post-transcriptional levels in LTP [13]. It remains to be determined, however, how GluN2A and GluN2B control miRNA expression. In the rat dentate gyrus, *miR-132* and *miR-212* increase following LTP induction by high-frequency stimulation of the medial perforant pathway. This increase requires transcription and is abolished by the group 1 mGluR antagonist AIDA [(*RS*)-1-aminoindan-1,5-dicarboxylic acid]. AIDA does not affect LTP induction or maintenance, but blocks activity-dependent depotentiation of LTP. miRNAs that are related to NMDA receptor-dependent synaptic plasticity are listed in Table 1, and the regulation of their expression is illustrated in Figure 1.

In addition to NMDA receptor-dependent synaptic plasticity, miRNAs participate in other forms of synaptic plasticity. *miR-124* inhibits serotonin-induced synaptic facilitation by regulating CREB (cAMP-response-element-binding protein), a transcription factor, in *Aplysia* [8], *miR-92* contributes to tetrodotoxin and AP5-induced homoeostatic synaptic scaling by controlling GluA1 expression [79], overexpression of *miR-132* increases the paired-pulse ratio (a form of short-term presynaptic plasticity) [88], knockout of *miR-132* and *miR-212* enhances in the hippocampus (but inhibits in the cortex) theta burst-induced LTP [89], and *miR-137* overexpression impairs mossy fibre LTP [90].

miRNA GENES IN THE AETIOLOGY OF PSYCHIATRIC DISORDERS

The structure, function and plasticity of synapses are pivotal for normal brain function, and their impairments are closely associated with brain disorders. Along with the findings of diverse and important functions influenced by miRNAs in synaptic physiology, human genetic studies indicate that miRNAs are associated with a risk of psychiatric disorders, including schizophrenia, ASD (autism spectrum disorder), bipolar disorder and panic disorder.

Analysis of CNVs (copy number variants), a form of rare structural genetic changes, reveals that people carrying the 22q11.2 deletion have an increased risk of mental illness such as schizophrenia [91, 92]. The 22q11.2 locus contains seven miRNA genes and *DGCR8* [19, 93]. DGCR8 haploinsufficiency causes miRNA deficiency and contributes to synaptic alterations found in the 22q11.2-deletion mouse model [94]. Moreover, a genome-wide survey of miRNAs in rare CNVs shows that the schizophrenia group is enriched in individuals with a rare CNV overlapping a miRNA gene [95].

GWAS (genome-wide association studies) also point out the contribution of miRNAs to the genetic basis of schizophrenia. The Psychiatric Genomics Consortium recently reported a GWAS using 36989 cases and 113075 controls, and identified 108 genomic loci that are associated with schizophrenia [96]. It was noted that the 108 loci contain 22 miRNA genes [96–98]. In a schizophrenia GWAS of >21856 individuals of European ancestry and a

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replication sample of 29839 independent subjects, the strongest genome-wide significant association identified is within the *MIR137* gene [99]. The association of *MIR137* with schizophrenia is corroborated by a later GWAS in a Swedish national sample (5001 cases, 6243 controls) that reported 22 genome-wide significant regions, one of which is the *MIR137* locus [100]. *miR-137* regulates presynaptic plasticity in human neurons [90]. In neurons differentiated from human fibroblasts, the minor allele SNPs (single nucleotide polymorphisms) associated with schizophrenia at the *MIR137* locus cause an increase in *miR-137* expression, down-regulation of its presynaptic target genes (complexin-1, Nsf and synaptotagmin-1), and impairment of vesicle release, mossy fibre LTP and hippocampus-dependent learning and memory [90]. *miR-137* may therefore contribute to the synaptopathology of schizophrenia. The genetic association of genes with schizophrenia implies that gene expression is altered in schizophrenia. Indeed, hundreds of genes are found to be altered in various brain regions of schizophrenics. These findings, however, are difficult to interpret, because almost all patients have been treated with antipsychotics, which probably affect gene expression in the brain. Giving this confounding factor and the comprehensive reviews in the literature on gene expression changes in schizophrenia [101–105], we focus the present review on genetic studies [102].

In addition to schizophrenia, miRNA genes are associated with other psychiatric disorders. The 22q11.2 deletion is also associated with ASDs [106]. The ASD-associated 3p14.1, 7q11.23 and 10q11.23-21.1 loci contain a total of four miRNA genes [107–109]. A gene-based analysis of all known autosomal miRNAs using a GWAS dataset of bipolar disorder (9747 patients and 14278 controls) found nine miRNAs that showed significant associations with bipolar disorder [110]. miRNAs are potentially involved in the aetiology of panic disorder [111]. A case–control study for SNPs tagging miRNA genes in patients with panic disorder showed that several miRNA genes are associated with the disease [112]. miRNAs that are genetically associated with psychiatric disorders are listed in Table 2.

CONCLUSIONS AND PERSPECTIVES

The experimental evidence discussed above indicates that miRNAs play both permissive and instructive roles in the modulation of NMDA receptor-dependent synaptic plasticity. They set the basal levels of synaptic proteins to enable the induction and expression of synaptic plasticity, and reset their expression in response to NMDA receptor activation to engage the signalling cascades for long-term modification of synapses. Although in both LTP and LTD, miRNAs are changed in a NMDA receptor-dependent manner, the isoform of NMDA receptors and the specific miRNAs that are involved differ. Hence the mechanisms underlying neuronal activity-dependent miRNA expression appear to vary by specific miRNAs. The mechanistic link between NMDA receptor activation and miRNA expression, however, is currently unknown. It is an interesting question for future research.

