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MicroRNA regulation of prefrontal cortex development and psychiatric risk in adolescence

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Abstract

In this review, we examine the role of microRNAs in the development of the prefrontal cortex (PFC) in adolescence and in individual differences in vulnerability to mental illness. We describe results from clinical and preclinical research indicating that adolescence coincides with drastic changes in local microRNA expression, including microRNAs that control gene networks involved in PFC and cognitive refinement. We highlight that altered levels of microRNAs in the PFC are associated with psychopathologies of adolescent onset, notably depression and schizophrenia. We show that microRNAs can be measured non-invasively in peripheral samples and could serve as longitudinal physiological readouts of brain expression and psychiatric risk in youth.

Keywords

Biomarkers; Vulnerability; Resilience; MiR-218; DCC receptors; Depression; Schizophrenia

1. Introduction

Adolescence is a developmental period marked by sexual maturation, novel-experience seeking, and transition in cognitive skills. This malleable window is sensitive to perturbations including drugs of abuse and stress, which can render individuals at risk for mental illness. Enhanced psychiatric vulnerability in adolescence has been attributed to substantial changes occurring in the maturing prefrontal cortex (PFC) during this time. Dysfunction of the PFC is linked to changes in personality, emotional response, memory, attention, and social behavior [1–7], and is observed in psychopathologies that emerge in adolescence [8–11]. The molecular mechanisms and the timeline underlying susceptibility or resilience to PFC dysfunction remain elusive. MicroRNAs are essential coordinators of developmental programing, and mediators between environmental factors and changes in gene expression. In this review we propose that microRNA-mediated shaping of PFC

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Declarations of interest

None.

circuitry maturation in adolescence may be an important determinant of lifetime mental health.

1.1. MicroRNAs: functional complexity

Microribonucleic acids, or microRNAs, are small RNA molecules that serve as key regulators of large-scale gene expression. MicroRNAs are non-coding RNA 19–25 nucleotides long and are single-stranded. They can match and bind seed regions of several different messenger RNAs (mRNAs). This property allows a single microRNA to control and coordinate activity of entire gene networks and cellular pathways [12]. MicroRNA biogenesis is a multi-step process. Briefly, the more common canonical biogenesis starts with the transcription of primary microRNAs, which are double-stranded long hairpin-like structures with a polyA tail. The polyA tail is then cleaved by the microprocessor complex (Drosha/DGCR8), generating a double-stranded precursor microRNA, which is exported from the nucleus to the cytoplasm by the Exportin-5 protein. Once in the cytoplasm, Dicer endoribonuclease cleaves the precursor microRNA, to produce a single-stranded and functional mature microRNA, either the forward 5’ (5p) or the reverse 3’ direction (3p) of the original strand. The mature microRNA is then loaded into an Argonaute family protein (AGO 1–4 in humans) to form a microRNA-induced silencing complex (miRISC) that interacts with the 3’-untranslated region (UTR) of the mRNA target (for detailed reviews see [13,14]).

The binding of microRNAs to perfectly complementary mRNA sequences (2–7 nucleotides) of target genes usually induces transcript degradation and/or prevention of mRNA translation [13]. However, increased mRNA translation upon microRNA binding to mRNAs targets has also been described [15,16]. Mature functional microRNAs can be found in the cell’s cytoplasm and in the nucleus, and their distribution can change in response to environmental factors [17,18]. MicroRNAs localized to the cytoplasm and those in the nucleus seem to be involved in different processes. Nuclear microRNAs can trigger gene transcription by binding and activating enhancer regions [19] or by directly binding to promoter regions [20]. The variety of mechanisms involved in microRNA control over gene expression indicates the complexity of the system and that much remains to be uncovered.

1.2. Contribution of microRNAs to early cortical development

The majority of microRNAs are evolutionary conserved and play analogous biological functions across species, including in neurodevelopment. In this review we focus on the role of microRNAs in the development of the cerebral cortex, the most superficial sheet of the mammalian brain, which is involved in higher-order cognitive function and sensory processing. MicroRNAs are proving to be essential regulators of cortical development [21], playing critical roles in the production of progenitor cells [22–25] and in the survival, differentiation and spatiotemporal organization of cortical neurons [26–29]. A microRNA network appears to have evolved to specifically shape the developmental fate of corticospinal and callosal projection neurons, which are at the root of mammalian (more specifically eutherian) brain anatomy and function [30]. Obstruction of microRNA function or of enzymes involved in microRNA synthesis (e.g. Dicer, DGCR8) induces dramatic disruption of cortical development, from cell viability and premature progenitor

differentiation during corticogenesis to cortical malformations [29,31,32]. MicroRNA control over cortical development extends to adolescence [33], when the prefrontal portion of the cortex continues to undergo substantial maturation [34–42], remaining particularly vulnerable to environmental factors.

