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REVIEW

Putative Risk Biomarkers of Bipolar Disorder in At-risk Youth

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Abstract Bipolar disorder is a highly heritable and functionally impairing disease. The recognition and intervention of BD especially that characterized by early onset remains challenging. Risk biomarkers for predicting BD transition among at-risk youth may improve disease prognosis. We reviewed the more recent clinical studies to find possible pre-diagnostic biomarkers in youth at familial or (and) clinical risk of BD. Here we found that putative biomarkers for predicting conversion to BD include findings from multiple sample sources based on different hypotheses. Putative risk biomarkers shown by perspective studies are higher bipolar polygenetic risk scores, epigenetic alterations, elevated immune parameters, front-limbic system deficits, and brain circuit dysfunction associated with emotion and reward processing. Future studies need to enhance machine learning integration, make clinical detection methods more objective, and improve the quality of cohort studies.

Keywords Bipolar disorder · Biomarker · At-risk youth · Early recognition

Introduction

Bipolar disorder (BD) is a developmental and progressive illness, with a high heritability of 60%–80% [1, 2]. Genetic, cognitive, emotional, behavioral, and physiological factors all contribute to BD, and earlier onset tends to be more difficult to treat [3–5]. In the recent 15 years, definable stages of evolution were established for BD [6–11], enabling a more precise stratification of the patients and at-risk populations. Generally, individuals with genetic/familial risk are often defined by their parents' or their first-degree relatives' BD diagnoses. However, till now, there is no consensus on criteria among studies defining bipolar clinical risk, and different scales and cut-offs were used to define subthreshold episodes [8, 12, 13]. Studies of different follow-up periods preliminarily indicate that about 8% to 54% of youth at clinical risk and 13% to 25% of youth at genetic risk converted to BD [14–16]. Thus, predicting who among at-risk youth will convert could facilitate timely disease recognition and intervention, thus leading to improved prognosis [14, 17, 18]. However, the prodromal stages of psychiatric disorders are not obvious and similar across future diagnoses, making biological measurements warranted to inform more precise evidence [5].

Biomarkers are typically evaluated by blood, urine, or soft tissue samples to indicate normal or pathogenic biological processes, and pharmacological responses to therapeutic interventions [19, 20]. For a biomarker to be of practical value, it must be tested clinically, with an acceptable level of sensitivity, specificity, and predictive value [21]. In 2020, Steardo *et al.* performed a narrative review [22] identifying clinical, genetic, and gene-image binding markers focusing on youth at genetic or clinical risk for BD. Focused on genetic at-risk populations, other reviews concluded the neurological imaging characteristics detected by structure magnetic resonance imaging (MRI) [23], diffusion tensor imaging (DTI) [24], tasked-based functional MRI (fMRI) [25], and alterations in basal and reactive cortisol [26]. These reviews included mostly retrospective studies, and evidence-based on other hypotheses (e.g., genetic variations, epigenetic modifications, brain metabolic alterations)

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remains unexamined [14, 22, 27]. A growing number of recent prospective studies may allow us to summarize the clinical value of plausible risk biomarkers.

In this review, we aimed to (1) review the cross-sectional and prospective evidence of biological changes among youth at risk for BD, including genetic, peripheral, and neuroimaging findings; (2) landscape the biomarkers with evidence on their performance in predicting conversion, and give hints for possible interventions.

Omics Biomarkers

Changes in Genomics

Based on a strong genetic component with a heritability of 60%–80% [1, 2], the genetic etiology of BD was explored in large-sample genome-wide association studies (GWAS). Recently, a GWAS study in more than 40,000 patients found 15 genes linked to BD [28]. The risk alleles were enriched in synaptic signaling pathways and brain-expressed genes, especially in those expressed in neurons of the prefrontal cortex (PFC) and hippocampus. Additionally, a novel locus near TMEM108 was found genome-wide associated with BD in Han Chinese individuals but not with Europeans [29], showing underlying ethic and environmental factors in genome studies.

To better convey the combined effects of common genetic variants in BD, the polygenic risk score (PRS) was constructed based on single-nucleotide variations identified by GWAS. Cross-sectional studies found young offspring and siblings of BD patients showed higher bipolar PRS than offspring of parents without BD [30–32]. In a family cohort followed up for 13 years, parental and offspring PRS (hazard ratio [HR] = 0.89 and 1.40, $P = 0.40$ and 0.02) for BD explained 6% of the BD onset variance among offspring [30]. However, parental BD had a stronger direct association (HR = 5.21, $P = 0.002$, explaining 30% of the variance) than parental or offspring bipolar PRS. This suggests the insufficiency of current bipolar PRS itself in explaining the BD's "heritability gap".

Changes in Epigenomics

Epigenetic changes include covalent modifications to DNA or histones (e.g., methylation and hydroxylation), RNA transcripts, and post-transcriptional alterations involving numerous non-coding RNAs. Recent hypotheses have been made to demonstrate its role in genetic and environmental interactions in psychiatric disorders [33, 34].

Most cross-sectional studies found differentially methylated DNA sites in youth at familial risk of BD [35–40]. One recent study investigated both genetic background and methylation signatures using Illumina PsychArray and Methylation BeadChips [38]. The DNA methylation differences between groups with high ($n = 41$) or low ($n = 41$) PRS were shown in the VARS2 gene, which encodes a mitochondrial aminoacyl-tRNA synthetase that plays a role in synthesis proteins within the mitochondria, supporting the mitochondrial dysfunction hypothesis in BD [41, 42]. Another study [37] analyzed the genome-wide expression and methylation levels in peripheral blood samples of 6 BD patients, 6 unaffected bipolar offspring, and 6 controls. The study identified 43 risk genes especially enriched in the glucocorticoid receptor pathway, emphasizing the role of stress in the prodromal stages of BD.

In addition, epigenomic studies tried to underpin the involvement of stress by coping with DNA epigenetic aging found in BD patients [36, 41]. Surprisingly, Alex *et al.* [39] found epigenetic age deacceleration in the Horvath and Hannum clocks in 53 youth at familial risk for BD compared to 64 controls. However, none of the environmental stressors assessed (i.e., the Lewis-Murray scale, the Hollingshead and Redlich scale, and the Stressful Life Events Schedule) was associated with the findings. Subsequent studies need to further explore the role of environmental factors in methylation patterns.

Changes in Proteomics

Proteomics is the large-scale study of proteins in a system, capturing their expression levels, isoforms, and posttranslational modifications at a specific time and condition [43, 44]. Protein detection is typically done using immunoassays like Enzyme-Linked ImmunoSorbent Assays, Western blots, and multiplex panels, or more powerful and reproducible mass-spectrometry methods [45].