Only a few of the hundreds of brain-expressed miRNAs have been examined for their functions. Given that a large number of miRNAs target to synaptic proteins or signalling proteins regulating synapses, it is predicted that more miRNAs function in synaptic plasticity. Laborious experimental testing is a major limiting step in characterizing individual miRNAs. High-throughput functional tests are needed to facilitate this process.

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The implication of synaptic plasticity in cognition and the genetic association of miRNAs with psychiatric disorders raise the possibility that miRNAs contribute to the pathogenesis of psychiatric disorders, in part, through their influence on synaptic plasticity. This notion is supported by the findings that some miRNAs (such as *miR-137*) conferring risk of psychiatric diseases regulate synaptic plasticity in rodents. However, it needs to be consolidated by more experiments testing the significance of synaptic plasticity for psychiatric disorders and functions of risk miRNAs.

Abbreviations

AGO	Argonaut
AIDA	(*RS*)-1-aminoindan-1,5-dicarboxylic acid
AMPA	α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
AP5	2R–amino-5-phosphonovaleric acid
ASD	autism spectrum disorder
CNV	copy number variant
DGCR8	DiGeorge syndrome critical region 8
FMRP	fragile X mental retardation protein
GWAS	genome-wide association studies
LTD	long-term depression
LTP	long-term potentiation
mGluR	metabotropic glutamate receptor
MRE	miRNA-response element
NGS	next-generation sequencing
NMDA	*N*-methyl-D-aspartate
pre-miRNA	precursor miRNA
pri-miRNA	primary miRNA
PSD	postsynaptic density
RISC	mRNA-induced silencing complex
SNP	single nucleotide polymorphism

References

1. Martinez NJ, Gregory RI. MicroRNA gene regulatory pathways in the establishment and maintenance of ESC identity. Cell Stem Cell. 2010; 7:31–35. [PubMed: 20621047]

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2. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009; 136:215–233. [PubMed: 19167326]
3. Friedman RC, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res. 2009; 19:92–105. [PubMed: 18955434]
4. Kim J, Krichevsky A, Grad Y, Hayes GD, Kosik KS, Church GM, Ruvkun G. Identification of many microRNAs that copurify with polyribosomes in mammalian neurons. Proc. Natl. Acad. Sci. U.S.A. 2004; 101:360–365. [PubMed: 14691248]
5. Sayed D, Abdellatif M. MicroRNAs in development and disease. Physiol. Rev. 2011; 91:827–887. [PubMed: 21742789]
6. Kye MJ, Liu T, Levy SF, Xu NL, Groves BB, Bonneau R, Lao K, Kosik KS. Somatodendritic microRNAs identified by laser capture and multiplex RT-PCR. RNA. 2007; 13:1224–1234. [PubMed: 17592044]
7. Lugli G, Torvik VI, Larson J, Smalheiser NR. Expression of microRNAs and their precursors in synaptic fractions of adult mouse forebrain. J. Neurochem. 2008; 106:650–661. [PubMed: 18410515]
8. Rajasethupathy P, Fiumara F, Sheridan R, Betel D, Puthanveettil SV, Russo JJ, Sander C, Tuschl T, Kandel E. Characterization of small RNAs in *Aplysia* reveals a role for miR-124 in constraining synaptic plasticity through CREB. Neuron. 2009; 63:803–817. [PubMed: 19778509]
9. Smalheiser NR, Lugli G. microRNA regulation of synaptic plasticity. Neuromol. Med. 2009; 11:133–140.
10. Pichardo-Casas I, Goff LA, Swerdel MR, Athie A, Davila J, Ramos-Brossier M, Lapid-Volosin M, Friedman WJ, Hart RP, Vaca L. Expression profiling of synaptic microRNAs from the adult rat brain identifies regional differences and seizure-induced dynamic modulation. Brain Res. 2012; 1436:20–33. [PubMed: 22197703]
11. Hu Z, Yu D, Gu QH, Yang Y, Tu K, Zhu J, Li Z. miR-191 and miR-135 are required for long-lasting spine remodelling associated with synaptic long-term depression. Nat. Commun. 2014; 5:3263. [PubMed: 24535612]
12. Hu Z, Zhao J, Hu T, Luo Y, Zhu J, Li Z. miR-501-53p mediates the activity-dependent regulation of the expression of AMPA receptor subunit GluA1. J. Cell Biol. 2015; 208:949–959. [PubMed: 25800054]
13. Gu QH, Yu D, Hu Z, Liu X, Yang Y, Luo Y, Zhu J, Li Z. miR-26a and miR-384-35p are required for LTP maintenance and spine enlargement. Nat. Commun. 2015; 6:6789. [PubMed: 25858512]
14. Issler O, Chen A. Determining the role of microRNAs in psychiatric disorders. Nat. Rev. Neurosci. 2015; 16:201–212. [PubMed: 25790865]
15. Delay C, Mandemakers W, Hebert SS. MicroRNAs in Alzheimer's disease. Neurobiol. Dis. 2012; 46:285–290. [PubMed: 22285895]
16. Kim DH, Yeo SH, Park JM, Choi JY, Lee TH, Park SY, Ock MS, Eo J, Kim HS, Cha HJ. Genetic markers for diagnosis and pathogenesis of Alzheimer's disease. Gene. 2014; 545:185–193. [PubMed: 24838203]
17. Yi R, Qin Y, Macara IG, Cullen BR. Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. Genes Dev. 2003; 17:3011–3016. [PubMed: 14681208]
18. Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ. Processing of primary microRNAs by the Microprocessor complex. Nature. 2004; 432:231–235. [PubMed: 15531879]
19. Gregory RI, Yan KP, Amuthan G, Chendrimada T, Doratotaj B, Cooch N, Shiekhattar R. The Microprocessor complex mediates the genesis of microRNAs. Nature. 2004; 432:235–240. [PubMed: 15531877]
20. Gwizdek C, Ossareh-Nazari B, Brownawell AM, Doglio A, Bertrand E, Macara IG, Dargemont C. Exportin-5 mediates nuclear export of minihelix-containing RNAs. J. Biol. Chem. 2003; 278:5505–5508. [PubMed: 12509441]
21. Jin P, Zarnescu DC, Ceman S, Nakamoto M, Mowrey J, Jongens TA, Nelson DL, Moses K, Warren ST. Biochemical and genetic interaction between the fragile X mental retardation protein and the microRNA pathway. Nat. Neurosci. 2004; 7:113–117. [PubMed: 14703574]
22. Vasudevan S, Tong Y, Steitz JA. Switching from repression to activation: microRNAs can up-regulate translation. Science. 2007; 318:1931–1934. [PubMed: 18048652]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