2. Adolescence is a critical period for PFC development, microRNA expression, and psychiatric vulnerability

The PFC is often characterized as the “executive” center where information is processed and integrated to carry out complex functions, including planning, decision-making and goal-directed behavior. One third of the cerebral cortex in primates is the anterior region of the frontal lobe [43], although in rodents the PFC takes smaller percentage of the total cortical area. As reviewed elsewhere, differences in PFC cytoarchitecture between primates and rodents are important limitations to the translation of findings across species [8,44,45]. However, both anatomically and functionally, the PFC is believed to be homologous between primates and rodents, with some disagreement remaining as to the specific correspondences between PFC subregions between primates and rodents [45].

A common feature of the PFC in rodents and primates is that it continues to sustain significant structural and functional maturation across the adolescent period and into early adulthood [34–38,42]. This protracted development is accompanied by corresponding transitions in behaviors and cognitive function, including the gradual stabilization of emotional reactivity, novelty seeking, cognitive control, and decision-making [36,46]. During adolescence, the PFC undergoes gray matter volume reduction, white matter content increase, and refinement in circuitry cytoarchitecture, including axonal myelinization, dendritic morphology and synaptic density [34,38,47]. The pari passu unfolding of structural and behavioral correlates indicates that proper PFC development is critical for the maturation of cognition and behavior. Adolescence is in fact a sensitive developmental time that sets the stage for lifelong mental health (see [48]).

Here we review evidence implicating microRNAs in adolescent maturation of the PFC and in the increased vulnerability to psychiatric disorders during this age. Nevertheless, changes in microRNA expression in the cortex at any point of the developmental continuum can affect the function of gene networks controlling ongoing homeostatic processes [49]. Emerging results from rodent studies supports the notion that microRNAs are key epigenetic mediators of early environmental programing on neurocircuitry, cognitive development and function throughout the lifespan [33,50,51], even lasting across generations [52, 53].

Human postmortem brain studies have shown that microRNA expression in the PFC is highly influenced by age with some microRNAs being differentially expressed between infancy, early and late childhood, and adolescence [54]. Remarkably, the adolescent period coincides with a shift in the pattern of global microRNA expression. A study analyzing average expression of microRNAs in the PFC from neonates to older adults found that precisely in adolescence the pattern of microRNA expression splits into two diverging directions: while some microRNAs begin to be upregulated, others are downregulated, with the new pattern of expression maintained for the rest of life [55]. To probe possible

biological implications of the age-associated microRNA expression split, the authors performed gene target, pathway and function analyses. They found that gene targets of the "split" microRNAs are involved in nervous system development and function, cell-to-cell signaling and interactions (e.g. synaptic transmission and axon and neurite morphology) and have been associated with schizophrenia, bipolar and other mood disorders. This study also revealed that the expression of genes involved in microRNA biogenesis, notably *EXPORTIN-5* and *DICER*, also switches from teenagehood onward [55]. These findings suggest that abnormalities in the adolescent pattern of microRNA expression trajectories in the PFC could lead to predisposition to mental illness.

Dysfunction of the PFC has been strongly implicated in the etiology of psychiatric disorders of adolescent onset, including schizophrenia, major depressive disorder (MDD) and substance use disorder (see: [8, 56–58]). An increasing number of studies, including those by our group, have identified alterations in microRNA expression in postmortem PFC samples of psychiatric patients. A summary of results from studies in schizophrenia, bipolar disorder, depression, and substance use disorder, are presented in Table 1. Some microRNAs have been found to be dysregulated in multiple disorders, suggesting that they may play a role in core neurodevelopmental processes. miR-29, for example, is involved in cortical maturation [59], neuronal differentiation [60], neuron survival [61], and synapse formation [62], and appears to be altered in both schizophrenia and bipolar disorder. In fact, a recent study in rodents links miR-29 to neurobehavioral deficits through the regulation of postnatal cortical maturation [63]. Studies are needed to assess the role and timing of specific microRNAs in the pathogenesis of these disorders.