Studies in BD have found differentially expressed proteins in a range of processes with diverse functions [46], with one showing early perturbations in lipid metabolism are independent of mood state [47]. Moreover, blood-based models have been recently constructed, which had a high performance for discriminating schizophrenia (SCZ), BD, major depressive disorder (MDD), and healthy controls with 11 to 13 proteins (area under the curve [AUC] = 0.890–0.955) [48]. For differentiating 110 pre-diagnostic BD youth and controls, multiplex immunoassay analyses using serum samples were carried out to construct a blood-based biomarker panel [49, 50]. The panel had a fair to good predictive performance (AUC = 0.79) with lasso regression, and identified 20 protein analytes that functioned as pro-inflammatory, anti-inflammatory, lipid transporting, metalloendopeptidase activating, cysteine protease inhibiting, and growth factors [50].

Peripheral Biomarkers

Mitochondrial Dysfunction and Oxidative Stress

From the 1990s, mitochondrial dysfunction and other linked pathological processes including oxidative stress, inflammation, stress response, and accelerated aging were found in BD [41, 42, 51, 52]. Excessive oxidative stress induces point mutations that lead to mitochondrial DNA deletion due to restricted DNA repair ability and the absence of histones in mitochondria [37, 53]. Greater levels of lipid peroxidation (i.e., lipid damage), DNA/RNA damage, and nitric oxide (NO) markers were found in BD [54, 55]. Lower lipid hydroperoxides (i.e., an early-stage lipid peroxidation marker) and a higher trend of 4-hyroxy-2-nonenal and 8-isoprostane (late-stage lipid peroxidation markers) were found in BD patients and at-risk youths than in controls [56]. Such findings showed possible accelerated conversion from early- into late-stage markers of lipid peroxidation in the pathology of BD [56].

Immune Dysregulation

There is considerable evidence supporting the hypotheses of chronic low-grade inflammation in BD [57, 58]. Patients showed elevated levels of immune parameters including pro-inflammatory cytokines, acute phase protein levels, and complement factors [59–66], which can change neurotransmitter signaling mainly by decreasing the availability of 5-HT and DA [67].

Peripheral changes of inflammatory markers have been found in both genetic and clinical at-risk youth of BD. The prospective Dutch studies [68, 69] found that bipolar offspring showed higher serum levels of (1) cytokines pentraxin 3, a regulatory protein that enhances the anti-inflammatory response [70]; (2) chemokine ligand 2, a chemokine known to recruit monocytes and macrophages during inflammation [71]; (3) S100 calcium-binding protein B, an astrocyte activation marker, which seems to appear sequentially from adolescence to adulthood; and (4) other immune factors including IL-7, Insulin-like Growth Factor-Binding Protein-2 (IGF-BP2) and stem cell factor. Of these, IGF-BP2, transporting Insulin-like Growth Factor-1 to the brain [72] to modulate neuroinflammation and neuroprotection [73], showed the closest prediction of conversion with a sensitivity of 81% and specificity of 50% (threshold: $>$ 150 ng/mL) [69]. Further, compared with asymptomatic ones, the symptomatic bipolar offspring showed higher Interleukin-6 in the serum sample [74], indicating a progressed dysregulation of the immune system among at-risk youth. Notably, such differences were not solid in plasma samples between youth at familial and (or) clinical risk of BD and healthy controls [56, 75]. One possible reason is the different ability to detect cytokines among sample sources [76], which needs further validation.

Hyperactivity of the Hypothalamic-Pituitary-Adrenal Axis

For a long time, people have believed that mood disorders might be linked to the overactivity of the hypothalamic-pituitary-adrenal (HPA) axis [77–80]. This is a key biological system that helps us respond to stress. Patients with BD have increased salivary and plasma basal cortisol, post-dexamethasone cortisol, adrenocorticotropic hormone, and increased response to the dexamethasone/corticotropin-releasing hormone test [81].

Hyperarousal of the HPA axis was consistently found in offspring of parents with MDD [26]. However, among youth at familial risk for BD, cortisol level is the most studied peripheral target but with uncertain conclusions [26, 82]. A series of studies reported higher salivary basal cortisol levels in offspring at familial risk for BD [83–87]. Moreover, one study found salivary cortisol levels at the mean age of 17.5 years predicted future conversion to affective disorders during the subsequent 2.5 years among 28 BD offspring and 31 healthy controls (Odds Ratio [OR] = 2.1, 95% confidence interval [95% CI] 1.0–4.1, $P < 0.05$) [86]. However, more recent studies measuring salivary and hair cortisol concentrations do not support such differences shown between bipolar offspring and controls [88–93]. The inconsistencies observed between recent and older studies could potentially be attributed to the limited sample sizes used in these investigations. Additionally, to differentiate MDD and BD at-risk status, comparisons should be down between youths with genetic risk or sub-clinical symptoms of both MDD and BD. For example, the ongoing Lausanne-Geneva cohort aimed to test HPA-axis dysregulation by measuring cortisol levels in a pre-diagnostic sample of BD, MDD, and controls, and psychological stress by life events questionnaires. The related endophenotypes will hopefully be identified in probands of mood disorders, their offspring, and spouses [94].

Changes in Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is the most studied neurotrophic factor in BD, involved in hypotheses of impaired neuroplasticity during the illness course [95]. Decreased levels of BDNF were found in brain tissue, plasma, and serum samples of BD patients [42, 96]. Moreover, it may have a role in the depressive component of BD because a negative correlation between levels of BDNF and depression score was found in patients [97]. Reduced peripheral levels of BDNF were also related to poor cognitive functions in patients [98, 99].

The prospective Dutch study [68] found a decreased expression of the BDNF genes in youth at familial risk compared to healthy controls, which is supported by serological tests in the same population [69]. While they did observe the positive result, the presence of both contradictory [75, 100] and negative [101] outcomes in similar comparisons suggests that pathological deficits and compensatory responses may coexist in at-risk youth. This complexity underscores the need for further research introducing assessments of emotional states to fully understand these dynamics.

Sleep Disturbances

One symptomatologic feature of BD is the delayed sleep-wake cycle (i.e., later timing of sleep and daily activities) [82, 102–104]. The chronotype can be characterized by the biosynthesis of melatonin throughout the day—less during the light phase and more during the night [105]. This is usually measured in saliva or blood tests. Higher levels of melatonin were observed during the manic episode of BD patients [106] and reduced and later melatonin secretion was observed during the depressive episode and euthymic phases [105, 107].

Identifiable circadian rhythm change was found in 7 youth at familial risk of BD [91], and they experienced an earlier saliva melatonin red light melatonin onset after a 200-lux light exposure compared with 7 controls [91]. However, this result is the opposite of an earlier report with similar but older participants [108], which warrants more status-isolated evidence to conclude the potential role of melatonin in the at-risk stage of BD.