23. Orom UA, Nielsen FC, Lund AH. MicroRNA-10a binds the 5′UTR of ribosomal protein mRNAs and enhances their translation. Mol. Cell. 2008; 30:460–471. [PubMed: 18498749]
24. Kawamata T, Tomari Y. Making RISC. Trends Biochem. Sci. 2010; 35:368–376. [PubMed: 20395147]
25. Mourelatos Z, Dostie J, Paushkin S, Sharma A, Charroux B, Abel L, Rappsilber J, Mann M, Dreyfuss G. miRNPs: a novel class of ribonucleoproteins containing numerous microRNAs. Genes Dev. 2002; 16:720–728. [PubMed: 11914277]
26. Hammond SM, Boettcher S, Caudy AA, Kobayashi R, Hannon GJ. Argonaute2, a link between genetic and biochemical analyses of RNAi. Science. 2001; 293:1146–1150. [PubMed: 11498593]
27. Cheng HY, Papp JW, Varlamova O, Dziema H, Russell B, Curfman JP, Nakazawa T, Shimizu K, Okamura H, Impey S, Obrietan K. microRNA modulation of circadian-clock period and entrainment. Neuron. 2007; 54:813–829. [PubMed: 17553428]
28. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004; 116:281–297. [PubMed: 14744438]
29. Zeng Y, Yi R, Cullen BR. MicroRNAs and small interfering RNAs can inhibit mRNA expression by similar mechanisms. Proc. Natl. Acad. Sci. U.S.A. 2003; 100:9779–9784. [PubMed: 12902540]
30. Rana TM. Illuminating the silence: understanding the structure and function of small RNAs. Nat. Rev. Mol. Cell Biol. 2007; 8:23–36. [PubMed: 17183358]
31. Lytle JR, Yario TA, Steitz JA. Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5′ UTR as in the 3′ UTR. Proc. Natl. Acad. Sci. U.S.A. 2007; 104:9667–9672. [PubMed: 17535905]
32. Forman JJ, Legesse-Miller A, Coller HA. A search for conserved sequences in coding regions reveals that the let-7 microRNA targets Dicer within its coding sequence. Proc. Natl. Acad. Sci. U.S.A. 2008; 105:14879–14884. [PubMed: 18812516]
33. Eulalio A, Huntzinger E, Nishihara T, Rehwinkel J, Fauser M, Izaurralde E. Deadenylation is a widespread effect of miRNA regulation. RNA. 2009; 15:21–32. [PubMed: 19029310]
34. Behm-Ansmant I, Rehwinkel J, Doerks T, Stark A, Bork P, Izaurralde E. mRNA degradation by miRNAs and GW182 requires both CCR4:NOT deadenylase and DCP1:DCP2 decapping complexes. Genes Dev. 2006; 20:1885–1898. [PubMed: 16815998]
35. Wakiyama M, Takimoto K, Ohara O, Yokoyama S. Let-7 microRNA-mediated mRNA deadenylation and translational repression in a mammalian cell-free system. Genes Dev. 2007; 21:1857–1862. [PubMed: 17671087]
36. Mathonnet G, Fabian MR, Svitkin YV, Parsyan A, Huck L, Murata T, Biffo S, Merrick WC, Darzynkiewicz E, Pillai RS, et al. MicroRNA inhibition of translation initiation *in vitro* by targeting the cap-binding complex eIF4F. Science. 2007; 317:1764–1767. [PubMed: 17656684]
37. Lugli G, Larson J, Martone ME, Jones Y, Smalheiser NR. Dicer and eIF2c are enriched at postsynaptic densities in adult mouse brain and are modified by neuronal activity in a calpain-dependent manner. J. Neurochem. 2005; 94:896–905. [PubMed: 16092937]
38. Lugli G, Larson J, Demars MP, Smalheiser NR. Primary microRNA precursor transcripts are localized at post-synaptic densities in adult mouse forebrain. J. Neurochem. 2012; 123:459–466. [PubMed: 22897173]
39. Schratt G. microRNAs at the synapse. Nat. Rev. Neurosci. 2009; 10:842–849. [PubMed: 19888283]
40. Hengst U, Cox LJ, Macosko EZ, Jaffrey SR. Functional and selective RNA interference in developing axons and growth cones. J. Neurosci. 2006; 26:5727–5732. [PubMed: 16723529]
41. Natera-Naranjo O, Aschrafi A, Gioio AE, Kaplan BB. Identification and quantitative analyses of microRNAs located in the distal axons of sympathetic neurons. RNA. 2010; 16:1516–1529. [PubMed: 20584895]
42. Aschrafi A, Schwechter AD, Mameza MG, Natera-Naranjo O, Gioio AE, Kaplan BB. MicroRNA-338 regulates local cytochrome *c* oxidase IV mRNA levels and oxidative phosphorylation in the axons of sympathetic neurons. J. Neurosci. 2008; 28:12581–12590. [PubMed: 19020050]
43. Kim HH, Kim P, Phay M, Yoo S. Identification of precursor microRNAs within distal axons of sensory neuron. J. Neurochem. 2015; 134:193–199. [PubMed: 25919946]