2.1. Role of miR-218 in psychiatric disorders of PFC dysfunction and adolescent onset

Major depression is one of the most widespread psychiatric disorders, ranked by the World Health Organization as the leading cause of disability worldwide [64], and as many as 40% of patients diagnosed with MDD do not respond to common antidepressant therapies [65–67]. The incidence of depression is high between the ages 12–25 [68–71] and an alarming 25% of adolescents meet the criteria for depression [72–75]. Experiencing a depressive episode in adolescence increases the risk of depression and of higher severity in adulthood up to 3-fold [76–78].

In our studies investigating microRNAs involved in PFC maturation and MDD vulnerability, we identified the microRNA miR-218-5p (whose matured sequence originates from the 5' strand of its miR-218-1 or miR-218-2 stem loop precursors), as a repressor of the *DCC* gene. DCC is a receptor for the guidance cue Netrin-1 [79] and is intimately involved in the formation of neuronal networks during early neurodevelopment. Notably, DCC-mediated Netrin-1 signaling controls the protracted maturation of the PFC circuitry specifically in adolescence [80–82]. Using postmortem brain samples, we showed that *DCC* expression in the PFC of adult individuals who were diagnosed with MDD and died by suicide is significantly upregulated compared to control individuals who died by sudden death [79]. We replicated this finding in two independent cohorts [79,80]. To probe the role of miR-218–5p (henceforth referred to as miR-218) in the *DCC* expression changes observed in MDD, we assessed its expression in the same postmortem PFC samples and found that

miR-218 is *downregulated* in MDD by approximately 50% compared to controls. Reduced levels of miR-218 correlate with elevated expression of *DCC* in the PFC of individuals with depression, suggesting a causal link between miR-218 and *DCC* alterations in MDD pathogenesis [79].

A rapidly increasing number of studies show that changes in *DCC* are linked to vulnerability to psychopathologies of adolescent onset and involving PFC dysfunction, most prominently MDD (reviews from [83, 84]). Furthermore, we have shown that variation in the *DCC* gene co-expression network within the PFC is associated with total brain volume across childhood, highlighting the role of this system in broad postnatal neurodevelopment [85]. Whether genetic variants (single nucleotide polymorphisms) within *DCC* (see Ref. [86]) affect the binding of microRNAs, or whether changes in expression of the *DCC* network are linked to altered microRNA function, remains to be shown.

Postmortem studies cannot reveal whether alterations in microRNA expression in MDD mediate atypical development of the PFC and/or play a causal role in disorder symptomatology. MicroRNAs are highly conserved, and miR-218-5p is homologous between humans, macaques, and rodents (UCSC genome browser [87]), offering a link between preclinical and translational studies. The social defeat stress paradigm is a well-established model used in rodents to study stress-induced behavioral abnormalities that resemble depression-like traits [88,89]. Using this model, we assessed the effects of reducing the levels of miR-218 directly in the PFC of adult male rodents via anti-sense oligonucleotides (“antagomirs”). Consistent with the reduced expression of miR-218 in the PFC of MDD patients, we found that downregulating miR-218 in the adult mouse PFC *increases Dcc* expression and elicits vulnerability to stress-induced depression-like behavioral abnormalities [90]. Furthermore, in mice that show resilience to stress, intranasal administration of miR-218 antagomir induces a similar vulnerability. Upregulating miR-218 in the PFC, via viral-mediated gene transfer, instead *reduces Dcc* expression and protects against stress-induced depression-like behavioral traits, pointing at miR-218 as a potential therapeutic target. Altered miR-218 levels in the PFC have also been reported in adult stress-exposed rats (either through the chronic stress paradigm or corticosterone injections) [91], and in adult mice exposed to chronic unpredictable mild stress [92].

Given that DCC receptors control the adolescent maturation of the PFC [80–82], we investigated miR-218 expression in the mouse PFC across postnatal life. Consistent with the adolescent shift in global microRNA expression observed in the PFC in humans [54,55], miR-218 levels in mice increase from early adolescence to adulthood. Postnatal PFC miR-218 and *Dcc* expression in mice correlate negatively [33]. Disrupting this developmental pattern has enduring behavioral consequences: downregulation of miR-218 in the PFC of adolescent mice via antagomir microinfusion, induces resilience to detrimental effects of chronic social defeat stress in adulthood. This finding is opposite to the effects seen following miR-218 downregulation in the adult matured PFC, yet in line with the idea that changes in the adolescent pattern of microRNA expression in the PFC are associated with vulnerability to developing psychiatric traits. Interestingly, results from a preliminary experiment show that intranasal administration of miR-218 antagomir in adolescent male mice leads to reduced anxiety-like behavior in adulthood, without affecting motor abilities

[93–95], indicating that targeting microRNA expression in adolescence may have enduring preventative and/or treatment benefits.

