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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - REVIEW ARTICLE

Heterogeneity and Individuality: microRNAs in Mental Disorders

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Abstract MicroRNAs are about 22 nucleotide long single-stranded RNA molecules, negatively regulating gene expression of a single gene or a gene network. In neural tissues, they have been implicated in developmental and neuroplasticity-related processes, such as neurogenesis, differentiation, apoptosis and long-term potentiation. Their molecular mode of action is reminiscent of findings of genome-wide association studies in mental disorders, unable to attribute the risk of disease to a specific gene, but rather to multiple genes, gene-networks and gene-environment interaction. As such, microRNAs are an attractive target for research. Here, we review clinical studies conducted in humans on microRNAs in mental disorders with a particular focus on schizophrenia, bipolar disorder, major depressive disorder and anxiety disorders. The majority of clinical studies have focused on schizophrenia. The most robust finding has been reported for rs1625579 located in *MIR137HG*, which was associated with schizophrenia on a genome-wide level. Concerning bipolar disorder, major depression and anxiety disorders, promising results have been published, but only a considerably smaller number of clinical studies is available and genome-wide association studies did not suggest a direct link to microRNAs so far. Expression of microRNAs as biomarkers of mental disorders and treatment response is currently emerging with preliminary results. Larger-scaled genetic and functional studies along with translational research are needed to enhance our understanding of microRNAs in mental disorders. These studies will aid in disentangling the complex genetic nature of these disorders and possibly contribute to the development of novel, individualized diagnostic and therapeutic approaches.

Keywords Psychiatric · miRNA · Review · Psychiatry · Disease · Clinical

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Introduction

The pathogenesis of mental disorders is a field of highly active research, and many aspects remain elusive. The molecular roles of microRNAs represent intriguing mechanisms, which may unify some aspects of competing disease models. Discovered more than 20 years ago (Lee et al. 1993), mature microRNAs are small, about 22 nucleotide long single-stranded RNA molecules, which canonically lead to downregulation of gene expression upon interference with the 3′-untranslated region (UTR) of one or several target mRNAs, thereby regulating gene networks (Bartel and Chen 2004). MicroRNAs are located within hostgenes (intronic protein coding, intronic non-protein coding or exonic non-protein coding) or located intergenic and about 50 % of microRNAs are found in clusters (Kim and Nam 2006). Genomic analysis has revealed that the density of polymorphisms within microRNA genes is low, emphasizing their master regulatory role (Han and Zheng 2013). However, genetic variation in microRNA-binding sites may cause expression of many genes to differ, further supporting a key regulatory role for microRNAs (Kim and Bartel 2009).

Several proteins are involved in the biogenesis and molecular action of microRNAs (Bartel 2004), and six major steps, summarized in Fig. 1, have been outlined: (I) RNA polymerase II transcribes double-stranded hairpin structures of up to 1,000 nucleotides length (primary (pri-)microRNA), which are (II) cleaved by a complex containing the endonuclease Drosha and the Drosha/DiGeorge syndrome critical region 8 (DGCR8) to about 100 nucleotide long microRNA precursors/stem loops (pre-microRNA). The precursors are (III) exported from the nucleus by two proteins, Exportin5 and Ras-related nuclear protein (RanGTP). In the cytoplasm they are (IV) further processed by the protein Dicer and its cofactor Tar RNA-binding protein (TRBP) to microRNA duplexes by cleaving the loop and finally (V) to single, mature microRNA strands upon disruption of the duplex by the protein Helicase. One or both strands are loaded (VI) onto the Argonaute homologue protein Ago2, leading to the formation of the RNA-induced silencing complex (RISC) in combination with a target mRNA.

Genes encoding microRNAs are named using the three-letter prefix "mir" with an identifying number (e.g. *MIR22* in *Homo sapiens*, *Mir22* in *Mus musculus*). To refer to a non-protein-coding hostgene of a given microRNA, the extension "HG" may be used (e.g. *MIR22HG*). Orthologs share the same number, regardless of organism, paralogs are distinguished by a lettered suffix and distinct genomic loci yielding identical mature microRNA sequences are indicated by numerical suffixes (e.g. *MIR15B, Mir15b* or *MIR16-1*). The name of a mature microRNA sequence contains at least three parts: (I) a prefix indicating the species in combination with (II) the prefix "miR" and (III) the number as used for the microRNA gene, all divided by a hyphen. If two mature sequences, derived from the 5′- and 3′-arm of the hairpin-structured precursor-microRNA (see below) have been identified, (IV) the suffixes "-5p" or "-3p" are used to indicate the strand (e.g. hsa-miR-22-3p in *Homo sapiens* or mmu-miR-15b-5p in *Mus musculus*). When referring to microRNA hairpin precursor sequences or microRNA gene families, the species-indicating prefix is omitted and the prefix "miR" is written in lowercase (e.g. miR-22). Nomenclature of microRNAs has been addressed in detail elsewhere (Ambros et al. 2003; Griffiths-Jones et al. 2006; Kozomara and Griffiths-Jones 2014).

In mammals, microRNAs work by imperfect base-pairing with the target mRNA (Ambros 2004). The "seed sequence" of the mature microRNA, involving at least nucleotides 2–7, canonically forms perfect base-pairing with the mRNA, being a crucial, but not the exclusive determinator of the stability of microRNA: mRNA interaction (Grimson et al. 2007). Several bioinformatic algorithms have been developed for the prediction of microRNA:mRNA interaction (Sethupathy et al. 2006; Mu and Zhang 2012; Peterson et al. 2014) and more than 60 %

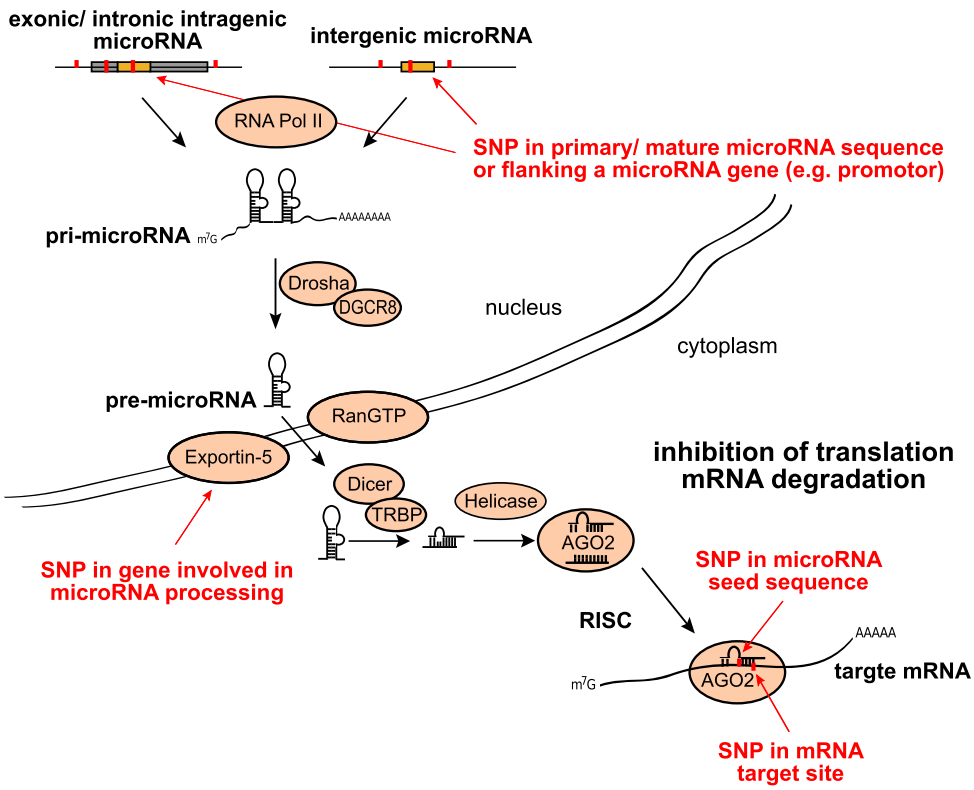

Fig. 1 Canonical mechanism of microRNA action and consequences of genetic variants. MicroRNAs are transcribed and processed from primary transcripts as explained in the text in six major steps, leading to single stranded, about 22 nucleotide long mature RNA molecules. Genetic variation such as single nucleotide polymorphisms (SNPs) may interfere with microRNA transcription, processing and microRNA action. Importantly, polymorphisms in mature microRNA sequences or mRNA target sites may not only lead to decreased or increased repression of target gene expression, but also to repression of previously untargeted genes

of human genes may be regulated by microRNAs (Friedman et al. 2009). However, most of these predictions still warrant experimental validation, since the complex mechanisms of microRNA:mRNA interaction result in a high false positive rate of these predictions (Kertesz et al. 2007), confounding pathway analyses.