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44. Nicoll RA, Schmitz D. Synaptic plasticity at hippocampal mossy fibre synapses. Nat. Rev. Neurosci. 2005; 6:863–876. [PubMed: 16261180]

45. Klug A, Borst JG, Carlson BA, Kopp-Scheinpflug C, Klyachko VA, Xu-Friedman MA. How do short-term changes at synapses fine-tune information processing? J. Neurosci. 2012; 32:14058–14063. [PubMed: 23055473]

46. Citri A, Malenka RC. Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology. 2008; 33:18–41. [PubMed: 17728696]

47. Bear MF, Malenka RC. Synaptic plasticity: LTP and LTD. Curr. Opin. Neurobiol. 1994; 4:389–399. [PubMed: 7919934]

48. Siegelbaum SA, Kandel ER. Learning-related synaptic plasticity: LTP and LTD. Curr. Opin. Neurobiol. 1991; 1:113–120. [PubMed: 1822291]

49. Xu J, Kang J. The mechanisms and functions of activity-dependent long-term potentiation of intrinsic excitability. Rev. Neurosci. 2005; 16:311–323. [PubMed: 16519008]

50. Bashir ZI, Bortolotto ZA, Davies CH, Berretta N, Irving AJ, Seal AJ, Henley JM, Jane DE, Watkins JC, Collingridge GL. Induction of LTP in the hippocampus needs synaptic activation of glutamate metabotropic receptors. Nature. 1993; 363:347–350. [PubMed: 8388549]

51. Oliet SH, Malenka RC, Nicoll RA. Two distinct forms of long-term depression coexist in CA1 hippocampal pyramidal cells. Neuron. 1997; 18:969–982. [PubMed: 9208864]

52. Dudek SM, Bear MF. Homosynaptic long-term depression in area CA1 of hippocampus and effects of *N*-methyl-d-aspartate receptor blockade. Proc. Natl. Acad. Sci. U.S.A. 1992; 89:4363–4367. [PubMed: 1350090]

53. Bortolotto ZA, Collingridge GL. Characterisation of LTP induced by the activation of glutamate metabotropic receptors in area CA1 of the hippocampus. Neuropharmacology. 1993; 32:1–9. [PubMed: 8381524]

54. Lee HK, Kameyama K, Huganir RL, Bear MF. NMDA induces long-term synaptic depression and dephosphorylation of the GluR1 subunit of AMPA receptors in hippocampus. Neuron. 1998; 21:1151–1162. [PubMed: 9856470]

55. Jahr CE, Stevens CF. Calcium permeability of the *N*-methyl-d-aspartate receptor channel in hippocampal neurons in culture. Proc. Natl. Acad. Sci. U.S.A. 1993; 90:11573–11577. [PubMed: 8265592]

56. Dan Y, Poo MM. Spike timing-dependent plasticity: from synapse to perception. Physiol. Rev. 2006; 86:1033–1048. [PubMed: 16816145]

57. Caporale N, Dan Y. Spike timing-dependent plasticity: a Hebbian learning rule. Annu. Rev. Neurosci. 2008; 31:25–46. [PubMed: 18275283]

58. Norris CM, Korol DL, Foster TC. Increased susceptibility to induction of long-term depression and long-term potentiation reversal during aging. J. Neurosci. 1996; 16:5382–5392. [PubMed: 8757251]

59. Lüscher C, Malenka RC. NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). Cold Spring Harb. Perspect. Biol. 2012; 4:a005710. [PubMed: 22510460]

60. Elias GM, Nicoll RA. Synaptic trafficking of glutamate receptors by MAGUK scaffolding proteins. Trends Cell Biol. 2007; 17:343–352. [PubMed: 17644382]

61. Matsuzaki M, Honkura N, Ellis-Davies GC, Kasai H. Structural basis of long-term potentiation in single dendritic spines. Nature. 2004; 429:761–766. [PubMed: 15190253]

62. Holtmaat A, Svoboda K. Experience-dependent structural synaptic plasticity in the mammalian brain. Nat. Rev. Neurosci. 2009; 10:647–658. [PubMed: 19693029]

63. Nagerl UV, Eberhorn N, Cambridge SB, Bonhoeffer T. Bidirectional activity-dependent morphological plasticity in hippocampal neurons. Neuron. 2004; 44:759–767. [PubMed: 15572108]

64. Huganir RL, Nicoll RA. AMPARs and synaptic plasticity: the last 25 years. Neuron. 2013; 80:704–717. [PubMed: 24183021]

65. Wang XB, Yang Y, Zhou Q. Independent expression of synaptic and morphological plasticity associated with long-term depression. J. Neurosci. 2007; 27:12419–12429. [PubMed: 17989307]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