The opposite effects that adolescent versus adult antagomir-218 microinfusions in the PFC have on stress vulnerability are intriguing [33,79,90], particularly within the context of miR-218 regulation of *Dcc* expression across postnatal life [33]. The Netrin-1/DCC guidance cue pathway organizes neural connectivity in the developing and matured brain via age-specific molecular and cellular processes. In adolescence, DCC-mediated Netrin-1 signaling is involved in axonal targeting and growth, whereas in the adult brain this signaling pathway controls the refinement of already established circuitries, by modifying neuronal structure, including dendritic spine morphology [83,84]. The role of miR-218 in shaping psychiatric vulnerability or resilience is likely to be dictated by the function of the Netrin-1/DCC pathway at that particular developmental period. Downregulating miR-218 in the adolescent PFC, when its levels are significantly lower than in adulthood, would prolong high expression of *Dcc* and likely extend the postnatal window of axonal targeting and growth and synapse formation. In contrast, reducing miR-218 in the adult PFC, would bring *Dcc* expression to levels observed in the immature brain, eliciting aberrant changes in the organization of synaptic circuitry. RNA sequencing based strategies assessing alterations in PFC gene expression under antagomir-218 treatment in adolescence versus adulthood would aid in elucidating gene networks and pathways involved in the distinct behavioral outcomes.

2.2. microRNAs may coordinate the organization of synaptic circuits in the developing adolescent PFC

The maturation of the PFC requires tight regulation of gene expression to drive proper neuronal connectivity and plasticity [42,96]. In cultured cortical neurons, microRNAs have been shown to modulate synaptogenesis [97] and axon extension [97–100]. In rodent studies with a focus on early postnatal life, microRNAs have been found to regulate cortical pyramidal neuron dendritic structure [101] and spine morphology [102], which are key determinants of intercellular communication and circuitry organization. The influence of microRNAs over PFC development in adolescence likely involves coordinating expression of gene networks that control the establishment of synaptic connections, including those influencing dendritic spine morphology and plasticity. Consistent with this idea, postnatal deficiency in microRNA production in pyramidal neurons, due to conditional downregulation or deletion of the DGCR8 microprocessor, results in altered dendritic morphology and synaptic transmission in the PFC [103,104]. miR-218 is highly expressed in dendritic spine compartments of PFC pyramidal neurons [102], and changes in its expression are associated with modification of spine morphogenesis in these cells [90]. Changes in somatodendritic properties of PFC pyramidal neurons are well documented in psychiatric disorders of adolescent onset [105,106]. Abnormal neuronal size [107], dendritic outgrowth [108], reduced basal dendrite [109] and spine density [110] have all been reported in schizophrenia. In MDD, modifications in dendritic spine morphology, density of PFC pyramidal neurons, and loss of synapses in PFC circuitry have also been consistently documented [106,111]. Altered microRNA expression in the PFC in adolescence may disrupt ongoing synaptic pruning and the balance of excitatory and inhibitory signaling, inducing psychiatric vulnerability [61,105].

3. Circulating microRNAs as biomarkers of psychiatric risk in adolescence

The neurobiological processes underlying the elevated risk for psychiatric disorders in adolescence has not been representatively studied and there is a pressing need to identify biological factors that would aid in early identification and prevention. Depressive symptoms and rates in adolescents have been on a rapid rise with the ongoing global viral pandemic [112–116]. The abrupt change in psychosocial interaction and elevated stress stemming from home confinement already appears to be disproportionately exacerbating depressive symptoms in youth [112,115,116]. Unfortunately, the number of studies in psychiatry aimed at discovering biological markers of risk in adolescence is scant. Using keywords “biomarker” and “psychiatry” in the Scopus® search engine yields a track record from the year 1989 with ~ 500 articles added per year in the last two decades (Fig. 1A). Adding the keyword “adolescence” to the search shows a track record from the year 2000 with only ~80 articles published annually in the last 6 years (Fig. 1B). More studies aimed at discovering biomarkers to detect psychiatric vulnerability in adolescence are urgently needed.