Since their initial discovery in 1993, 1,881 human microRNA loci have been annotated in miRBase 21, leading to more than 2,500 mature microRNA transcripts (Kozomara and Griffiths-Jones 2014). Contrary to the protein level, only a fraction of microRNAs and target sequences are conserved between species, which leaves many annotated human microRNAs waiting for their functional characterization. A plethora of interactions and regulations is possible, as one can estimate that on average more than 20 microRNAs may regulate a single target gene (Arnold et al. 2012). MicroRNA expression and function thus depend on tissue, cell-type and developmental stage-specific expression patterns (Bartel and Chen 2004; Landgraf et al. 2007; Ziats and Rennert 2014). The interplay between transcription factors, gene networks and microRNAs may therefore become very intricate, as paradigmatically illustrated by two microRNAs acting in a double-negative feedback loop to control neuronal cell fate (Johnston et al. 2005).

About 75 % of annotated microRNAs were detected in human brain with regional and developmental specificity (Shao et al. 2010; Hu et al. 2011; Boudreau et al. 2014; Ziats and Rennert 2014). MicroRNAs have been implicated in the regulation of basic neuronal processes in development, differentiation and synaptic plasticity, as reviewed (Kosik 2006; Schratt 2009a, b; Im and Kenny 2012; McNeill and Van Vactor 2012; Serafini et al. 2012; Sun et al. 2013). Some examples may be given: miR-124 is expressed in post-mitotic neurons and involved in (I) adult neurogenesis in the subventricular zone stem cell niche by targeting *Sox9*, thereby allowing neuronal differentiation (Cheng et al. 2009), (II) in regulating synaptic plasticity through CREB (Rajasethupathy et al. 2009) and (III) in mediating neural progenitor mitotic exit and dendritic morphogenesis by targeting *Baf53a* in combination with miR-9 (Yoo et al. 2009). MiR-134 is localized in the synapto-dendritic compartment and negatively regulates the size of dendritic spines (Schratt et al. 2006). Mir-138 is highly enriched in the brain, localized within dendrites and negatively regulates the size of dendritic spines by controlling the expression of *Apt1*, an enzyme regulating palmitoylation status of proteins such as the $G\alpha_{13}$ subunit of G proteins (Siegel et al. 2009).

MicroRNAs in human diseases have been largely investigated in cancer (Ryan et al. 2010) and cardiovascular disorders (Thum et al. 2007), but are also involved in autoimmune diseases (Sayed and Abdellatif 2011) and in neurodegenerative disorders (Van den Hove et al. 2014). Regulatory genetic variations affecting microRNA activity has thus become an emerging field of research. Chromosomal alterations, epigenetic modification, polymorphic promoter elements and polymorphism within microRNAs (*cis* factors), as well as mutations in genes of proteins involved in microRNA processing and in the target site itself (*trans* factors) have been described (Sethupathy and Collins 2008).

Here, we review clinical studies on microRNAs in mental disorders and summarize data on the potential use of microRNAs as biomarkers. We searched Medline using the following search string and yielded 895 results (October 2014): "(microRNA OR miRNA OR miR) AND (Schizophrenia OR SCZ OR psychosis OR bipolar disorder OR BPD OR depression OR depressive OR depress* OR affective OR MDD OR anxiety OR panic OR agoraphobia OR trait OR psychiatry OR psychiatric)". To focus the review on human data of schizophrenia, bipolar disorder, major depressive disorder and anxiety disorders, only research articles related to humans, human tissue or human cell lines in a clinical context were considered. We deliberately opted for this limitation of our review to evaluate the contribution of microRNAs to clinical heterogeneity and individuality in terms of phenotypic variance and treatment response. We complemented our literature search by reviewing the references of included articles. Taken together, 112 publications remained for primary review.

Schizophrenia

Genetic studies

Early association studies on single nucleotide polymorphisms (SNPs) related to microRNA reported an association for *MIR206* (rs17578796) in a Scandinavian (Hansen et al. 2007) and for *MIR30E* (rs112439044) in a Han Chinese (Xu et al. 2010a) sample of patients with schizophrenia (SCZ). A recent study replicated the finding regarding *MIR30E* in a Japanese sample (Watanabe et al. 2013). Negative findings were published for *MIR130B* (rs861843), which was investigated due to its localization within the risk locus for SCZ on chromosome 22q11 in a Russian sample (Burmistrova et al. 2007), *MIR146A* and *MIR499* in a Chinese sample (Zou et al. 2012) and for *MIR185*, which is located closely to *MIR130B* and deleted in the 1.5 megabase 22q11.2 microdeletion associated with SCZ, in the sample of the Psychiatric Genomics Consortium and a German sample (Forstner et al. 2014).

Concerning individual risk induced by rare variants, an investigation of microRNA genes on the X-chromosome identified 8 ultra-rare variants in the precursor or mature

microRNA sequence (let-7f-2, miR-18b, miR-188, miR-325, miR-502, miR-505, miR-509-3, miR-510, miR-660) in 8 of 192 American males suffering from SCZ, which were not found in a large and diverse control sample (Feng et al. 2009). A recent study reported an enrichment of rare copy number variations (CNVs) overlapping with microRNAs in SCZ with 25 microRNAs implicated by rare CNVs in two or more unrelated subjects (Warnica et al. 2014). Most of these microRNAs are presently uncharacterized and pathway analysis suggested a functional enrichment of microRNA targets in neurodevelopmental processes, including axonogenesis and neuron projection. Due to the high false positive rate of prediction algorithms, data warrant experimental confirmation.

Several investigations have studied polymorphic microRNA-binding sites in target genes related to SCZ. Focusing on quantifiable phenotypes of SCZ, a German case–control sample reported a polymorphism in the 3′UTR of *CPLX2* (rs3822674) to be associated with cognition and to interfere with repression of *CPLX2* expression by hsa-miR-498 (Begemann et al. 2010). Binding of microRNAs to polymorphic sites in the 3′UTR of the *BDNF* gene was investigated in a study confirming two SNPs involved in hsa-miR-26a-5p and hsa-miR-26b-5p binding (rs11030100 and rs11030099), yet both SNPs were not found to be associated with SCZ in an Italian sample (Caputo et al. 2011). Previously, a decreased expression of the BDNF targeting microRNA hsa-miR-195-5p was reported in postmortem prefrontal cortex samples of SCZ cases (Mellios et al. 2009), but genetic variation was not tested. A SNP in the 3′UTR of *DRD2* (rs1130354) was reported to interfere with hsa-miR-326-mediated repression of *DRD2* expression, yet failed to be associated with SCZ in an American sample (Shi et al. 2014). Another study focused on rs11122396 in the 3′UTR of *DISC1* and reported hsa-miR-135b-5p to interfere with *DISC1* expression for the major (A), but not for the minor (G) allele (Rossi et al. 2014). Yet association of rs11122396 with SCZ or its symptoms was not tested, leaving room for further investigations.