Altered Gut Microbiota

The human gut microbiota consists of microbes which include bacteria, archaea, bacteriophages, viruses, and fungi coexisting on human body surfaces and cavities [109]. Gut flora modifications might influence our behavior through the gut-brain axis, and induce altered neurodevelopment in the at-risk construct of severe mental illness [110]. As a proxy of intestinal microbiota, clinical samples are mostly collected from feces for sequencing [111]. Higher *Bifidobacterium* and *Oscillibacter* were observed in BD, while no study has investigated the gut microbiome in at-risk youth so far. Results from the adult first-degree relatives of BD patients showed no group difference [112–114].

Neuroimaging Biomarkers

Changes in Brain Structure

Magnetic Resonance Imaging

Structural MRI provides images that describe the shape, size, and integrity of the ventricles, white matter, and gray matter structures of the brain [115]. Parental BD psychopathology has been linked to the altered brain structure of their offspring. Compared to controls, youth at familial risk for BD showed reduced cortical thickness in parietal, frontal, and temporal areas, thickening of the anterior cingulate cortex (ACC), and larger caudate volume [23, 116–119]. Recent studies from the Early-BipoLife project also found that youths at clinical risk defined by BPSS-P showed a higher volume of the medial nucleus of the amygdala [120], and a thinner whole brain thickness than controls [121]. These findings are generally in line with structural changes associated with emotional regulation and reward reported in BD [42]. Further, research based on the Pittsburgh Bipolar Offspring Study [122] constructed a machine learning model elucidating cortical thickness and neural activity predictors of future mixed/mania factor score after 29 months, which explained 39.8% of the variance ($F = 3.71$, $P = 0.002$, clinical variables and age explained 31.5%, and neuroimaging variables added 8.3%) [116]. Captured neural predictors include lower bilateral parietal cortical thickness, greater left ventrolateral PFC (VLPFC) thickness, and lower right transverse temporal cortex thickness, emphasizing the role of evaluating cortical thickness as a biomarker of BD risk.

Diffusion Tensor Imaging

DTI assesses the structure, myelination, and connectivity of white matter based on tissue diffusivity [123]. The fractional anisotropy (FA) measure ranges from 0 to 1, with low FA suggesting decreased fiber density, reduced myelination, or less directionally organization of fibers [124]. Consistent with the dysconnectivity of front-limbic regions found in BD [42, 125], studies in youth offspring and siblings of patients with BD showed disease-specific decreased FA in tracts relating to emotional regulation and face recognition, including the left inferior longitudinal fasciculus (ILF), the corpus callosum and the left optic radiations [24, 126]. A 6-year study focused on a part of the brain called the right uncinate fasciculus, which is thought to play a role in emotion regulation. They found that FA of the right uncinate fasciculus was associated with the onset of BD (AUC = 0.859, sensitivity = 88.9%, specificity = 77.3%) in 45 youth at both clinical and familial risk [127]. Thus, future research is warranted to replicate and extend DTI findings on emotional regulation circus; in addition, complementary measures to

FA including axial diffusivity, mean diffusivity, and radial diffusivity are suggested to provide more sensitive information [128].

Changes in Brain Function

Resting-State fMRI

Resting-state fMRI is aimed at estimating correlations between brain regions while no task is performed at the time of the scan. Integral measures of functional connectivity are extracted from the blood oxygen level-dependent (BOLD) signals, indicating the strength of the brain networks [129]. Regional measures include the amplitude of low-frequency fluctuations, the fractional amplitude of low-frequency fluctuations, and regional homogeneity. Decreased prefrontal-temporal and cortico-limbic functional connectivity were repeatedly found among youth at risk of BD, involving the amygdala, hippocampus, ACC, insula, and striatum [130–132]. These findings are in line with the abnormalities relating to emotional and cognitive deficits reported in BD [133], and with structural alterations mentioned earlier. Interestingly, one study showed increased functional connectivity between the posterior cingulate cortex (PCC) and clusters in the subcallosal cortex, amygdala, and hippocampus in bipolar offspring [134]. Similar to patterns found in depressed patients [135], the findings may represent an overactivated default mode network [134].

Prospective studies also showed the relation between abnormal functional connectivity and the future risk of BD. In one trial with a 6-year follow-up, the logistic regressive model on the functional connectivity between the left hippocampus and left precuneus, and between right hippocampus and left PCC showed a discriminative capacity for predicting future mood disorder (AUC = 0.76 and 0.75) as well as BD onset (AUC = 0.77 and 0.82) among 80 bipolar offspring [136]. Another cohort study did not show such predictive ability by baseline functional connectivity differences relative to the amygdala and striatal network. Instead, among youth offspring of parents with affective disorders, youth converted to psychopathology (i.e., meet diagnostic criteria for any psychiatric disorder) had lower right amygdala-orbitofrontal cortex (OFC) and left ventral striatum-dorsal ACC voxel-based functional connectivity than resilient at-risk youth (P<0.05) after an average of 4.5-year follow-up [137].

Task-Based fMRI

Task-based fMRI also acquires the BOLD signals, and the difference between task activity and rest/control activity are compared for analyses [138]. Of note, individuals with BD show deficits of the front-limbic network in emotional and reward processing, and working memory even during euthymic periods [139, 140], supporting its state-independent property as a potential biomarker.

Youth at risk of BD are associated with aberrant brain activation. Although no significant behavior difference was found in the experimental setting, hyperactivation in the amygdala relative to healthy controls was repeatedly reported across different emotion processing designs [141–145]. Other inconclusive alterations reported in single studies were cortical regions including the VLPFC [142], the dorsolateral PFC (DLPFC) [146], the middle temporal gyrus [146], the SFG [147], the IFG [148], the ACC [141], the visual cortical regions [142, 147], the insula [147], and the subcortical structure including putamen [149] and hippocampus [147]. Differences in brain activity during reward processing are mainly shown in frontal and medial cortical areas between familial at-risk youth and controls [25]. Specifically, during reward feedback versus non-reward feedback, the OFC [150, 151], the right frontal pole [143], and the right posterior insular cortex [152] were reported as hyperactivated; the thalamus [153] and the right pregenual cingulate cortex [151] were reported as hyperactivated. In addition, small studies reported hypoactivation during high versus low working memory load in the left VLPFC, the left cerebellum, the bilateral insular cortex, the right brainstem, and the right parahippocampal gyrus/amygdala [149, 154] among youth with familial risk of BD.

Brain areas involved in emotion and reward processing were also shown predictive value by 2 prospective studies. A study among 29 bipolar offspring found that decreased left and right putamen activation ($P < 0.05$), and decreased left putamen and right PCC connectivity during emotion processing tasks were correlated with a higher risk of conversion to a mood or anxiety disorder (HR = 8.28, $P < 0.01$) [155]. In another study with 22 bipolar offspring and 22 healthy control offspring, interacting effects were found between scores of a previously developed risk calculator of clinical indicators [156], scores of negative stressful life events schedule, and task-based fMRI changes during the emotion and reward processing tasks [157].