66. Redondo RL, Morris RG. Making memories last: the synaptic tagging and capture hypothesis. Nat. Rev. Neurosci. 2011; 12:17–30. [PubMed: 21170072]
67. Bramham CR, Alme MN, Bittins M, Kuipers SD, Nair RR, Pai B, Panja D, Schubert M, Soule J, Tiron A, Wibrand K. The Arc of synaptic memory. Exp. Brain Res. 2010; 200:125–140. [PubMed: 19690847]
68. van Spronsen M, van Battum EY, Kuijpers M, Vangoor VR, Rietman ML, Pothof J, Gumy LF, van Ijcken WF, Akhmanova A, Pasterkamp RJ, Hoogenraad CC. Developmental and activity-dependent miRNA expression profiling in primary hippocampal neuron cultures. PLoS One. 2013; 8:e74907. [PubMed: 24098357]
69. Dotti CG, Sullivan CA, Banker GA. The establishment of polarity by hippocampal neurons in culture. J. Neurosci. 1988; 8:1454–1468. [PubMed: 3282038]
70. Kaech S, Banker G. Culturing hippocampal neurons. Nat. Protoc. 2006; 1:2406–2415. [PubMed: 17406484]
71. Corbel C, Hernandez I, Wu B, Kosik KS. Developmental attenuation of *N*-methyl-d-aspartate receptor subunit expression by microRNAs. Neural Dev. 2015; 10:20. [PubMed: 26381867]
72. Mollinari C, Racaniello M, Berry A, Pieri M, de Stefano MC, Cardinale A, Zona C, Cirulli F, Garaci E, Merlo D. miR-34a regulates cell proliferation, morphology and function of newborn neurons resulting in improved behavioural outcomes. Cell Death Dis. 2015; 6:e1622. [PubMed: 25633291]
73. Hollmann M, Heinemann S. Cloned glutamate receptors. Annu. Rev. Neurosci. 1994; 17:31–108. [PubMed: 8210177]
74. Lecointre M, Vézier C, Bénard M, Ramdani Y, Dupré N, Brasse-Lagnel C, Henry VJ, Roy V, Marret S, Gonzalez BJ, et al. Age-dependent alterations of the NMDA receptor developmental profile and adult behavior in postnatally ketamine-treated mice. Dev. Neurobiol. 2015; 75:315–333. [PubMed: 25220981]
75. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell. 2005; 120:15–20. [PubMed: 15652477]
76. Wang X, El Naqa IM. Prediction of both conserved and nonconserved microRNA targets in animals. Bioinformatics. 2008; 24:325–332. [PubMed: 18048393]
77. Harraz MM, Eacker SM, Wang X, Dawson TM, Dawson VL. MicroRNA-223 is neuroprotective by targeting glutamate receptors. Proc. Natl. Acad. Sci. U.S.A. 2012; 109:18962–18967. [PubMed: 23112146]
78. Edbauer D, Neilson JR, Foster KA, Wang CF, Seeburg DP, Batterton MN, Tada T, Dolan BM, Sharp PA, Sheng M. Regulation of synaptic structure and function by FMRP-associated microRNAs miR-125b and miR-132. Neuron. 2010; 65:373–384. [PubMed: 20159450]
79. Letellier M, Elramah S, Mondin M, Soula A, Penn A, Choquet D, Landry M, Thoumine O, Favereaux A. miR-92a regulates expression of synaptic GluA1-containing AMPA receptors during homeostatic scaling. Nat. Neurosci. 2014; 17:1040–1042. [PubMed: 25017011]
80. Ho VM, Dallalzadeh LO, Karathanasis N, Keles MF, Vangala S, Grogan T, Poirazi P, Martin KC. GluA2 mRNA distribution and regulation by miR-124 in hippocampal neurons. Mol. Cell. Neurosci. 2014; 61:1–12. [PubMed: 24784359]
81. Saba R, Störchel PH, Aksoy-Aksel A, Kepura F, Lippi G, Plant TD, Schratt GM. Dopamine-regulated microRNA MiR-181a controls GluA2 surface expression in hippocampal neurons. Mol. Cell. Biol. 2012; 32:619–632. [PubMed: 22144581]
82. Earls LR, Fricke RG, Yu J, Berry RB, Baldwin LT, Zakharenko SS. Age-dependent microRNA control of synaptic plasticity in 22q11 deletion syndrome and schizophrenia. J. Neurosci. 2012; 32:14132–14144. [PubMed: 23055483]
83. Konopka W, Kiryk A, Novak M, Herwerth M, Parkitna JR, Wawrzyniak M, Kowarsch A, Michaluk P, Dzwonek J, Arnsperger T, et al. MicroRNA loss enhances learning and memory in mice. J. Neurosci. 2010; 30:14835–14842. [PubMed: 21048142]
84. Krek A, Grün D, Poy MN, Wolf R, Rosenberg L, Epstein EJ, MacMenamin P, da Piedade I, Gunsalus KC, Stoffel M, Rajewsky N. Combinatorial microRNA target predictions. Nat. Genet. 2015; 37:495–500.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

85. Park CS, Tang SJ. Regulation of microRNA expression by induction of bidirectional synaptic plasticity. J. Mol. Neurosci. 2009; 38:50–56. [PubMed: 18998061]

86. Wibrand K, Panja D, Tiron A, Ofte ML, Skaftnesmo KO, Lee CS, Pena JT, Tuschl T, Bramham CR. Differential regulation of mature and precursor microRNA expression by NMDA and metabotropic glutamate receptor activation during LTP in the adult dentate gyrus *in vivo*. Eur. J. Neurosci. 2010; 31:636–645. [PubMed: 20384810]

87. Kim MJ, Dunah AW, Wang YT, Sheng M. Differential roles of NR2A- and NR2B–containing NMDA receptors in Ras-ERK signaling and AMPA receptor trafficking. Neuron. 2005; 46:745–760. [PubMed: 15924861]

88. Lambert TJ, Storm DR, Sullivan JM. MicroRNA132 modulates short-term synaptic plasticity but not basal release probability in hippocampal neurons. PLoS One. 2010; 5:e15182. [PubMed: 21206919]

89. Remenyi J, van den Bosch MW, Palygin O, Mistry RB, McKenzie C, Macdonald A, Hutvagner G, Arthur JS, Frenguelli BG, Pankratov Y. miR-132/212 knockout mice reveal roles for these miRNAs in regulating cortical synaptic transmission and plasticity. PLoS One. 2013; 8:e62509. [PubMed: 23658634]