Applying a different methodological approach, SNPs in the 3′UTR of SCZ candidate genes were analyzed for free energy of microRNA binding in silico. Two SNPs previously reported to be associated with SCZ were experimentally identified to interfere with hsa-miR-124-3p-mediated repression of *RGS4* expression (rs10759) and hsa-miR-138-5p-mediated repression of *COMT* expression (rs165599). The same study also suggested a previously unreported SNP (rs3219151) in the 3′UTR of *GABRA6* to be associated with SCZ in a Han Chinese sample (Gong et al. 2013), but interference with microRNA binding was not experimentally studied. Hsa-miR-138-5p was recently also reported to be a potential regulator of memory performance in humans (Schröder et al. 2014). This study combined GWAS data on 13 traits of episodic and working memory performance of a German sample aged older than 60 years ($n = 1318$) with molecular studies. A SNP upstream of *MIR138-1* (rs9882688) modulated expression of hsa-miR-138-5p and was among the three top hits of the GWAS on memory performance. Previous molecular studies had suggested important roles of miR-138 in spine morphogenesis and miR-124 in neuronal fate, as explained in the introduction and reviewed (Sun et al. 2013).

Two studies have focused on microRNA processing, and both were conducted in Han Chinese case–control samples. Analysis of 967 SNPs within 59 microRNA processing genes suggested an intronic SNP in *EIF4ENIF1* (rs7289941) to be associated with SCZ (Zhang et al. 2012). A second, smaller-sized investigation reported rs3757 in *DGCR8* as well as rs3742330 in *DICER* to be associated with SCZ (Zhou et al. 2013). The influence of these SNPs on microRNA processing has not been experimentally evaluated.

Several investigations have focused on a polymorphism in the hostgene of hsa-miR-137 (rs1625579), with genome-wide significance in genome-wide association studies (GWAS) of SCZ so far (The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium 2011; Cross-Disorder Group of the Psychiatric Genomics Consortium 2013a; Ripke et al. 2013). The SNP is located 8,692 bp downstream of *MIR137*. It should be noted, that *MIR137HG* also codes for *MIR2682*, which is located only 7,864 bp downstream of rs1625579 and presently uncharacterized. Four replication studies were published so far, all conducted in Han Chinese case–control samples. Among 33 SNPs spanning *MIR137HG* and the hsa-miR-137 target *CACNA1C,* a nominally significant association with SCZ was reported for rs1625579 (*MIR137HG*) and both rs1006737 and rs4765905 in *CACNA1C* (Guan et al. 2014). More recently, rs1625579 was associated with SCZ and working memory performance of SCZ patients as tested by Brief Assessment of Cognitions in Schizophrenia (Ma et al. 2014). However, no association was found in two case–control samples, yet the samples sizes were not adequatly powered to reliably detect an association, given the GWAS-reported odds ratio between 1.07 and 1.19 (Wang et al. 2014a; Yuan et al. 2014).

A recent, smaller sized, European–Australian GWAS of psychosis phenotypes (schizophrenia, schizoaffective disorder, psychotic bipolar disorder) tagged rs1625579 by rs1782810, which is located 594 bp downstream of rs1625579 in an intron of *MIR137HG*, yet only a trend towards nominal association was reported, possibly due to limited power of this study (Psychosis Endophenotypes International Consortium et al. 2014).

Sequencing of *MIR137HG* revealed (I) four sequence variations, yet contributing no SCZ risk in a Japanese case–control sample (Egawa et al. 2013), and (II) two rare variants in a northern Swedish case–control sample, leading to reduced hsa-miR-137 expression in heterologous expression systems (Strazisar et al. 2014). Both cases and controls showed a trend towards decreased expression of hsa-miR-137 for the TT risk genotype of rs1625579 in postmortem prefrontal cortex (Guella et al. 2013).

On a molecular level, hsa-miR-137 was reported to regulate several SCZ candidates such as *CACNA1C*, *CSMD1*, *C10orf26* and *TCF4* (Kwon et al. 2013), as well as *ZNF804A* (Kim et al. 2012) and the autism candidate *RORA* (Devanna and Vernes 2014) using luciferase reporter assays. Also, a rare variable number tandem repeat (VNTR) polymorphism at the 5′ end of the hsa-miR-137 precursor was reported to reduce hsa-miR-137 expression for 9 and 13 VNTR alleles, yet the association to SCZ needs to be determined (Mamdani et al. 2013). Interestingly, *DRD2* and *COMT* expression may be indirectly regulated via the hsa-miR-137 target *ZNF804A*, providing a link to the dopamine hypothesis of schizophrenia (Girgenti et al. 2012). Translational studies had previously suggested an important role of miR-137 in modulating differentiation of adult neuronal stem cells by repressing *Ezh2* (Szulwach et al. 2010), differentiation of embryonic stem cells by targeting *Lsd1* (Sun et al. 2011) as well as neuronal maturation and dendritic spine morphogenesis by interference with *Mib1* (Smrt et al. 2010). Two recent reviews focus on these findings and its possible impact on SCZ (Wright et al. 2013; Yin et al. 2014).

On a functional level, several studies have investigated rs1625579. The amplitude of the P300 auditory event-related potential and the N100 amplitude of the "odd-ball" paradigm were nominally associated with rs1625579 in a Belgian SCZ patient sample (Decoster et al. 2012) and a European ancestry case–control sample for bipolar disorder (BPD) and SCZ (Hall et al. 2014). The rs1625579 TT risk genotype was reported to confer subtle changes in terms of fewer, rather mood-congruent psychotic symptoms, reduced episodic memory and attentional control in an Irish SCZ sample (Cummings et al. 2013). An Australian SCZ sample reported no association of rs1625579 with cognitive deficits, but prediction of impaired cognitive performance using rs1625579 gentoype in combination with negative symptoms (Green et al. 2013).

On a neuronal network level, a fMRI study in healthy Scottish individuals at genetic risk for SCZ or BPD due to one first-degree or two second-degree affected relatives revealed reduced brain activation across several regions for the TT risk genotype using the Hayling sentence completion paradigm (Whalley et al. 2012). The TT risk genotype was associated with dorsolateral prefrontal cortex hyperactivation (considered to be a measure of insufficient cortical control) in SCZ patients using the Sternberg Item Response Paradigm, but not with lower working memory performance and longer response times (van Erp et al. 2014). Two studies have focused on healthy individuals. The TT risk genotype showed increased functional connectivity between right amygdala and frontal regions involved in emotional processing in a healthy Irish sample using a face-processing task (Mothersill et al. 2014). Dorsolateral prefrontal-hippocampal functional connectivity was suggested to depend on the rs1625579 genotype and to correlate with working memory performance in healthy Han Chinese individuals by resting state fMRI (Liu et al. 2014).

Structural MRI studies yielded contradictory results: an initial case–control study reported reduced hippocampal and increased lateral ventricle volume for SCZ patients being carriers of the TT risk genotype (Lett et al. 2013), which was not replicated in a recent study of multiple brain structures in a larger number of SCZ patients (Rose et al. 2014). Four studies in healthy individuals reported no association of rs1625579 with brain volume. No impact of rs1625579 on the variability of white matter structure was observed using diffusion tensor imaging (DTI) in healthy Irish participants (Kelly et al. 2014). Two samples (Han Chinese and European) previously used for analysis of genetic effects on brain volume in healthy individuals (Li et al. 2012; Stein et al. 2012) yielded no significant association with rs1625579 using MRI (Li and Su 2013). Likewise, a study investigating SNPs within *MIR137HG*, *TCF4* and *ZNF804A* in relation to the brain structure of 1,300 healthy adults reported no effect on total brain volume, gray matter, white matter or hippocampal volume using volumetry and voxel-based morphometry (Cousijn et al. 2014). Given the large sample size of this study, rs1625579 exerts most likely only a very small effect on brain volume in healthy adults.

Taken together, while rs1625579 represents a genome-wide risk variant for SCZ, available evidence points towards only a modest impact on phenotypic variance of SCZ (see Table 1 for summary). Yet, larger functional studies are needed to fully assess rs1625579 in SCZ.

Expression studies

Most studies on microRNA expression in SCZ have investigated postmortem brain samples and focused on the prefrontal cortex. More recent studies address microRNA expression as a potential biomarker of SCZ and a predictor of treatment response using peripheral tissue or blood serum samples.