Changes in Brain Metabolism

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) detects radio frequency electromagnetic signals and can be applied to nuclei such as proton (^{1}H), phosphorus-31 (^{31}P), and fluorine-19 (^{19}F) [158]. This method measures brain metabolites, such as glutamate (Glu), glutamine (Gln), gamma-aminobutyric acid (GABA), choline (Cho), creatine (Cr), phosphocreatine (PCr), myoinositol (mI), lactate (Lac) and N-acetyl-aspartate (NAA) [159]. Glutamatergic hyperactivity decreased Cr and

NAA in frontal cortical areas and increased ACC Cho in BD patients, with several key neurometabolic alterations appearing state-dependent [159, 160].

The PCr/adenosine triphosphate ratio in the frontal lobe detected by ^{31}P-MRS was reduced in 21 youths at familial risk for BD compared to controls [161]. Moreover, a longitudinal study reported PCr plus Cr levels in the left VLPFC predicted future mood episodes in bipolar offspring (HR = 0.47, 95% CI 0.27–0.82, $P = 0.008$) in survival analyses [162]. A ^{1}H-MRS study reported decreased myoinositol and Cho in the cerebellar vermis of bipolar offspring compared to healthy offspring [163]. However, there are studies detecting NAA, Cr, myoinositol, and Cho reported no group difference [164–167]. Also, a prospective ^{1}H-MRS study with a 5-year follow-up reported no group difference in NAA/Cr and myoinositol/Cr in the DLPFC [168]. Together, the current findings may support the reduced PCr as one of the indicators of BD genetic risk, suggesting the inability to maintain ATP levels during increased energy demand in the prodromal stages of BD [169].

Positron Emission Tomography

Positron emission tomography (PET) measures tissue metabolic activity by detecting the metabolism of the injected radiopharmaceutical tracer. The most widely utilized radiopharmaceutical for brain PET imaging is ^{18}F-fluorodeoxyglucose, which quantifies the metabolism of glucose [170]. In a study comparing three groups with 60 samples, patients with BD demonstrated hypoactive glucose utilization in the DLPFC and hyperactive utilization in the amygdala, similar patterns were insignificantly shown in adult bipolar siblings [131].

Landscape of Current Findings and Combined Strategies

Perspective researches showing the predictive value of potential biomarkers are concluded in Table 1. Accordingly, a prospective predicting model and hints at possible interventions ahead of solid evidence are suggested, indicating a variety of early intervention strategies can be developed and tested in at-risk populations (Fig. 1).

Combined biomarkers should be further investigated, as they may better characterize complex dysregulated pre-disease states [171]. For example, a recent study [172] found a negative association between methylation profile score with the volume of the medial geniculate thalamus ($\beta = -0.472$, $P = 0.003$) among 47 individuals with BD or subthreshold BD. The medial geniculate thalamus relays auditory sensory information to the auditory cortex, suggesting that the methylation signatures may mediate affected brain structure due to environmental sensors [172]. Bipolar PRS was found not associated with any brain measures in the same study [172] but was shown to be associated with EEG coherence in adolescents with BD [173]. Another study combining blood tests and structural neuroimaging biomarkers showed a divergent relationship between serum BDNF levels and regional brain volumes detected by MRI, which is negatively correlated among 67 bipolar offspring, while positively correlated among 45 healthy controls [100]. A similar trend of correlation was also reported in BD patients [174], with a possible explanation of the preventive and repairing role of BDNF in neural damage. Moreover, a study found increased coupling between structural and functional connectivity in long-distance connections in offspring of both groups of parents with SCH and BD compared to community control subjects[175], which may reflect higher anatomical constraints on functional brain dynamics in at-risk youth [176, 177]. Fig. 2 concludes the current landscape of sample sources in at-risk youth in finding putative risk biomarkers (Fig. 2).

Conclusions and Future Perspectives

This review summarized pieces of evidence on risk biomarkers and their value in predicting conversion among youth at familial or (and) clinical risk of developing BD while most of the perspectives are still in a proof-of-concept phase. Consistent with findings from BD patients, at-risk youth repeatedly showed deficits in the front-limbic system and dysfunction in brain circuits associated with emotion and reward processing [23–25, 119, 130, 132]. Higher bipolar PRS [30, 31], epigenetic alterations [37, 38], and elevated immune parameters [68, 69, 74] were also detected in peripheral samples. A few prospective studies yielded promising results toward developing risk biomarkers for predicting conversion among at-risk youth. In addition, biomarkers with predictive value toward converting to BD include serum tests of immune parameters [69], salivary tests of daytime cortisol [86], and bipolar PRS [30], as well as various neuroimaging methods detecting brain areas associated with emotion processing [116, 127, 136, 155, 162]. Applying these enlightening findings to clinical risk prediction is still a long way to go. To further investigate and validate the clinical value of the putative biomarkers, future studies need to enhance machine learning integration, make clinical detection methods more objective, and improve the quality of cohort studies.

In addressing problems of misdiagnosis and diagnostic delay in BD, different machine-learning models have been developed [178, 179]. However, most algorithms were developed based on symptomatological data from clinically diagnosed BD patients. Integrated machine-learning models including biological indicators are of great value

Table 1 Perspective studies on biomarkers toward predicting conversion in at-risk youth.