90. Siegert S, Seo J, Kwon EJ, Rudenko A, Cho S, Wang W, Flood Z, Martorell AJ, Ericsson M, Mungenast AE, Tsai LH, et al. The schizophrenia risk gene product miR-137 alters presynaptic plasticity. Nat. Neurosci. 2015; 18:1008–1016. [PubMed: 26005852]

91. Rees E, Kirov G, Sanders A, Walters JT, Chambert KD, Shi J, Szatkiewicz J, O'Dushlaine C, Richards AL, Green EK, et al. Evidence that duplications of 22q11.2 protect against schizophrenia. Mol. Psychiatry. 2014; 19:37–40. [PubMed: 24217254]

92. Karayiorgou M, Simon TJ, Gogos JA. 22q11.2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia. Nat. Rev. Neurosci. 2010; 11:402–416. [PubMed: 20485365]

93. Karayiorgou M, Morris MA, Morrow B, Shprintzen RJ, Goldberg R, Borrow J, Gos A, Nestadt G, Wolyniec PS, Lasseter VK, et al. Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. Proc. Natl. Acad. Sci. U.S.A. 1995; 92:7612–7616. [PubMed: 7644464]

94. Stark KL, Xu B, Bagchi A, Lai WS, Liu H, Hsu R, Wan X, Pavlidis P, Mills AA, Karayiorgou M, Gogos JA. Altered brain microRNA biogenesis contributes to phenotypic deficits in a 22q11-deletion mouse model. Nat. Genet. 2008; 40:751–760. [PubMed: 18469815]

95. Warnica W, Merico D, Costain G, Alfred SE, Wei J, Marshall CR, Scherer SW, Bassett AS. Copy number variable microRNAs in schizophrenia and their neurodevelopmental gene targets. Biol. Psychiatry. 2015; 77:158–166. [PubMed: 25034949]

96. Ripke S, Neale BM, Corvin A, Walters JT, Farh KH, Holmans PA, Lee P, Bulik-Sullivan B, Collier DA, Huang H, et al. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014; 511:421–427. [PubMed: 25056061]

97. Merico D, Costain G, Butcher NJ, Warnica W, Ogura L, Alfred SE, Brzustowicz LM, Bassett AS. MicroRNA dysregulation, gene networks, and risk for schizophrenia in 22q11.2 deletion syndrome. Front. Neurol. 2014; 5:238. [PubMed: 25484875]

98. Xu B, Hsu PK, Stark KL, Karayiorgou M, Gogos JA. Derepression of a neuronal inhibitor due to miRNA dysregulation in a schizophrenia-related microdeletion. Cell. 2013; 152:262–275. [PubMed: 23332760]

99. Ripke S, Sanders AR, Kendler KS, Levinson DF, Sklar P, Holmans PA, Lin DY, Duan J, Ophoff RA, Andreassen OA, et al. Genome-wide association study identifies five new schizophrenia loci. Nat. Genet. 2011; 43:969–976. [PubMed: 21926974]

100. Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kähler AK, Akterin S, Bergen SE, Collins AL, Crowley JJ, Fromer M, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat. Genet. 2013; 45:1150–1159. [PubMed: 23974872]

101. Lin CY, Sawa A, Jaaro-Peled H. Better understanding of mechanisms of schizophrenia and bipolar disorder: from human gene expression profiles to mouse models. Neurobiol. Dis. 2012; 45:48–56. [PubMed: 21914480]

102. Iwamoto K, Kato T. Gene expression profiling in schizophrenia and related mental disorders. Neuroscientist. 2006; 12:349–361. [PubMed: 16840711]