Studies focusing on postmortem brain expression in SCZ yielded heterogeneous results so far, with reports of

Table 1 Summary of clinical studies on rs1625579 located in *MIR137HG*

Study	Sample	Results	References
GWAS	European Ancestry, discovery $n_{SCZ} = 9{,}394$, $n_{controls} = 12{,}462$; replication $n_{SCZ} = 8{,}432$, $n_{controls} = 21{,}397$	First report of genome-wide significant association with SCZ	The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium (2011)
GWAS	Discovery: Swedish, $n_{SCZ} = 5{,}001$, $n_{controls} = 6{,}243$; replication 1: European ancestry, $n_{SCZ} = 8{,}832$, $n_{controls} = 12{,}067$; replication 2: European ancestry, $n_{SCZ} = 7{,}413$, $n_{controls} = 19{,}762$	Replication of genome-wide significant association with SCZ	Ripke et al. (2013)
GWAS	European ancestry, $n_{cases} = 33{,}332$, $n_{controls} = 27{,}888$	Association specific for SCZ, not ASD, BPD, MDD and ADHD	Cross-Disorder Group of the Psychiatric Genomics Consortium (2013a, b)
Association Study	Han Chinese, $n_{SCZ} = 1{,}430$, $n_{controls} = 1{,}570$	Nominal significant association with SCZ	Guan et al. (2014)
Association Study	Han Chinese, $n_{SCZ} = 611$, $n_{controls} = 621$	Association with SCZ and working memory performance (BACS)	Ma et al. (2014)
Association Study	Han Chinese, $n_{SCZ} = 300$, $n_{controls} = 300$	No association with SCZ	Wang et al. (2014a)
Association Study	Han Chinese, $n_{SCZ} = 506$, $n_{controls} = 522$	No association with SCZ	Yuan et al. (2014)
Post-mortem expression	UCI brain bank: $n_{SCZ} = 7$, $n_{BPD} = 9$, $n_{controls} = 10$; Stanley Medical Research Institute: $n_{SCZ} = 35$, $n_{BPD} = 31$, $n_{controls} = 33$	Non-significant reduced hsa-miR-137 expression in DLPFC for TT genotype across all samples	Guella et al. (2013)
Neuropsych. test	Australian, $n_{SCZ} = 617$	No association with SCZ symptoms	Green et al. (2013)
Neuropsych. test	Irish, clinical profile: $n_{SCZ} = 573$, $n_{Schizoaffective} = 123$, $n_{BPD1} = 125$; neurocognitive performance: $n_{SCZ} = 399$, $n_{controls} = 171$	Lower scores for OPCRIT-derived positive symptoms and psychosis incongruity; pronounced cognitive deficits for TT genotype	Cummings et al. (2013)
Neurophysiology	Belgian, $n_{SCZ} = 336$	Nominal association with P300 auditory event-related potential amplitude	Decoster et al. (2012)
Neurophysiology	European Ancestry, $n_{SCZ} = 70$, $n_{BPD} = 129$, $n_{controls} = 74$	Nominal association with N100 amplitude in the auditory "odd-ball" paradigm for SCZ/BPD cases, but not controls	Hall et al. (2014)
fMRI	Scottish (healthy at familial risk), $n_{SCZ} = 44$, $n_{BPD} = 90$, $n_{controls} = 81$	Reduced brain activation across several regions for TT genotype in a sentence completion task	Whalley et al. (2012)
fMRI	Han Chinese (healthy), $n = 290$	Correlation between DLPFC-HF coupling and working memory performance for TG genotype	Liu et al. (2014)
fMRI	Irish (healthy), $n = 81$	Increased functional connectivity between right amygdala and frontal cortex for TT genotype	Mothersill et al. (2014)
fMRI	North American, $n_{SCZ} = 48$, $n_{Controls} = 63$	Increased left DLPFC activation for TT genotype independent of diagnosis during SIRP	van Erp et al. (2014)
sMRI	Han Chinese (healthy), $n = 299$; European ancestry (healthy), $n = 5{,}775$	No association of total or regional brain volume	Li and Su (2013)
sMRI	North American, $n_{SCZ} = 510$ (age of onset); $n_{SCZ} = 92$, $n_{Controls} = 121$ (imaging)	Early onset of disease, increased lateral ventricle volume and reduced hippocampal volume for TT genotype	Lett et al. (2013)
sMRI	Irish, $n_{SCZ} = 163$, $n_{Controls} = 150$	No association of brain or subcortical structure volume	Rose et al. (2014)
DTI	Irish (healthy), $n = 123$	No association with brain white matter microstructure	Kelly et al. (2014)

GWAS genome-wide association study, *fMRI* functional magnetic resonance imaging, *sMRI* structural magnetic resonance imaging, *DTI* diffusion tensor imaging, *SCZ* schizophrenia, *BPD* bipolar disorder, *BPD1* bipolar disorder 1, *ASD* autism spectrum disorder, *MDD* major depressive disorder, *ADHD* attention deficit hyperactivity disorder, *DLPFC* dorsolateral prefrontal cortex, *HF* hippocampal formation, *BACS* Brief Assessment of Cognitions in Schizophrenia, *OPCRIT* operational criteria checklist for psychotic and affective illness, *SIRP* Sternberg item response paradigm

increased microRNA expression (Beveridge et al. 2008, 2010; Kim et al. 2010; Santarelli et al. 2011; Wong et al. 2013) or decreased microRNA expression (Perkins et al. 2007; Mellios et al. 2009; Zhu et al. 2009; Moreau et al. 2011; Miller et al. 2012; Scarr et al. 2013; Guella et al. 2013), gender-specific effects (Mellios et al. 2012) or no effects at all (Burmistrova et al. 2007). These studies differ in several factors such as the sample size, the number of investigated microRNAs as well as the method applied for microRNA isolation and detection. Robust replication of any of these results has not been published so far. Results and methodological issues have been reviewed in greater detail elsewhere (Kolshus et al. 2013; Maffioletti et al. 2014).

One study focused on exosomes, which are cellular secretory vesicles containing microRNAs in neuronal tissue isolated from postmortem prefrontal cortex and suggested an increase in microRNA expression in mental disorders, with hsa-miR-497-5p significantly upregulated in SCZ and hsa-miR-29c-3p in bipolar disorder (Banigan et al. 2013).

Two recent studies have investigated the same individuals from the Stanley Neuropathology Consortium, suffering from SCZ, bipolar disorder (BPD) or major depressive disorder (MDD) compared to healthy controls ($n = 15$ each). The first study assessed expression of microRNAs in dorsolateral prefrontal cortex by high-throughput quantitative real-time PCR and additionally compared individuals grouped into those having completed suicide and those having died from a natural death (Smalheiser et al. 2014). For a subset of three patients and six controls, next-generation sequencing of synaptosomes was performed, thereby evaluating all annotated microRNAs and mRNA simultaneously, contrary to high-throughput real-time PCR relying on preselected microRNA panels (typically 384 microRNAs). Synaptosomes may reflect neuron-specific microRNA expression more adequately than whole brain tissue samples (Lugli et al. 2012). Most microRNAs were only modestly dysregulated, rarely exceeding a factor of two, with reduced expression in SCZ. Hsa-miR-219-5p (highly enriched in synaptosomes by a factor of five) was most strongly downregulated by 70 % in SCZ. The NMDA-receptor antagonist dizocilpine, which induces schizophrenia-like behavioral deficits in mice, was identified to downregulate miR-219 expression (Kocerha et al. 2009). The pattern of microRNA dysregulation was partially similar between SCZ and BPD, but both were different from MDD or individuals having completed suicide. These results correspond to reports on the genetic architecture of major mental disorders, suggesting a partial overlap between SCZ and BPD (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013a). Of note, hsa-miR-508-3p showed reduced levels in SCZ, BPD and MDD, yet no specific reports on miR-508 in a neuronal context are available.