Study	Follow-up period	Study sample	Type of biomarker	Biomarkers included	Predicting performance
Peripheral biomarkers					
Ellenbogen *et al.* [86]	2.5-year	Offspring of parents with BD (n = 28); Offspring of parents with no affective disorder (n = 31); Baseline average age: 17.5 years	Hyperactivity of the HPA axis	Saliva sample: Daytime cortisol (collected at awakening, 30 and 60min post-awakening, 15:00, 20:00, and at bedtime)	Mean daytime cortisol levels predicted the development of an affective disorder (OR: 2.1, 95% confidence interval = 1.0–4.1, $P < 0.05$)
Snijders *et al.* [69]	12-year	Offspring of parents with BD (n = 96); Age- and gender-matched healthy controls (n = 50); Baseline average age: 16 years	Immune dysregulation	Serum sample: SCF, IGF-BP2, EGF, IL-7, sCD25	IGF-BP2 showed a sensitivity of 81% and specificity of 50% for predicting a future mood disorder (cut-off > 150 ng/mL)
Birmaher *et al.* [30]	13-year	The sample is from Pittsburgh BIOS: Parents with BD (n = 156); Parents without BD (n = 180); Offspring of parents with BD (n = 251); Offspring of parents without BD (n = 158); Offspring baseline average age: 10 years	Genetic and epigenetic biomarkers	Saliva sample: BD Polygenic Risk Score (PRS)	Parental BD had a stronger direct association than parental or offspring BD PRS with offspring BD risk (HR = 5.21, 95% CI = 1.86–14.62, $P = 0.002$, explaining 30% of the variance); Parental and offspring BD PRS explained 6% of the BD onset variance beyond parental diagnosis
Neuroimaging biomarkers					
Bertocci *et al.* [116]	2.1- to 2.5-year	The modeling sample is from Pittsburgh BIOS: Offspring of parents with BD (n = 20); Offspring with a parent with a non-BD Axis-1 disorder (n = 21); Baseline average age: 14 years The validating sample is from LAMS: Youth with a variety of psychiatric disorders presenting with behavioral and emotional dysregulation (n = 55); Baseline average age: 13.7 years	Changes in brain structure	Structural MRI scan & task-based fMRI scan: Neural activity during reward and emotion processing, gray matter structure	Lower bilateral parietal cortical thickness, greater left ventrolateral prefrontal cortex thickness, lower right transverse temporal cortex thickness, greater self-reported depression, mania severity, and age at scan predicted greater future mixed/mania factor score ($F = 3.71$, $P = 0.002$, clinical variables and age explained 31.5%, and neuroimaging variables added 8.3%)
Li *et al.* [127]	6-year	Symptomatic offspring of parents with BD (n = 45, baseline average age: 17.0 years); Asymptomatic offspring of parents with BD (n = 46, baseline average age: 17.6 years); Age-matched healthy controls (n = 35, baseline average age: 15.1 years)	Changes in brain structure	DTI scan: FA and MD uncinate fasciculus	The right uncinate fasciculus FA predicted BD onset (AUC = 0.859, P = 0.038) with a sensitivity of 88.9% and specificity of 77.3%

Table 1 (continued)

Study	Follow-up period	Study sample	Type of biomarker	Biomarkers included	Predicting performance
Zou *et al.* [136]	6-year	The sample is from the REI-PBD project: Symptomatic offspring of parents with BD (n = 39, baseline average age: 17.4 years); Asymptomatic offspring of parents with BD (n = 41, baseline average age: 16.8 years); Patients with BD (n = 50, baseline average age: 17.7 years); Matched healthy controls (n = 40, baseline average age: 16.0 years)	Changes in brain function	Resting-state fMRI scan: FC of hippocampus and parahippocampus	The FCs between the left hippocampus and left precuneus, and between right hippocampus and left posterior cingulate, showed a discriminative capacity for predicting future mood disorder (AUC = 75.76% and 75.00% respectively), and for predicting BD onset (AUC = 77.46% and 81.63%, respectively)
Nimarko *et al.* [155]	3.7-year	Offspring of parents with BD (n = 29); Youth has no personal or first- and second-degree relatives with a history of any Axis I disorder (n = 28); Offspring baseline average age: 13.64 years	Changes in brain function	Task-based fMRI scan: Whole-brain neural activation	Decreased left and right putamen activation ($P < 0.05$), and decreased left putamen and right posterior cingulate cortex connectivity (HR =8.28, $P < 0.01$) during emotion processing task was correlated with a higher risk of conversion to a mood or anxiety disorder in BD-risk group
Nery *et al.* [162]	2.4-year	Offspring of parents with BD (n = 117); The youth have no personal or first-degree relatives with a history of any mood or psychotic disorder (n = 61)	Changes in brain metabolism	^{1}H-MRS scan: Levels of NAA, PCr + Cr, choline-containing compounds, myoinositol, and glutamate	Baseline PCr + Cr levels in the left ventrolateral prefrontal cortex significantly predicted a mood episode during follow-up in the at-risk group (HR = 0.47, 95% CI = 0.27–0.82, P = 0.008)

BD, Bipolar Disorder; HPA, hypothalamic-pituitary-adrenal; SCF, Stem Cell Factor; IGF-BP2, Insulin-like Growth Factor Binding Protein-2; EGF, Epidermal Growth Factor; IL-7, Interleukin-7; sCD25, soluble CD25; BIOS, Bipolar Offspring Study; CI, Confidence Interval; MRI, Magnetic Resonance Imaging; FMRI, functional Magnetic Resonance Imaging; LAMS, Longitudinal Assessment of Manic Symptoms study; FA, Fractional Anisotropy; MD, Mean Diffusivity; AUC, Area Under Curve; FC, Functional Connectivity; REI-PBD, the Recognition and Early intervention on Prodromal Bipolar Disorder; NAA, N-acetyl aspartate; PCr, phosphocreatine; Cr, creatine; MRS, Magnetic Resonance Spectroscopy; OR, Odds Ratio; HR, Hazard Ratio

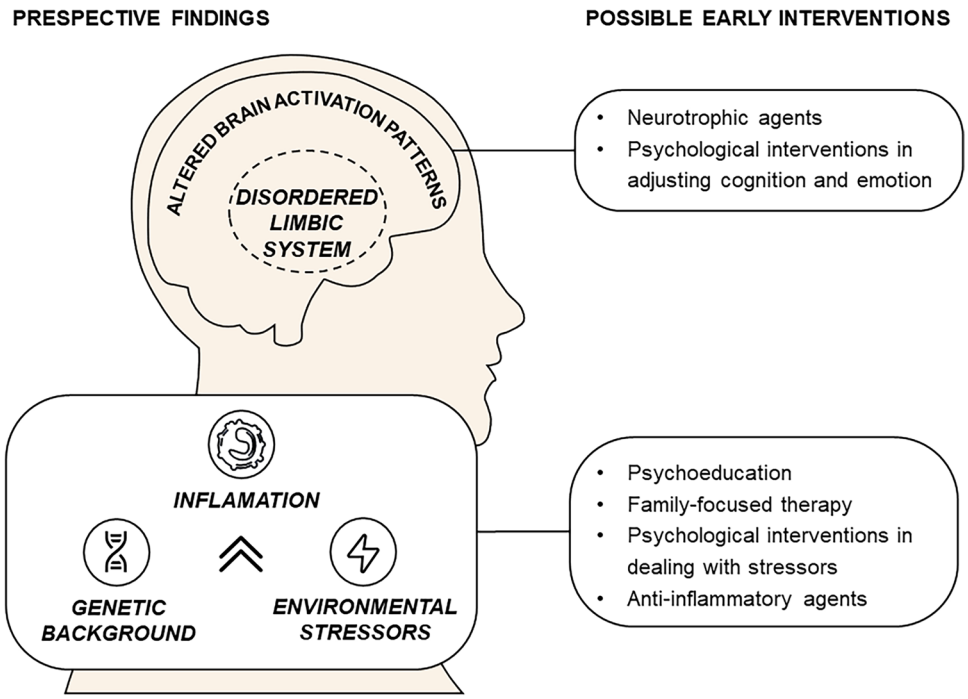

Fig. 1 The prospective predicting model in at-risk youth and hints at possible interventions.