MicroRNAs are emerging as promising diagnostic and therapeutic tools in human disease [117]. They are very stable, do not degrade due to heat [118] or after prolonged storage [119,120], and are abundant and readily detectable in a variety of peripheral fluids, such as blood, saliva, and urine [121,122]. MicroRNAs are secreted into peripheral fluids and transported out of cells via exosomes, microvesicles, or by binding to proteins, achieving post-transcriptional regulation of gene expression at far away targets. Parallel changes in microRNA expression have been observed between brain and peripheral samples [33,79, 123–126]. In our miR-218 studies in mice, we have found that the dynamic pattern of miR-218 expression in the postnatal PFC is also observed in blood and that stress-induced reduction of miR-218 levels in the PFC is also detected in blood samples [33]. In humans, miR-218 levels in blood also appear to be downregulated in MDD, as observed in a study in aging individuals with MDD and cognitive impairment [127]. Remarkably, direct upregulation and downregulation of miR-218 in the PFC of adult mice, including specifically within pyramidal neurons, lead to corresponding changes in peripheral blood [79]. MicroRNAs in peripheral fluids may serve as readout of brain expression and function, and be used for early prediction of risk severity for mental illness [128].

To address whether peripheral microRNAs in adolescence could serve as biomarkers of psychiatric vulnerability, we collected blood samples from adolescent male mice that were subjected to chronic social defeat stress in adulthood. We found that circulating miR-218 in adolescence predictsvulnerability to stress-induced depression-like behavioral abnormalities in adulthood. In comparison to control and resilient groups, adult mice that showed susceptibility to stress had elevated blood levels of miR-218 in adolescence [33]. Previous studies assessing the role of microRNAs as early biomarkers of psychiatric risk in humans have provided an exciting direction for the field. However these studies have focused on associating participant-reported adverse childhood events with later outcomes or diagnosis [50], or comparing a child cohort with a separate adult group [129], rather

than longitudinally following up on adolescent cohorts. We propose that future longitudinal studies be designed to identify microRNA profiles in peripheral samples from adolescent boys and girls to determine whether they can serve as identification markers of risk and guide preventative and intervention measures specifically during this age (Fig. 2). Analysis of global microRNA expression through unbiased small RNA sequencing of peripheral sampling is a promising strategy we are currently using to investigate changes associated with the development of maladaptive behaviors in longitudinal adolescent cohorts. These studies may identify microRNAs not previously linked to psychiatric traits as well as provide more information regarding the potential role of microRNAs differentially expressed in psychiatric disorders (e.g. Table 1) in adolescent neurodevelopment. Finding associations between circulating microRNAs and changes in cognitive function and behavior during adolescence may also shed light into whether specific microRNAs play a role in shaping developmental trajectories in the human brain.

The transition from adolescence to adulthood does not have a clearly defined differentiating boundary [130–132]. Given our studies in rodents showing that circulating miR-218 levels in adolescence and in adulthood predict opposite outcomes regarding stress susceptibility, diagnosis prediction using peripheral microRNAs in late adolescence may be limited and would need to be considered with caution. Assessing microRNA biomarkers in combination with clinical observations and markers of developmental stages, including the Tanner pubertal staging and hypothalamic-pituitary-adrenal axis responses [133], is an important next step.

4. Conclusions and future directions

This review shows that microRNA control over gene networks that organize PFC circuitry during adolescence may be a key mechanism in the development of vulnerability or resilience to mental illness. MicroRNAs measured in saliva or blood in adolescence may serve as indicators of PFC maturational stage and function and be used to predict behavioral outcomes to stress later in life. In biofluids, microRNAs are enriched in exosomes [134] and the approach of isolating circulating brain-specific exosomes [135–137] during adolescence could serve as a more objective measure of brain function and maturational state, enhancing the specificity and sensitivity of microRNAs as diagnostic tools. In this review we focused on microRNA expression in the PFC. However, microRNAs in non-cortical regions are also likely to contribute to PFC development and to the etiology of MDD, schizophrenia and substance use disorders. Indeed, miR-218 levels have been shown to be also elevated in the postmortem lateral amygdala of individuals with neuroticism and anxiety [138]. In rodents, the disruption of PFC dopamine development by exposure to recreational-like doses of stimulant drugs of abuse in adolescence requires miR-218 upregulation in the ventral tegmental area [139]. Manipulations of brain-wide microRNA expression via systemic administration of antagomir will aid in prevention, and in the discovery of therapeutic treatments [117].