The second study performed transcriptome sequencing of dentate gyrus cells isolated from postmortem brain by laser capture microdissection and reported disrupted signaling of hsa-miR-182-5p (Kohen et al. 2014). In healthy controls and BPD patients, but not in SCZ and MDD patients, expression of *MIR182* depended on rs76481776. Interestingly, a previous study reported rs76481776 to be associated with late insomnia in major depression and to modulate miR-182 expression, assessed in heterologous expression systems (HeLa cells) using luciferase activity assays, but not in brain tissue of MDD patients (Saus et al. 2010).

Peripheral tissue expression of microRNAs was studied in several ways. 33 microRNAs were significantly, but only modestly (not exceeding 0.75-fold) downregulated in SCZ, with 17 microRNAs located within the *DLK-DIO3* region on chromosome 14q32 in peripheral mononuclear blood cells of 112 Australian SCZ patients and 76 controls using microarrays (Gardiner et al. 2012). Interestingly, hsa-miR-134-5p was among the most robustly downregulated microRNAs. However, expression of hsa-miR-134-5p was increased in postmortem prefrontal cortex samples of SCZ (Santarelli et al. 2011) and molecular studies suggested increased, not decreased miR-134 to lead to reduced synaptic development, maturation or plasticity (Schratt et al. 2006).

Another study tested directly, whether microRNA expression in white blood cells may serve as a valid biomarker of SCZ using a Taiwanese sample consisting of 30 cases and 30 controls applying high-throughput real-time PCR (Lai et al. 2011). Seven microRNAs (hsa-miR-34a-5p, hsa-miR-432-5p, hsa-miR-449a, hsa-miR-548d-3p, hsa-miR-564, hsa-miR-572 and hsa-miR-652-3p) were suggested to predict SCZ as well as its clinical symptoms with low correlation coefficients. Dysregulation of hsa-miR-34a-5p (Kim et al. 2010) and hsa-miR-652-3p) was reported for postmortem prefrontal cortex samples of SCZ; miR-432 and miR-572 were implicated in autism (Abu-Elneel et al. 2008; Mundalil Vasu et al. 2014) and miR-449 in Alzheimer's disease (Cogswell et al. 2008). A more recent study aimed to investigate microRNA expression directly in neural tissue. The olfactory neuroepithelium, which is one of the few accessible neural tissues containing neurons and stem cells, was evaluated in a small (18 patients and controls) American sample using high-throughput real-time PCR. An increase of about twofold in hsa-miR-382-5p, which could not be detected in lymphoblastoid cell lines, as well as a decrease in hsa-miR-532-3p and hsa-miR-660 expression in SCZ patients was reported (Mor et al. 2013). Notably, the microRNA level of each individual participant is illustrated, allowing to assess the

large variance between individuals and highlighting an important problem of microRNA expression studies. Previous reports suggested a rare mutation in *MIR660* to be associated with SCZ (Feng et al. 2009). Hsa-miR-532-5p, but not -3p, was upregulated and hsa-miR-382-5p was downregulated in postmortem dorsolateral prefrontal cortex in SCZ (Santarelli et al. 2011). Translational studies suggested miR-382 to be regulated in a MeCP2-dependent fashion (Urdinguio et al. 2010) and to be involved in alcohol addiction (Li et al. 2013a).

Whether microRNAs may serve as predictors of antipsychotic treatment response has been tested in three studies. One study investigated serum levels of microRNAs previously reported to be associated with SCZ pre- and post-treatment with risperidone in a Han Chinese patient sample. A decrease in hsa-miR-365a-3p and hsa-miR-520c-3p serum levels compared to baseline was observed after 1 year of treatment, but no correlation of expression level with clinical symptoms was reported (Liu et al. 2013). A second study suggested plasma levels of hsa-miR-346, a microRNA located in the intron of the SCZ candidate *GRID1* (Zhu et al. 2009), to become dysregulated in patients upon treatment with risperidone (Shi et al. 2012). More recently, a naturalistic study, yet involving only 20 Han Chinese patients, observed a decrease in serum levels of hsa-miR-181b-5p, a microRNA previously reported to be upregulated in the prefrontal cortex in SCZ (Beveridge et al. 2008), to correlate with successful antipsychotic treatment after 6 weeks (Song et al. 2014).

Indirect evidence for microRNA was given by a transcriptome study of lymphoblastoid cell lines derived from a SCZ case–control sample using microarrays (Sanders et al. 2013). *DICER1* was reported to be upregulated in SCZ, in line with previous reports on postmortem prefrontal cortex samples (Beveridge et al. 2010; Santarelli et al. 2011) and genetic association studies (Zhou et al. 2013), potentially leading to increased microRNA expression.

Taken together, while many results are promising and appear to relate to each other, preselection of tested microRNAs, methodological issues and sample sizes sets important limits to the interpretation of data. The variance of detected microRNA expression levels between individuals, the different methods applied in microRNA extraction, detection and normalization as well as the inherent noise of high-throughput methods are the main limitations.

Bipolar disorder

Genetic studies

Studies on microRNA in bipolar disorder (BPD) have mainly been conducted in the context of mixed SCZ and BPD case–control studies, since a high genetic correlation between SCZ and BPD has been described (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013b). In a cross-disorder analysis of five major psychiatric disorders, *MIR137HG* rs1625579 was not among the top hits of BPD, contrary to SCZ and autism spectrum disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013a). Only one genetic study in a Han Chinese case–control sample has focused on microRNAs in BPD specifically, investigating a microRNA reported to regulate *BDNF* expression. An epistatic effect of *MIR206* (rs16882131) and *BDNF* (rs6255) concerning BPD-I susceptibility and treatment response was reported (Wang et al. 2014b). In another study, a SNP in the 3′UTR of *GRM7* (rs56173829) was associated with BPD (Kandaswamy et al. 2014). Bioinformatic analysis by PolymiRTS 3.0 (Bhattacharya et al. 2014) suggested this SNP to modulate binding of several microRNAs, most likely hsa-miR-4295, hsa-miR-130a-3p and hsa-miR-130b-3p. However, experimental validation was not conducted. A previous study had suggested lithium- and valproate-dependent regulation of *Grm7* by miR-34a in rat neuronal tissue (Zhou et al. 2009) However, rs56173829 was not predicted to modulate binding of miR-34a and experimental evidence is missing.

Most importantly, a large-scale genome-wide association study of BPD ($n_{cases} = 7{,}481$, $n_{controls} = 9{,}250$ in the discovery sample and $n_{cases} = 4{,}496$, $n_{controls} = 42{,}422$ in the replication sample) did not report variants directly affecting microRNAs (Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011). However, a genome-wide significant association was reported for *ODZ4*, which harbors *MIR708 and MIR5579* in its first intron. Till now, these results have not been taken up and investigated in more detail. Functional studies on both microRNAs focusing on their potential neurobiological role have not yet been conducted.

Expression studies

Studies on gene expression in mixed SCZ/BPD and SCZ/BPD/MDD studies have been mentioned in the context of the review on SCZ (Banigan et al. 2013; Kohen et al. 2014; Smalheiser et al. 2014).

Two studies have focused on microRNA levels in the context of treatment with mood stabilizers in human tissue. The first study was conducted in lymphoblastoid cell lines from 10 BPD patients and 10 unaffected family members to assess the impact of lithium on microRNA expression (Chen et al. 2009). 13 microRNAs, previously suggested to respond to lithium and valproate treatment in rodents were assessed. Four microRNAs were dysregulated after 16 days of treatment (hsa-miR-34a-5p, hsa-miR-152-3p, hsa-miR-155-5p, hsa-miR-221-3p). The overall change of

microRNA expression was small and no microRNA reached a twofold change. Contrary to a previous report in rat hippocampus, hsa-miR-34a-5p and hsa-miR-221-3p were upregulated in humans upon lithium treatment. A second study focused on hsa-miR-134-5p, which was previously reported to negatively regulate dendritic spine volume and synapse formation (Schratt et al. 2006). A decrease in hsa-miR-134-5p plasma levels was observed during manic phases and correlated with symptom severity. This decrease was reversed upon successful treatment with different mood stabilizers (Rong et al. 2011). In SCZ, a modest increase of hsa-miR-134-5p was reported in the dorsolateral prefrontal cortex of postmortem samples (Santarelli et al. 2011), putatively reflecting the molecular function of miR-134 in terms of decreased synaptic plasticity. The relevance of these three reports regarding the etiology of the corresponding disorder needs to be further explored. Moreover, these findings underscore the necessity of several lines of evidence to draw a consistent conclusion on putative molecular disease processes and evaluation of risk factors.