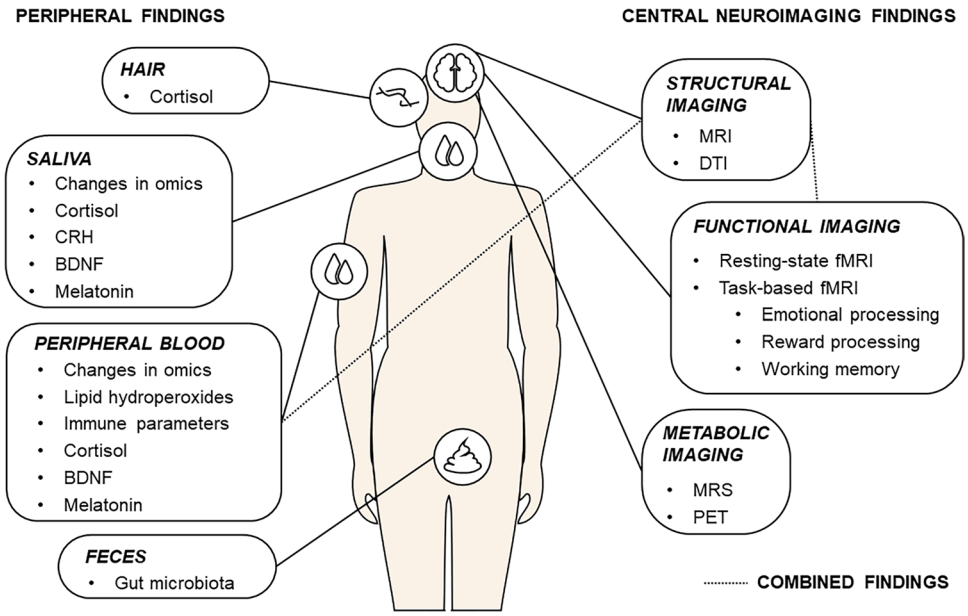

Fig. 2 The landscape of sample sources in at-risk youth in finding early biomarkers. *CRH* Corticotropin-releasing hormone, *BDNF* Brain-derived neurotrophic factor, *MRI* Magnetic resonance imaging, *DTI* Diffusion tensor imaging, *MRS* Magnetic resonance spectroscopy, *PET* Positron emission tomography.

for risk prediction among at-risk youth with less obvious symptoms [179, 180]. With the development of machine learning-based predictive methods, data from a series of omics such as genetics, epigenomics, and radiomics can be holistically understood and may contribute to precision medicine for psychiatric disorders [181, 182]. For example, support vector machines may help classify subjects fulfilling vs. not fulfilling the Bipolar Prodrome Symptom interview and Scale–Prospective (BPSS-P) criterion by data of structural imaging [121]. In addition, in an fMRI emotional task, depressed and/or anxious youth with genetic risk of BD showed different brain connectome patterns than controls, which was tested by a case-control classifier using machine learning (topological metrics) with an accuracy of 78.4%) [147]. Thus, future models should make more efforts to use clinically measurable, high-performance multi-dimensional biomarkers to improve the efficiency of predicting tools.

To make the study results more reliable and applicable to a wider range, clinical detection methods that follow sound methodology and standardized processes will promote the

selection and implementation of putative biomarkers [183]. Despite the remaining controversy in the representativeness of some biomarkers, efforts have been made to compare in vitro diagnostic techniques and instant test products for peripheral biomarkers in BD (e.g., cortisol, melatonin, interleukins, and oxidative stress biomarkers) [184]. This study could pave the way for creating and standardizing future products that can help in detecting BD at early stages.

Finally, larger cohorts and new perspectives on research are still warranted in this issue of great public health significance. Existing cohorts (e.g., the Bipolar Offspring Study (BIOS) [122, 185] founded by the National Institute of Mental Health, the Longitudinal Assessment of Mania Symptoms (LAMS) study [186–188], the Recognition and Early Intervention on Prodromal Bipolar Disorders (REI-PBD) study [189] and the Danish High Risk and Resilience Study [190]) all contributed a lot to the recognition and evaluation of early biomarkers for BD. Besides, considerable data shows stressful life events seem to affect multiple biological processes in youth [191–193], and to precede the occurrence of BD [194–196], and youth offspring of parents with BD were exposed to stress as early as infancy [197]. The ongoing Lausanne-Geneva cohort and the Early-Bipolife study aim to assess combined markers and environmental factors with a clear definition of the at-risk states [94, 198, 199]. These cohorts may provide a rich source of data and insights that can guide the direction of future research in BD risk identification, which will hopefully advance the pathological interpretation and biotype identification in the early courses of BD [200, 201].

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Conflict of interest The authors declare that they have no competing interests.