The incidence rate and onset of PFC-related psychiatric disorders that emerge during adolescence are sex specific [140,141]. This poses an important limitation to the results derived from studies assessing the role of microRNAs on PFC development and adolescent

risk, which have largely been conducted exclusively in males. As the prevalence of mental illness in adolescent boys and girls is on a rise, there is a pressing need for basic and clinical research in both males and females. In our own unpublished studies we are finding sexual dimorphisms in the pattern of microRNA expression in the postnatal PFC and in our translational studies we are prioritizing cohorts with representative male and female ratios.

How experiences in adolescence impact microRNA systems in the developing brain needs to be assessed in more detail. Particularly, whether they are regulated by adaptive and coping mechanisms, including biological, psychological, or social factors, that result in resilience despite adversity-related risk [142]. Individuals with the highest risk for mental illness are often the ones who benefit the most from early positive interventions [143]. A few recent studies have begun to address the involvement of microRNAs in this regard [123,144–148], but the developmental adolescent perspective in this line of research is missing. Efforts to understand microRNA function in PFC development prior to the closing of the formative adolescent window may ultimately help improving mental health outcomes for youth.

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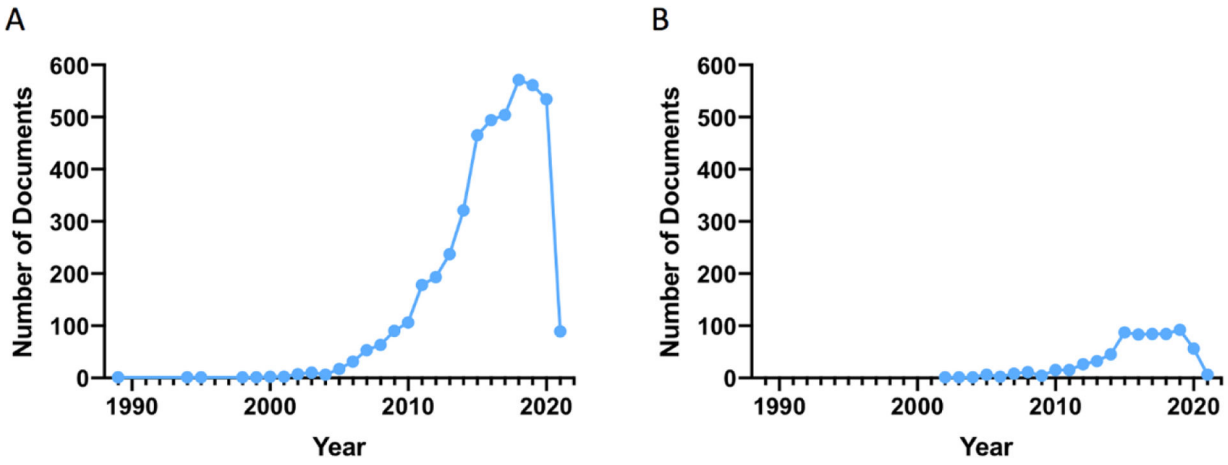

Fig. 1.

Number of articles published in the topic of biomarkers for psychiatric risk according to searches using Scopus ® Elsevier B.V. (A) Using keywords “biomarker” and “psychiatry” yields a track record, as of February 2021, from the year 1989 with ~ 500 articles added per year in the last two decades. (B) Using the keywords “biomarker”, “psychiatry” and “adolescence” to the search shows a track record from the year 2000 with only ~80 articles published annually in the last 6 years.