Indirect evidence was given by a study investigating microRNA expression in blood monocytes during postpartum psychosis. Downregulation of hsa-miR-146a-5p during first time postpartum psychosis was reported. A subgroup of 11 out of 20 postpartum psychosis patients, having previously been diagnosed with bipolar disorder, also showed downregulation of hsa-miR-212-3p and hsa-miR-92a-3p (Weigelt et al. 2013). However, the small sample size renders the results primarily hypothesis generating.

Concerning a potential application of microRNAs as biomarkers of BPD and treatment success, all these results have to be considered preliminary.

Major depressive disorder

Genetic studies

Early genetic investigation of microRNAs in MDD reported a rare SNP in the precursor of *MIR30E* (rs112439044), previously found in the context of SCZ (Xu et al. 2010a), to be associated with MDD in a Han Chinese population (Xu et al. 2010b). In an analysis of five microRNAs involved in the circadian clock, a SNP in *MIR182* (rs76481776) was reported to be associated with late insomnia in MDD (Saus et al. 2010). Another study reported rs1653625 in the 3′UTR of *P2RX7* to be associated with MDD in a Hungarian case–control sample. This SNP was predicted to interfere with binding of several microRNAs, yet none were experimentally tested (Rahman et al. 2010). In a subsequent study of the same group, this finding could not be replicated, while an association with the severity of depression symptoms in BPD patients was reported (Halmai et al. 2013). A recent study conducted genome-wide DNA methylation profiling of neuronal and glial nuclei and reported an additive genetic and epigenetic association of rs7208505, located in the 3′UTR of *SKA2*, with suicide (Guintivano et al. 2014). Suicidal ideation was associated with rs7208505. *SKA2* gene expression was significantly lower in those who died by suicide and was associated with genetic and epigenetic variation of rs7208505. Hsa-miR-301a-3p was previously reported to regulate expression of *SKA2* (Cao et al. 2010). *MIR301A* is located intronically within *SKA2* and upstream of rs7208505. In combination with epigenetic variation (methylation) proximal to *MIR301A*, 40 % of *SKA2* gene expression could be explained by this SNP.

Most importantly, a meta-analysis of GWAS data for major depressive disorder did not report variants directly related to microRNAs reaching genome-wide significance or to be among the top hits (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium 2013). Given the large sample size ($n_{cases} = 9{,}240$, $n_{controls} = 9{,}519$ in the discovery sample and $n_{cases} = 6{,}783$, $n_{controls} = 50{,}695$ in the replication sample), this finding is of major importance. However, four microRNA genes were located in regions (±300 kb) showing a p value below 0.005 (*MIR1224*, *MIR1471*, *MIR708*, *MIR30E* and *MIR30C1*), thereby providing modest further support for *MIR30E*. However, due to specific statistical issues concerning MDD (Flint and Kendler 2014), the study may not have reached the same power as GWAS on SCZ.

Concerning genes involved in microRNA processing, one study reported an increased risk for MDD driven by a SNP (rs3757) in the 3′UTR of the *DGCR8* gene and a SNP (rs636832) in *AGO1* (He et al. 2012). Yet, interference with microRNA binding was not experimentally confirmed.

Taken together, present data suggest a smaller contribution of microRNAs towards the risk for MDD compared to SCZ. Functional studies or data on dimensional phenotypes are presently not available.

Expression studies

Studies on mixed SCZ/BPD/MDD samples have been mentioned in the context of SCZ (Kohen et al. 2014; Smalheiser et al. 2014). MicroRNA expression in postmortem brain samples have reported a global downregulation of microRNA expression in depressed suicide completers (Smalheiser et al. 2012), but also an upregulation of microRNAs (hsa-miR-139-5p, hsa-miR-320c and hsa-miR-34c-5p), targeting two polyamine genes (*SAT1* and *SMOX*), which have been observed to be

downregulated in depressed suicide completers (Lopez et al. 2014a). It should be noted, that the control groups differed between those two studies, potentially explaining the divergent findings, although the same brain bank was used. A larger study reported the brain and primate-specific hsa-miR-1202 to be downregulated in MDD. A target of hsa-miR-1202 is the metabotropic glutamate receptor 4 (*GRM4*), previously implicated in anxiety-like behavior in translational studies (Davis et al. 2013). Importantly, serum levels of hsa-miR-1202 were reported to predict clinical response to citalopram treatment of MDD patients (Lopez et al. 2014b).

Two studies focused on microRNA levels as potential biomarkers of MDD. In a candidate-driven approach, levels of *BDNF*-regulating hsa-miR-132-3p and hsa-miR-182-5p were increased in MDD, corresponding to decreased BDNF levels and clinical symptomatology (Li et al. 2013b). Mmu-miR-132-3p was previously identified to regulate MeCP2 translation, thereby indirectly regulating BDNF in mice (Klein et al. 2007). Recently, using microarrays, mRNA and microRNA expression was studied in fibroblasts, and a distinct panel of 38 microRNAs associated with altered gene expression in predicted targets related to cell-to-cell communication, innate/adaptive immunity and cell proliferation was reported (Garbett et al. 2014).

More studies have focused on changes of microRNA expression along with antidepressant treatment in human tissues. Initial investigations were reported in U87 MG primary human glioblastoma-astrocytoma cell lines, incubated with 7 µmol/l paroxetine (dissolved in DMSO). Increased BDNF expression and its transcriptionally inhibiting microRNA hsa-miR-30a-5p was observed within 6–12 h, however, these experiments were not controlled for dissolving paroxetine in DMSO and may thus represent an epiphenomenon (Angelucci et al. 2011). In a naturalistic design, microRNA and mRNA expression were assessed in peripheral mononuclear blood cells in a French case–control sample. Two microRNAs (hsa-miR-589-5p and hsa-miR-941) were consistently upregulated in MDD patients during the entire course of the study, while treatment response was not predicted by up- or downregulation of any microRNA investigated. The small sample size of 16 patients and 13 controls renders these findings to be considered preliminary (Belzeaux et al. 2012). Another study focused on changes of microRNA and mRNA expression upon paroxetine treatment of cultured lymphoblastoid cells of healthy donors of Ashkenazi Jewish ancestry to identify possible predictors of treatment response as modelled by cell lines showing an inhibition of growth in response to paroxetine. In female donors, an upregulation of hsa-miR-151a-3p along with downregulation of its predicted, but not experimentally confirmed, target *CHL1* (Oved et al. 2012) was reported. In male donors, downregulation of hsa-miR-221-3p and hsa-miR-222-3p and upregulation of their predicted, but not experimentally confirmed target *ITGB3* was observed (Oved et al. 2013). In a small study investigating peripheral blood microRNA levels in 10 previously untreated Italian patients with MDD over 12 weeks of treatment with escitalopram, 30 microRNAs were reported to be dysregulated upon treatment, with most of those microRNAs related to brain function in a pathway analysis (Bocchio-Chiavetto et al. 2013). While these results are hypothesis generating, a potential application of microRNAs as biomarkers of MDD and treatment response warrants further studies.

Anxiety disorders and related traits

Genetic studies

Only some studies focused on microRNAs in anxiety. The majority of studies has been conducted in translational models of murine anxiety-like behavior, which has been reviewed in detail elsewhere (Malan-Müller et al. 2013). The most comprehensive study in humans evaluated 712 SNPs in three case–control samples of Spanish, Estonian and Finnish patients with panic disorder. SNPs in *MIR22HG* (rs6502892) and *MIR339* (rs11763020) were reported to be nominally associated with panic disorder with and without agoraphobia. Functional analysis of hsa-miR-22-3p suggested regulation of anxiety disorder candidate gene expression such as *BDNF*, *HTR2C*, *MAOA* and *RGS2* (Muiños-Gimeno et al. 2011). Previously, the same group had investigated the *NTRK3* gene due to its suggested role in neuronal plasticity and reported association of a SNP in the 5′ UTR with panic disorder (Armengol et al. 2002). In obsessive–compulsive disorder, a SNP (rs28521337) in the 3′UTR of the *NTRK3* was found to be involved in binding of hsa-miR-485-3p and to be associated with the hoarding phenotype (Muiños-Gimeno et al. 2009).