References

1. Johansson V, Kuja-Halkola R, Cannon TD, Hultman CM, Hedman AM. A population-based heritability estimate of bipolar disorder—in a Swedish twin sample. Psychiatry Res 2019, 278: 180–187.
2. Kerner B. Genetics of bipolar disorder. Appl Clin Genet 2014, 7: 33–42.
3. Colom F, Reinares M, Pacchiarotti I, Popovic D, Mazzarini L, Martínez-Arán A. Has number of previous episodes any effect on response to group psychoeducation in bipolar patients? A 5-year follow-up post hoc analysis. Acta Neuropsychiatr 2010, 22: 50–53.
4. Reinares M, Colom F, Rosa AR, Bonnín CM, Franco C, Solé B, *et al*. The impact of staging bipolar disorder on treatment outcome of family psychoeducation. J Affect Disord 2010, 123: 81–86.
5. Kupfer DJ, Frank E, Ritchey FC. Staging bipolar disorder: What data and what models are needed? Lancet Psychiatry 2015, 2: 564–570.
6. Berk M, Post R, Ratheesh A, Gliddon E, Singh A, Vieta E, *et al*. Staging in bipolar disorder: From theoretical framework to clinical utility. World Psychiatry 2017, 16: 236–244.
7. Duffy A. The nature of the association between childhood ADHD and the development of bipolar disorder: A review of prospective high-risk studies. Am J Psychiatry 2012, 169: 1247–1255.
8. Kapczinski F, Dias VV, Kauer-Sant'anna M, Frey BN, Grassi-Oliveira R, Colom F, Berk M. Clinical implications of a staging model for bipolar disorders. Expert Rev Neurother 2009, 9(7): 957–966.
9. Post RM. Monitoring children's mood and behavior. Am J Psychiatry 2015, 172: 909.
10. Post RM, Altshuler LL, Kupka R, McElroy SL, Frye MA, Rowe M, *et al*. Illnesses in siblings of US patients with bipolar disorder relate to multigenerational family history and patients severity of illness. J Affect Disord 2017, 207: 313–319.
11. Serdarevic F, Jansen PR, Ghassabian A, White T, Jaddoe VWV, Posthuma D, *et al*. Association of genetic risk for schizophrenia and bipolar disorder with infant neuromotor development. JAMA Psychiatry 2018, 75: 96–98.
12. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: A heuristic framework for choosing earlier, safer and more effective interventions. Aust N Z J Psychiatry 2006, 40: 616–622.
13. Post RM. Mechanisms of illness progression in the recurrent affective disorders. Neurotox Res 2010, 18: 256–271.
14. Keramatian K, Chakrabarty T, Saraf G, Yatham LN. Transitioning to bipolar disorder: A systematic review of prospective high-risk studies. Curr Opin Psychiatry 2022, 35: 10–21.
15. Bechdolf A, Nelson B, Cotton SM, Chanen A, Thompson A, Kettle J, *et al*. A preliminary evaluation of the validity of at-risk criteria for bipolar disorders in help-seeking adolescents and young adults. J Affect Disord 2010, 127: 316–320.
16. Kochman FJ, Hantouche EG, Ferrari P, Lancrenon S, Bayart D, Akiskal HS. Cyclothymic temperament as a prospective predictor of bipolarity and suicidality in children and adolescents with major depressive disorder. J Affect Disord 2005, 85: 181–189.
17. Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rössler A, Schultze-Lutter F, *et al*. The psychosis high-risk state: A comprehensive state-of-the-art review. JAMA Psychiatry 2013, 70: 107–120.
18. Post RM, Goldstein BI, Birmaher B, Findling RL, Frey BN, Del-Bello MP, *et al*. Toward prevention of bipolar disorder in at-risk children: Potential strategies ahead of the data. J Affect Disord 2020, 272: 508–520.
19. Group BDW. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharmacol Ther 2001, 69: 89–95.
20. Hirsch MS, Watkins J. A comprehensive review of biomarker use in the gynecologic tract including differential diagnoses and diagnostic pitfalls. Adv Anat Pathol 2020, 27: 164–192.
21. Halfon O, Laget J, Barrie M. An epidemiological and clinical approach to adolescent suicide. A comparison between suicidal and non-suicidal clinical groups in a health foundation center for French students. Eur Child Adolesc Psychiatry 1995, 4: 32–38.
22. Steardo L Jr, Manchia M, Carpiniello B, Pisanu C, Steardo L, Squassina A. Clinical, genetic, and brain imaging predictors of risk for bipolar disorder in high-risk individuals. Expert Rev Mol Diagn 2020, 20: 327–333.
23. Kemp JVA, Bernier E, Lebel C, Kopala-Sibley DC. Associations between parental mood and anxiety psychopathology and offspring brain structure: A scoping review. Clin Child Fam Psychol Rev 2022, 25: 222–247.