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103. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol. Psychiatry. 2005; 10:40–68. [PubMed: 15263907]
104. Mirnics K, Middleton FA, Lewis DA, Levitt P. Delineating novel signature patterns of altered gene expression in schizophrenia using gene microarrays. ScientificWorldJournal. 2001; 1:114–116.
105. Kumarasinghe N, Tooney PA, Schall U. Finding the needle in the haystack: a review of microarray gene expression research into schizophrenia. Aust. N.Z. J. Psychiatry. 2012; 46:598–610. [PubMed: 22441207]
106. Radoeva PD, Coman IL, Salazar CA, Gentile KL, Higgins AM, Middleton FA, Antshel KM, Fremont W, Shprintzen RJ, Morrow BE, Kates WR. Association between autism spectrum disorder in individuals with velocardiofacial (22q11.2 deletion) syndrome and PRODH and COMT genotypes. Psychiatr. Genet. 2014; 24:269–272. [PubMed: 25325218]
107. Girirajan S, Brkanac Z, Coe BP, Baker C, Vives L, Vu TH, Shafer N, Bernier R, Ferrero GB, Silengo M, et al. Relative burden of large CNVs on a range of neurodevelopmental phenotypes. PLoS Genet. 2011; 7:e1002334. [PubMed: 22102821]
108. Vaishnavi V, Manikandan M, Tiwary BK, Munirajan AK. Insights on the functional impact of microRNAs present in autism-associated copy number variants. PLoS One. 2013; 8:e56781. [PubMed: 23451085]
109. Sanders SJ, Ercan-Sencicek AG, Hus V, Luo R, Murtha MT, Moreno-De-Luca D, Chu SH, Moreau MP, Gupta AR, Thomson SA, et al. Multiple recurrent *de novo* CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. Neuron. 2011; 70:863–885. [PubMed: 21658581]
110. Forstner AJ, Hofmann A, Maaser A, Sumer S, Khudayberdiev S, Mühleisen TW, Leber M, Schulze TG, Strohmaier J, Degenhardt F, et al. Genome-wide analysis implicates microRNAs and their target genes in the development of bipolar disorder. Transl. Psychiatry. 2015; 5:e678. [PubMed: 26556287]
111. Muiños-Gimeno M, Espinosa-Parrilla Y, Guidi M, Kagerbauer B, Sipilä T, Maron E, Pettai K, Kananen L, Navinés R, Martín-Santos R, et al. Human microRNAs miR-22, miR-138-132, miR-148a, and miR-488 are associated with panic disorder and regulate several anxiety candidate genes and related pathways. Biol. Psychiatry. 2011; 69:526–533. [PubMed: 21168126]
112. Hommers LG, Domschke K, Deckert J. Heterogeneity and individuality: microRNAs in mental disorders. J. Neural Transm. (Vienna). 2015; 122:79–97. [PubMed: 25395183]
113. Kawashima H, Numakawa T, Kumamaru E, Adachi N, Mizuno H, Ninomiya M, Kunugi H, Hashido K. Glucocorticoid attenuates brain-derived neurotrophic factor-dependent upregulation of glutamate receptors via the suppression of microRNA-132 expression. NeuroScience. 2010; 165:1301–1311. [PubMed: 19958814]
114. Zheng H, Tang R, Yao Y, Ji Z, Cao Y, Liu Z, Peng F, Wang W, Can D, Xing H, et al. miR-219 protects against seizure in the kainic acid model of epilepsy. Mol. Neurobiol. 2016; 53:1–7. [PubMed: 25394384]
115. Wright C, Calhoun VD, Ehrlich S, Wang L, Turner JA, Bizzozero NI. Meta gene set enrichment analyses link miR-137-regulated pathways with schizophrenia risk. Front. Genet. 2015; 6:147. [PubMed: 25941532]
116. Xu Y, Li F, Zhang B, Zhang K, Zhang F, Huang X, Sun N, Ren Y, Sui M, Liu P. MicroRNAs and target site screening reveals a pre-microRNA-30e variant associated with schizophrenia. Schizophr. Res. 2010; 119:219–227. [PubMed: 20347265]
117. Zhao D, Lin M, Chen J, Pedrosa E, Hrabovsky A, Fourcade HM, Zheng D, Lachman HM. MicroRNA profiling of neurons generated using induced pluripotent stem cells derived from patients with schizophrenia and schizoaffective disorder, and 22q11.2 del. PLoS One. 2015; 10:e0132387. [PubMed: 26173148]
118. Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, Nord AS, Kusenda M, Malhotra D, Bhandari A, et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science. 2008; 320:539–543. [PubMed: 18369103]

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119. Kirov G, Grozeva D, Norton N, Ivanov D, Mantripragada KK, Holmans P, Craddock N, Owen MJ, O'Donovan MC. Support for the involvement of large copy number variants in the pathogenesis of schizophrenia. Hum. Mol. Genet. 2009; 18:1497–1503. [PubMed: 19181681]
120. Levinson DF, Duan J, Oh S, Wang K, Sanders AR, Shi J, Zhang N, Mowry BJ, Olincy A, Amin F, et al. Copy number variants in schizophrenia: confirmation of five previous findings and new evidence for 3q29 microdeletions and VIPR2 duplications. Am. J. Psychiatry. 2011; 168:302–316. [PubMed: 21285140]
121. Ghahramani Seno MM, Hu P, Gwadry FG, Pinto D, Marshall CR, Casallo G, Scherer SW. Gene and miRNA expression profiles in autism spectrum disorders. Brain Res. 2011; 1380:85–97. [PubMed: 20868653]
122. Levy D, Ronemus M, Yamrom B, Lee YH, Leotta A, Kendall J, Marks S, Lakshmi B, Pai D, Ye K, et al. Rare *de novo* and transmitted copy-number variation in autistic spectrum disorders. Neuron. 2011; 70:886–897. [PubMed: 21658582]
123. Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, Regan R, Conroy J, Magalhaes TR, Correia C, Abrahams BS, et al. Functional impact of global rare copy number variation in autism spectrum disorders. Nature. 2010; 466:368–372. [PubMed: 20531469]
124. Marshall CR, Noor A, Vincent JB, Lionel AC, Feuk L, Skaug J, Shago M, Moessner R, Pinto D, Ren Y, et al. Structural variation of chromosomes in autism spectrum disorder. Am. J. Hum. Genet. 2008; 82:477–488. [PubMed: 18252227]
125. Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, Yamrom B, Yoon S, Krasnitz A, Kendall J, et al. Strong association of de novo copy number mutations with autism. Science. 2007; 316:445–449. [PubMed: 17363630]