Recently, rs41305272 in *MAP2K5*, modulating translational repression by hsa-miR-330-3p, was reported to be associated with panic disorder with and without agoraphobia and depression in a combined European–American and African–American case–control sample of patients suffering from comorbid substance or alcohol abuse (Jensen et al. 2014).

In a different approach, genetic variation in 13 genes previously reported to be differentially expressed between non-anxious and anxious inbred mouse strains was tested for association with anxiety disorders in a Finnish case–control sample. An association of rs817782, located in the 3′UTR of *ALAD,* with social phobia was reported (Donner et al. 2008). This SNP is predicted to create a binding site

for hsa-miR-204-5p and hsa-miR-211-5p by PolymiRTS (Bhattacharya et al. 2014), although with a very low score. Experimental validation of microRNA binding was not conducted.

A recent study reported a SNP in the 3′UTR of *ACHE* (rs17228616) to modulate regulation of *ACHE* expression by hsa-miR-608 (Hanin et al. 2014), pointing towards a relevant fine tuning of the parasympathetic nervous system. Carriers of the minor allele showed reduced cortisol levels and elevated blood pressure, possible risk factors for anxiety and hypertension. Moreover, increased *ACHE* expression was reported for homozygous minor allele carriers in postmortem brain samples. However, whether these findings suggest a clinical relevant risk for anxiety disorders needs to be further explored by directly testing categorical or dimensional anxiety phenotypes in case–control samples.

A SNP (rs13212041) in the putative 3′UTR of the serotonin receptor *HTR1B* was reported to interfere with hsa-miR-96-5p-mediated repression of gene expression and was found to be associated with aggression, conduct disorder behavior (Jensen et al. 2009) as well as with self-reported anger and hostility in men, but not in women (Conner et al. 2010). The same SNP was also associated with trait impulsivity (Varga et al. 2012). These results correspond to a hyperaggressive behavior (Saudou et al. 1994) and impaired impulse control (Bouwknecht et al. 2001) of mice lacking 5-HT_{1B} receptors. Recent reports suggest an adaptive regulatory role for mir-96 in rats not becoming helpless during an inescapeable shock paradigm (Smalheiser et al. 2011). In a broader context, *MIR96* is located with *MIR182* and *MIR183* in a 10 kb cluster on chromosome 7. Two SNPs (rs2402959 and rs6965643) within 5 kb upstream of the cluster were reported to be associated with attention deficit hyperactivity disorder (ADHD) in a Spanish sample (Sánchez-Mora et al. 2013). However, some limitations concerning the functional role of miR-96 must be considered. Expression of miR-96 was predominantly found in sensory structures but not brain tissue, and functional variants of *MIR96* were reported to cause progressive hearing loss in mice and humans, but not behavioral changes (Mencía et al. 2009; Lewis et al. 2009). However, hsa-miR-1271-5p was reported to be a brain expressed, non-conserved microRNA sharing the seed sequence of hsa-miR-96-5p and thus also repressing *HTR1B* (Jensen and Covault 2011). Moreover, only the microRNA response element and not the complete 3′UTR of *HTR1B* were tested in luciferase reporter assays and, as of October 2014, rs13212041 is not any longer localized within the currently annotated 3′UTR of *HTR1B*. Further molecular studies will enhance our understanding of these microRNAs.

Concerning aggressive behavior, a SNP (rs1046322) in *WFS1* was reported to interfere with hsa-miR-668-3p targeting and to be associated with self-reported aggression in healthy probands (Kovacs-Nagy et al. 2013). *WFS1* was chosen due to behavioral abnormalities reported for the Wolfram Syndrome (which is mediated by rare mutations in *WFS1*) and translational data on behavior of *Wfs1* deletion mouse models. A second study by the same group identified two SNPs in the 3′UTR of *SNAP-25* (rs3746544 and rs1051312), previously reported to be associated with ADHD (Kim et al. 2007), to interfere with binding and repression of *SNAP-25* expression by hsa-miR-641 and to be associated with impulsivity (Németh et al. 2013). Presently, no molecular or translational study on the role of these two microRNAs concerning neuronal function is available.

Expression studies

No microRNA expression studies have been conducted for anxiety disorders and related traits. An increase in whole blood microRNA levels during and after a stressful condition (academic examination) was reported in healthy probands (Katsuura et al. 2012; Honda et al. 2013), with hsa-miR-144-5p being significantly dysregulated in both samples. Mir-144 was suggested to relate to cytokine function. Moreover, a nominal significant dysregulation was reported for hsa-miR-16-5p, a microRNA implicated in regulating expression of the serotonin transporter SLC6A4 in mice and humans (Moya et al. 2013) and to be decreased upon chronic selective serotonin reuptake inhibitor administration in mice (Baudry et al. 2010).

Discussion

Clinical studies have assessed heterogeneity and individuality of mental disorders induced by microRNAs on the level of genetic variation in microRNA genes, microRNA-binding sites as well as genes related to microRNA processing and on the level of microRNA expression in postmortem brain samples as well as peripheral tissue. The strength of genetic studies is to assess the risk induced by a variant towards a disorder or a certain psychopathological phenotype, whereas expression studies aim to identify dysregulation of gene expression in a disorder, giving direct evidence for involvement of a certain microRNA or leading to biomarkers of diagnosis or treatment success. We have focused the review on clinical studies conducted in humans or with human tissue for two reasons: (I) Any translational study is only an approximation towards the divergent clinical aspects of human disorders, and (II) microRNAs and their binding sites are less well conserved than proteins, allowing only limited conclusions on heterogeneity and individuality of human mental disorders in the absence of direct human evidence.

Studies have mainly focused on schizophrenia, putatively promoted by the finding of rs1625579 in *MIR137HG* as a genome-wide risk variant for SCZ. In conclusion, genetic evidence points towards a rather modest impact of microRNAs on phenotypic variance in SCZ, and some reports are presently conflicting, e.g. concerning modulation of SCZ symptoms, or brain activation patterns and brain volume. While molecular characterization of miR-137 has been undertaken, there is no research on *MIR2682*, the second and human-specific microRNA located in *MIR137HG*. It will be interesting to see, whether miR-2682 is also involved in synaptic plasticity and development. Data on polymorphic microRNA-binding sites as well as SNPs in microRNA processing genes have been reported, but replications studies are rare and more specific investigations are needed. For instance, it is known, that deletion of 22q11.2, predisposing for SCZ, involves *DGCR8* and *MIR185*, yet both were not among the top hits in GWAS data, thus future research is needed.

Concerning bipolar disorder and major depressive disorder, GWAS data and a cross-disorder analysis did not specifically report variants related to microRNAs for BPD and MDD. Although microRNAs were located in top-regions of these studies, apart from *MIR30E* in MDD, replication studies or large-scale microRNA-specific investigations have not been reported. This raises the possibility, that microRNAs exert small effects on individual risk in these disorders, but studies may not have been adequately powered due to specific statistical issues, e.g. in MDD (Flint and Kendler 2014).

Independent of mental disorder, more data on dimensional or intermediate phenotypes, which have been proposed to reflect the underlying genetic risk factors of mental disorders more adequately, would be very helpful to complete the picture. In anxiety disorders, several neuropsychological traits such as behavioral inhibition or anxiety sensitivity as well as a variety of neurobiological markers (e.g. peripheral sympathetic activity, carbon dioxide reactivity, response to cholecystokinin (CCK) challenge, startle reflex) have been suggested as valid intermediate phenotypes (for review see Domschke and Deckert 2012). Particularly neural activation correlates of emotional processing as captured by functional magnetic resonance imaging (fMRI) have been proposed as an intermediate phenotype of anxiety as well as affective disorders viable to genetic and therefore also future microRNA analyses applying an imaging genetic approach (Domschke and Dannlowski 2010). Comparable concepts also apply for SCZ, BPD and MDD, with imaging genetics thus providing promising additional information on microRNAs in mental disorders (Meyer-Lindenberg and Weinberger 2006), yet statistical analysis makes large sample size for adequate power mandatory (Bowman 2014).