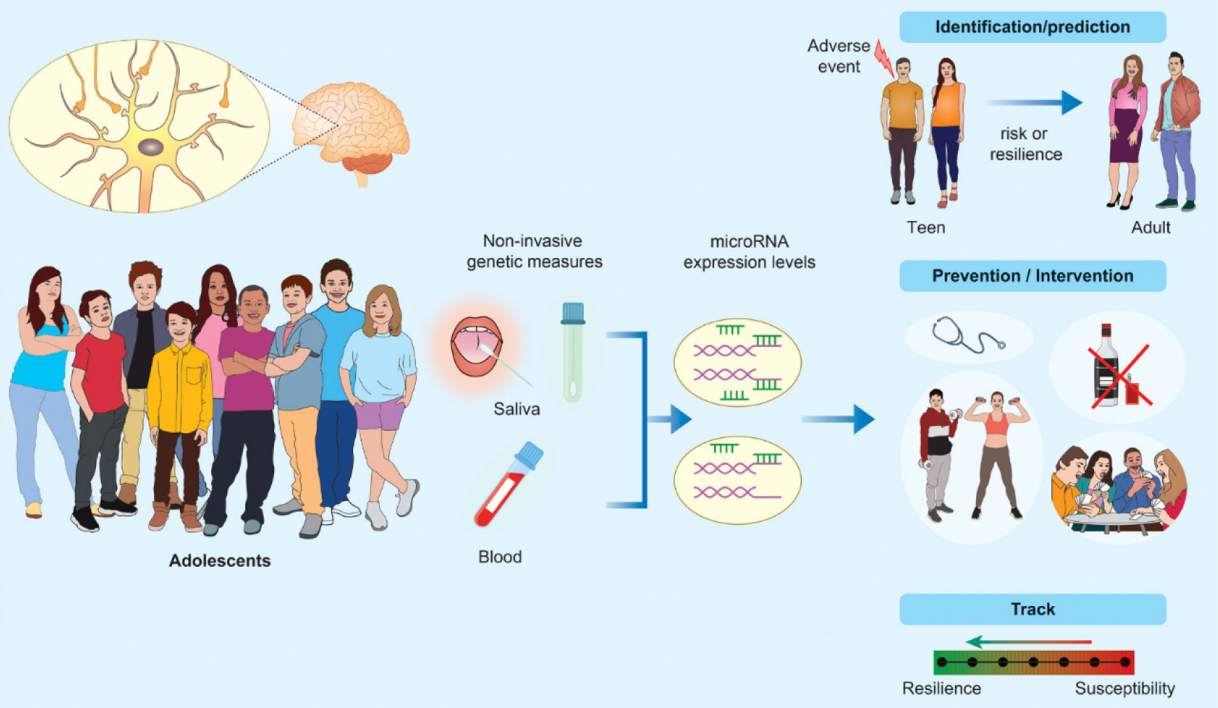

Fig. 2.

Peripheral microRNAs in adolescence as indicators of neurodevelopmental state and psychiatric risk. Assessment of microRNA profiles in peripheral samples from adolescent boys and girls in longitudinal studies could (i) help identifying markers of risk and resilience, (ii) guide prevention and intervention programs specifically for this age, and (ii) allow monitoring of disease severity.

Table 1

Evidence showing alterations in microRNA expression in postmortem prefrontal cortex samples of psychiatric patients. The methods for measuring microRNA expression vary across studies, most likely explaining the variability of findings.