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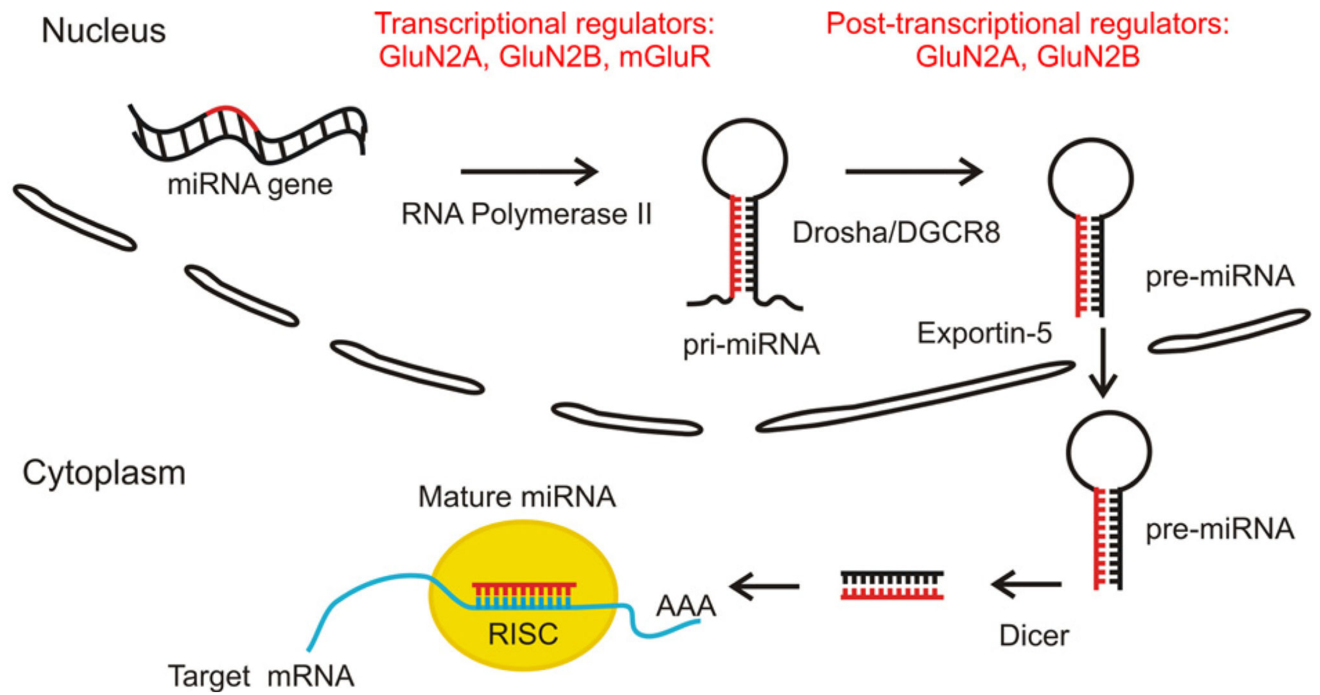

Figure 1.

The biogenesis and regulation of miRNAs relevant to NMDA receptor-dependent synaptic plasticity

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Table 1

miRNAs relevant to NMDA receptor-dependent synaptic plasticity

miRNA	Links to NMDA receptor-dependent synaptic plasticity	Reference(s)
miR-19a	Regulates GluN2A expression	[71]
miR-26a	Down-regulated by GluN2A–dependent mechanisms in LTP, required for protein synthesis-dependent maintenance (but not induction) of LTP	[13]
miR-34a	Decreases the density of NMDA-evoked currents and facilitates synaptic response	[72]
miR-92a	Mediates tetrodotoxin and AP5-induced down-regulation of GluA1	[79]
miR-124	Controls GluA2 surface expression	[80]
miR-125b	Targets GluN2A, increases longer and thinner dendritic protrusions, and weakens synaptic strength	[78]
miR-132	Down-regulated by NMDA receptor activation, up-regulated by BDNF (brain-derived neurotrophic factor), mediates BDNF-induced increases in GluN2A and GluN2B, increases the width of dendritic protrusions, and enhances synaptic strength	[78, 86, 113]
miR-135	Required for maintenance of spine restructuring in NMDA receptor-dependent LTD by regulating AMPA receptor exocytosis	[11]
miR-181	Enriched at medium spiny neuron synapses of the nucleus accumbens, induced by dopamine signalling in primary neurons, reduces GluA2 surface expression, spine formation and mEPSC (miniature excitatory postsynaptic current) frequency in hippocampal neurons	[81]
miR-191	Required for maintenance of spine restructuring in NMDA receptor-dependent LTD by regulating actin depolymerization	[11]
miR-212	Down-regulated by NMDA receptor activation	[86]
miR-219	Down-regulated by NMDA receptor activation, inhibits NMDA receptor function by targeting CaMKIIγ (Ca^{2+}/calmodulin-dependent protein kinase IIγ)	[86, 114]
miR-223	Reduces GluN2B and inhibits NMDA-induced Ca^{2+} influx	[77]
miR-384-5p	Down-regulated by GluN2A–dependent mechanisms in LTP, required for protein synthesis-dependent maintenance (but not induction) of LTP	[13]
miR-501-3p	Up-regulated locally in dendrites by GluN2A activation, and this increase is required for NMDA-induced suppression of GluA1 expression and long-lasting remodelling of dendritic spines	[12]
miR-539	Regulates GluN2B expression	[71]

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Table 2

miRNAs implicated in psychiatric disorders by GWAS and CNV studies

miRNA	Disease	Reference(s)
miR-499, *miR-708*, *miR-1908*	Bipolar disorder	[110]
miR-23a-5p, *miR-29b2*, *miR-29c*, *miR-30e*, *miR-130a*, *miR-137*, *miR-146b-3p*, *miR-185*, *miR-211*, *miR-548AJ2*, *miR-648*, *miR-649*, *miR-650*, *miR-767-5p*, *miR-1228*, *miR-1281*, *miR-1286*, *miR-1306*, *miR-1307*, *miR-2682*, *miR-3160-1*, *miR-3160-2*, *miR-3618*, *miR-3655*, *miR-3667-3P*, *miR-3667-5p*, *miR-4301*, *miR-4304*, *miR-4529*, *miR-4677*, *miR-4761*, *miR-4771*, *miR-6773*, *miR-6816*, *miR-6889*, *miR-8064*, *miR-8072*	Schizophrenia	[95–98, 115–120]
miR-34a, *miR-124*, *miR-181b*, *miR-195*, *miR-200b*, *miR-211*, *miR-429*, *miR-486*, *miR-497*, *miR-548f*, *miR-570*, *miR-590-3p*, *miR-605*, *miR-630*, *miR-944*, *miR-1286*, *miR-1306*, *miR-3136*, *miR-3618*, *miR-4284*, *miR-4715*	Autism spectrum disorders	[108, 109, 121–125]
miR-22, *miR-138-2*, *miR-148a*, *miR-488*, *miR-491*	Panic disorders	[111]