However, the genetic approach has limitations, e.g. cases and controls need to be properly matched regarding ethnicity or gender, deviation of control samples from Hardy–Weinberg equilibrium may confound the results and genetic association studies do not assess the risk by de novo and ultra-rare mutations, which may be overcome by next-generation sequencing data. It may also be conceivable, that a polymorphism has a protective role during development, but may predispose to disorders at later time points and vice versa. On a more general level, identified genetic variation of microRNAs may affect their expression, maturation and processing, but experimental validation is necessary to assess, whether a polymorphism has a functional role at all. Moreover, human evidence suggests that individual genetic variance is rather small for microRNA genes, given their importance in numerous regulatory pathways (Han and Zheng 2013). Putatively, interference of microRNAs at more redundant points of biological pathways, e.g. mutations in 3′UTR microRNA-binding sites, may therefore be more important. However, in most instances it is still an open question whether an identified regulation of a target gene by a microRNA is biologically relevant. How to detect small short-term and long-term effects of functionally relevant microRNA polymorphisms in cellular signaling networks may thus be of great scientific importance for our biological understanding of mental disorders.

It should be mentioned, that other non-coding RNA molecules may be involved in neuronal processes putatively related to mental disorders. Long non-coding RNA molecules may counteract microRNA action by scavenging microRNAs or compete at microRNA-binding sites (Barry 2014). As a consequence, positive or negative regulation of microRNA signaling may be mediated independent of genetic variation or altered microRNA levels.

Expression studies of microRNAs are even more difficult to interpret. While in other disorders, e.g. heart failure (Thum et al. 2007) a considerably larger dysregulation of specific microRNAs was reported, most microRNAs were observed to be dysregulated within a factor of two in mental disorders. Several limitations need to be considered. Expression patterns of microRNAs differ in various brain regions, are cell-type specific, and may thus derive from a change on the cell types present, e.g. due to gliosis or invasion by microglia (Smalheiser et al. 2014). Limiting analysis to synaptosome or exosomes may give more selective information (Lugli et al. 2012). The impact of the agony process on neuronal microRNA expression is currently not fully known, yet hypoxia- and anoxia-stress are known to change microRNA expression and may thus be physiological confounders (Kulshreshtha et al. 2007; Peng et al. 2011). Concerning peripheral tissues and blood cell lines, viral load, energy level, growth rate, sex and age are

known to influence results (Sanders et al. 2013). Moreover, technical issues may also need to be considered. High-throughput quantitative real-time PCRs often do not apply same-sample technical replicates as well as dilution rows, making it more difficult to assess technical issues of the investigated sample. The methods of analyzing sequencing data and normalization of microRNA expression to a reference microRNA are important confounders, affecting both real-time PCR based as well as next-generation sequencing data (Kohen et al. 2014). For instance, microRNA expression in postmortem prefrontal cortex suggested canonical reference RNAs U6, U44 and U48 and their geometric mean to be not equally distributed and balanced across the investigated diagnostic groups (Smalheiser et al. 2014). A second layer of limitations results from methodological issues of (high-throughput) quantitative real-time PCR. It would be very helpful, if all studies provide raw Ct values along with standard deviation for all tested microRNAs. An interesting insight allows the supplement of a recent study assessing peripheral blood mononuclear cell (PBMC) microRNA expression in MDD (Belzeaux et al. 2012): the two microRNAs showing a dysregulation in PBMCs over the complete time course of the study had a mean Ct value of 32.25 $\pm$ 1.83 (hsa-miR-941) and 32.86 $\pm$ 1.84 (hsa-miR-589) across all cases and controls. This is very close to the authors' cutoff for background, represented by Ct values above 33, like many dysregulated microRNAs exhibit very low expression.

In light of these limitations, translational research provides a valuable second line of evidence. Data from murine models of depression-like and anxiety-like traits presently complement human studies to a large extent. As the focus of the review is on presently available human evidence, we would like to refer the reader to excellent reviews by others for a more general perspective of this topic (Mouillet-Richard et al. 2012; Hansen and Obrietan 2013; Dwivedi 2014). Main foci of microRNA-related translational research on major depression and suicidal behavior have been neurogenesis and neuroplasticity, BDNF-signaling, stress-induced neuronal adaptations, as well as the action of antidepressants (Serafini et al. 2012). Mir-16 was suggested to be induced by administration of selective serotonin reuptake inhibitors (Baudry et al. 2010). Putatively, the action of mood stabilizers may also involve miR-16, as well as miR-15, by repressing *BCL2* (Cimmino et al. 2005), and lithium was reported to increase *BCL2* levels (for review see Marmol 2008). However, direct experimental evidence is missing and an increase, rather than a decrease in miR-15a was reported upon valproate administration in rat hippocampus (Zhou et al. 2009). More recently, miR-135 was reported to repress expression of the serotonin transporter and the serotonin 5-HT_{1A}-receptor, and to increase upon chronic imipramine administration in mice (Issler et al. 2014). These studies are very important for understanding basic molecular processes and identifying novel molecular mechanism, which help understanding current therapeutic options and may allow development of future therapeutic approaches. Local regulation of protein synthesis at synapses may be important in learning. CREB-BDNF pathways may exhibit important roles in regulating the homeostasis of neural pathways by microRNAs, and thus represent another interesting novel pharmaceutical target (Serafini et al. 2012). However, contrary to proteins, microRNAs and their binding sites are less conserved than proteins, emphasizing the necessity of reciprocal human and clinical validation of translational research.

Finally and relating to all types of studies, the ratio of the number of patients to the number of microRNAs analyzed is often rather small, seriously raising the possibility of false-positive discoveries and making independent (not same-team or same-sample) validation mandatory (Ioannidis 2005). Even then, current pathway analysis of microRNAs suffers from the high false-positive rate of microRNA:mRNA interaction prediction, thus reflecting the need of experimental validation.

Conclusion

Although microRNAs are known for more than 20 years, our understanding of their functional roles is still evolving and research on mental disorders has just recently turned on them. The rapidly increasing number of annotated microRNAs has opened a large field of possible interactions, which may be important in pathology, but may also be applied to novel pharmacological approaches. Concerning disease mechanisms and new pharmacological approaches, translational research is promising, but issues of conservation of microRNA biology across species may be a relevant limitation. It will thus be an important field of research to identify the molecular roles for human-specific microRNAs in neural tissues. Recent methodological advances may greatly accelerate the identification of microRNA-binding sites in the human brain (Boudreau et al. 2014).

Genetic studies directly assess the contribution of known genetic variants to heterogeneity in terms of disorder risk and individuality in terms of phenotypic variance. As such, the encouraging results on *MIR137HG* and its SNP rs1625579 in schizophrenia represent paradigmatic research, which should be applied to all mental disorders. However, data also point out, that only large studies can really assess the importance and relevance of microRNAs in mental disorders (Kendler 2013). Once more results have been replicated in adequately powered samples, e.g. by GWAS or meta-analyses as well as functional

investigations such as fMRI, we will almost certainly be able to better understand the individuality of our patients due to genetic variation in microRNAs.

Expression studies are presently in an early stage and often limited by technical issues and a lack of replication. Once the methods of microRNA extraction, detection and normalization have been reliably standardized, it will be interesting to see, whether microRNAs can really help as biomarkers of disorder or treatment response to better understand the individuality of our patients and develop individualized therapeutic approaches.

Based on our present knowledge, microRNAs thus add an increasingly complex layer of heterogeneity and individuality to mental disorders and might give rise to more differentiated and individualized therapeutic approaches in the future.

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