microRNAs	Cortex region	Human condition	Reference
miR-26b, miR-30b, miR-29b, miR-195, miR-92, miR-30a-5p, miR-30d, miR-20b, miR-29c, miR-29a, miR-212, miR-106b, miR-7, miR-24, miR-30e, miR-9-3p	PFC BA-9	Schizophrenia vs. non-psychiatric control subjects	Perkins et al., 2007 [149]
miR-346	BA46		Zhu et al., 2009 [150]
miR-34a, miR-132, miR-212, miR-544, miR-7, miR-154,	Dorsolateral PFC BA-46	Schizophrenia vs. control individuals	Kim et al., 2010 [151]
miR-504, miR-454, miR-29a, miR-520c-3p, miR-140-3p, miR-145, miR-767-5p, miR-22, miR-145, miR-874, miR-133b, miR-154, miR-32, miR-573, miR-889		Bipolar vs. control individuals	
let-7d, miR-128a, miR-16, miR-181a, b, miR-20a, miR-219, miR-27a, miR-29c, miR-7	Dorsolateral PFC BA-9	Schizophrenia vs. control individuals	Beveridge et al., 2010 [152]
miR-553, miR-369-3p, miR-18a, miR-339-5p, miR-1, miR-7, miR-196a, miR-301a, miR-144, let-7g, miR-153, let-7f, miR-203, miR-34c-5p, miR-101, miR-376c, miR-665, miR-152, miR-194, miR-423-5p, miR-515-3p, miR-374b, miR-140, miR-519b-3p, miR-586, miR_135b, miR-92a, miR-15b, miR-580, miR-146a, miR-454-3p, miR-380, miR-652, miR-802, miR-196b	PFC	Alcohol user vs. control	Lewohl et al., 2011 [153]
miR-328, miR-17-5p, miR-134, miR-652, miR-382, and miR-107	Dorsolateral PFC BA-46	Schizophrenia/schizoaffective disorder vs. control individuals	Santarelli et al., 2011 [154]
miR-330, miR-33, miR-193b, miR-545, miR-138, miR-151, miR-210, miR-324-3p, miR-22, miR-425, miR-181a, miR-106b, miR-193a, miR-192, miR-301, miR-27b, miR-148b, miR-338, miR-639, miR-15a, miR-186, miR-99a, miR-190, miR-339	BA-9	Schizophrenia vs. control individuals AND Bipolar vs. control individuals	Moreau et al., 2011 [155]
miR-132	Dorsolateral BA-46	Schizophrenia vs. control individuals	Miller et al., 2012 [156]
miR-383, miR-32, miR-490-5p, miR-165b, miR-513-5p, miR-876-3p, miR-449b, miR-297, miR-188-5p, miR-187	miR-142-5p, miR-137, miR-489, miR-148b, miR-101, miR-324-5p, miR-301a, miR-146a, miR-335, miR-494, miR-20b, miR-376a, miR-190, miR-155, miR-660, miR-130a, miR-27a, miR-497, miR-10a, miR-20a, miR-142-3p	Bipolar vs. control individuals PFC BA-9	Depressed suicide vs. control individuals
Smalheiser et al., 2012 [157]			
miR-185	Anterior PFC BA-10	Depression vs. control individuals	Maussion et al., 2012 [158]
hsa-miR-375, hsa-miR-3065-5p, hsa-miR-488-star, hsa-miR-299-3p, hsa-miR-377, hsa-mir-516a-2, hsa-miR-767-5p, hsa-miR-493, hsa-miR-379, hsa-miR-105, hsa-miR-29b, hsa-miR-149	Frontal BA-9	Alcohol user vs. control	Manzardo et al., 2013 [159]
miR-31, miR-33, miR-96, miR-28, miR-30e-5p, miR-199a, miR-501, miR-504, miR-15b, miR-29c, miR-455, miR-380-3p, miR-323,	PFC BA-9	Differential expression for schizophrenia, bipolar and control groups	Banigan et al., 2013 [160]

microRNAs	Cortex region	Human condition	Reference
miR-527, miR-93, miR-32, miR-20b, miR-516-5p, miR-92, miR-30a-3p, miR-497 etc.			
miR-17-5p, miR-331-5p, miR-16-5p, miR-187-3p, miR-106b-5p, miR-485-5p, miR-129-2-3p, miR-454-3p, miR-185-5p, miR-429-3p, miR-511, miR-18a-5p, miR-590-5p, miR-106a-5p, miR-145-5p, miR-642a-5p, miR-625-5p, miR-508-3p, miR-219-2-3p	PFC BA-10	Schizophrenia vs. control individuals	Smalheiser et al., 2014 [161]
miR-17-5p, miR-145-5p, miR-579, miR-106b-5p, miR-485-5p, miR-370, miR-500a-5p, miR-34a-5p, miR-29c-3p		Bipolar vs. control individuals	
miR-508-3p, miR-152-3p		Depression vs. control individuals	
miR-34c-5p, miR-139-5p, miR-195, miR-320c	Ventrolateral PFC BA-44	Depression vs. control individuals	Lopez et al., 2014 [162]
miR-1202	Ventrolateral PFC BA-44	Depression vs. control individuals	Lopez et al., 2014 [163]
miR-218	Ventrolateral PFC BA-44	Depression vs. control individuals	Torres-Berrio et al., 2017 [79]
miR-124	Dorsolateral PFC BA-46	Depression vs. control individuals	Roy et al., 2017 [164]
miR-146a-5p, miR-146b-5p, miR-24-3p, miR-425-3p	Ventrolateral PFC BA-44	Depression vs. control individuals	Lopez et al., 2017 [165]
miR-19a-13p	Dorsolateral BA-10	Depression vs. control individuals	Wang et al., 2018 [166]
miR-3162, miR-936	BA-46	Schizophrenia vs. control individuals	Hu et al., 2019 [167]
miR-30e	Dorsolateral PFC BA-9	Depression vs. control individuals	Gorinski et al., 2019 [168]