24. Xu M, Zhang W, Hochwalt P, Yang C, Liu N, Qu J, *et al*. Structural connectivity associated with familial risk for mental illness: A meta-analysis of diffusion tensor imaging studies in relatives of patients with severe mental disorders. Hum Brain Mapp 2022, 43: 2936–2950.
25. Johnsen LK, Ver Loren van Themaat AH, Larsen KM, Burton BK, Baaré WFC, Madsen KS, *et al*. Alterations in task-related brain activation in children, adolescents and young adults at familial high-risk for schizophrenia or bipolar disorder —A systematic review. Front Psychiatry 2020, 11: 632.
26. Klimes-Dougan B, Papke V, Carosella KA, Wiglesworth A, Mirza SA, Espensen-Sturges TD, *et al*. Basal and reactive cortisol: A systematic literature review of offspring of parents with depressive and bipolar disorders. Neurosci Biobehav Rev 2022, 135: 104528.
27. Menculini G, Balducci PM, Attademo L, Bernardini F, Moretti P, Tortorella A. Environmental risk factors for bipolar disorders and high-risk states in adolescence: A systematic review. Medicina 2020, 56: 689.
28. Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JRI, Qiao Z, *et al*. Genome-wide association study of more than 40, 000 bipolar disorder cases provides new insights into the underlying biology. Nat Genet 2021, 53: 817–829.
29. Li HJ, Zhang C, Hui L, Zhou DS, Li Y, Zhang CY, *et al*. Novel risk loci associated with genetic risk for bipolar disorder among Han Chinese individuals: A genome-wide association study and meta-analysis. JAMA Psychiatry 2021, 78: 320–330.
30. Birmaher B, Hafeman D, Merranko J, Zwicker A, Goldstein B, Goldstein T, *et al*. Role of polygenic risk score in the familial transmission of bipolar disorder in youth. JAMA Psychiatry 2022, 79: 160–168.
31. Fullerton JM, Koller DL, Edenberg HJ, Foroud T, Liu H, Glowinski AL, *et al*. Assessment of first and second degree relatives of individuals with bipolar disorder shows increased genetic risk scores in both affected relatives and young at-risk individuals. Am J Med Genet B Neuropsychiatr Genet 2015, 168: 617–629.
32. Jefsen OH, Nudel R, Wang Y, Bybjerg-Grauholm J, Hemager N, Christiani CAJ, *et al*. Genetic assortative mating for schizophrenia and bipolar disorder. Eur Psychiatry 2022, 65: e53.
33. Alameda L, Trotta G, Quigley H, Rodriguez V, Gadelrab R, Dwir D, *et al*. Can epigenetics shine a light on the biological pathways underlying major mental disorders? Psychol Med 2022, 52: 1645–1665.
34. Hu B, Won H, Mah W, Park RB, Kassim B, Spiess K, *et al*. Neuronal and glial 3D chromatin architecture informs the cellular etiology of brain disorders. Nat Commun 2021, 12: 3968.
35. Duffy A, Goodday SM, Keown-Stoneman C, Scotti M, Maitra M, Nagy C, *et al*. Epigenetic markers in inflammation-related genes associated with mood disorder: A cross-sectional and longitudinal study in high-risk offspring of bipolar parents. Int J Bipolar Disord 2019, 7: 17.
36. Fries GR, Bauer IE, Scaini G, Wu MJ, Kazimi IF, Valvassori SS, *et al*. Accelerated epigenetic aging and mitochondrial DNA copy number in bipolar disorder. Transl Psychiatry 2017, 7: 1283.
37. Fries GR, Quevedo J, Zeni CP, Kazimi IF, Zunta-Soares G, Spiker DE, *et al*. Integrated transcriptome and methylome analysis in youth at high risk for bipolar disorder: A preliminary analysis. Transl Psychiatry 2017, 7: e1059.
38. Hesam-Shariati S, Overs BJ, Roberts G, Toma C, Watkeys OJ, Green MJ, *et al*. Epigenetic signatures relating to disease-associated genotypic burden in familial risk of bipolar disorder. Transl Psychiatry 2022, 12: 310.
39. Segura AG, de la Serna E, Sugranyes G, Baeza I, Valli I, Díaz-Caneja C, *et al*. Epigenetic age deacceleration in youth at familial risk for schizophrenia and bipolar disorder. Transl Psychiatry 2023, 13: 155.
40. Walker RM, Sussmann JE, Whalley HC, Ryan NM, Porteous DJ, McIntosh AM, *et al*. Preliminary assessment of pre-morbid DNA methylation in individuals at high genetic risk of mood disorders. Bipolar Disord 2016, 18: 410–422.
41. Fries GR, Zamzow MJ, Andrews T, Pink O, Scaini G, Quevedo J. Accelerated aging in bipolar disorder: A comprehensive review of molecular findings and their clinical implications. Neurosci Biobehav Rev 2020, 112: 107–116.
42. Scaini G, Valvassori SS, Diaz AP, Lima CN, Benevenuto D, Fries GR, *et al*. Neurobiology of bipolar disorders: A review of genetic components, signaling pathways, biochemical changes, and neuroimaging findings. Braz J Psychiatry 2020, 42: 536–551.
43. Bot M, Chan MK, Jansen R, Lamers F, Vogelzangs N, Steiner J, *et al*. Serum proteomic profiling of major depressive disorder. Transl Psychiatry 2015, 5: e599.
44. Taurines R, Dudley E, Grassl J, Warnke A, Gerlach M, Coogan AN, *et al*. Proteomic research in psychiatry. J Psychopharmacol 2011, 25: 151–196.
45. Geyer PE, Holdt LM, Teupser D, Mann M. Revisiting biomarker discovery by plasma proteomics. Mol Syst Biol 2017, 13: 942.
46. Comes AL, Papiol S, Mueller T, Geyer PE, Mann M, Schulze TG. Proteomics for blood biomarker exploration of severe mental illness: Pitfalls of the past and potential for the future. Transl Psychiatry 2018, 8: 160.
47. Song YR, Wu B, Yang YT, Chen J, Zhang LJ, Zhang ZW, *et al*. Specific alterations in plasma proteins during depressed, manic, and euthymic states of bipolar disorder. Braz J Med Biol Res 2015, 48: 973–982.
48. Shin D, Lee J, Kim Y, Park J, Shin D, Song Y, *et al*. Evaluation of a nondepleted plasma multiprotein-based model for discriminating psychiatric disorders using multiple reaction monitoring-mass spectrometry: Proof-of-concept study. J Proteome Res 2024, 23: 329–343.
49. Schwarz E, Guest PC, Rahmoune H, Martins-de-Souza D, Niebuhr DW, Weber NS, *et al*. Identification of a blood-based biological signature in subjects with psychiatric disorders prior to clinical manifestation. World J Biol Psychiatry 2012, 13: 627–632.
50. Haenisch F, Cooper JD, Reif A, Kittel-Schneider S, Steiner J, Leweke FM, *et al*. Towards a blood-based diagnostic panel for bipolar disorder. Brain Behav Immun 2016, 52: 49–57.
51. Kato T. Neurobiological basis of bipolar disorder: Mitochondrial dysfunction hypothesis and beyond. Schizophr Res 2017, 187: 62–66.
52. Mondin TC, de Azevedo Cardoso T, Moreira FP, Wiener C, Oses JP, de Mattos Souza LD, *et al*. Circadian preferences, oxidative stress and inflammatory cytokines in bipolar disorder: A community study. J Neuroimmunol 2016, 301: 23–29.
53. Yamaki N, Otsuka I, Numata S, Yanagi M, Mouri K, Okazaki S, *et al*. Mitochondrial DNA copy number of peripheral blood in bipolar disorder: The present study and a meta-analysis. Psychiatry Res 2018, 269: 115–117.
54. Andreazza AC, Kauer-Sant'anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, *et al*. Oxidative stress markers in bipolar disorder: A meta-analysis. J Affect Disord 2008, 111: 135–144.
55. Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. Psychiatry Res 2014, 218: 61–68.
56. Scola G, McNamara RK, Croarkin PE, Leffler JM, Cullen KR, Geske JR, *et al*. Lipid peroxidation biomarkers in adolescents with or at high-risk for bipolar disorder. J Affect Disord 2016, 192: 176–183.
57. Brietzke E, Mansur RB, Soczynska JK, Kapczinski F, Bressan RA, McIntyre RS. Towards a multifactorial approach for prediction of bipolar disorder in at risk populations. J Affect Disord 2012, 140: 82–91.

58. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, *et al*. Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev 2011, 35: 804–817.
59. Barbosa IG, Bauer ME, Machado-Vieira R, Teixeira AL. Cytokines in bipolar disorder: Paving the way for neuroprogression. Neural Plast 2014, 2014: 360481.
60. Rosenblat JD, McIntyre RS. Bipolar disorder and immune dysfunction: Epidemiological findings, proposed pathophysiology and clinical implications. Brain Sci 2017, 7: 144.
61. Sayana P, Colpo GD, Simões LR, Giridharan VV, Teixeira AL, Quevedo J, *et al*. A systematic review of evidence for the role of inflammatory biomarkers in bipolar patients. J Psychiatr Res 2017, 92: 160–182.
62. Tonin PT, Valvassori SS, Lopes-Borges J, Mariot E, Varela RB, Teixeira AL, *et al*. Effects of ouabain on cytokine/chemokine levels in an animal model of mania. J Neuroimmunol 2014, 276: 236–239.
63. Valvassori SS, Tonin PT, Varela RB, Carvalho AF, Mariot E, Amboni RT, *et al*. Lithium modulates the production of peripheral and cerebral cytokines in an animal model of mania induced by dextroamphetamine. Bipolar Disord 2015, 17: 507–517.
64. Valvassori SS, Resende WR, Dal-Pont G, Sangaletti-Pereira H, Gava FF, Peterle BR, *et al*. Lithium ameliorates sleep deprivation-induced mania-like behavior, hypothalamic-pituitary-adrenal (HPA) axis alterations, oxidative stress and elevations of cytokine concentrations in the brain and serum of mice. Bipolar Disord 2017, 19: 246–258.
65. Valvassori SS, Dal-Pont GC, Tonin PT, Varela RB, Ferreira CL, Gava FF, *et al*. Coadministration of lithium and celecoxib attenuates the behavioral alterations and inflammatory processes induced by amphetamine in an animal model of mania. Pharmacol Biochem Behav 2019, 183: 56–63.
66. Pereira AC, Oliveira J, Silva S, Madeira N, Pereira CMF, Cruz MT. Inflammation in bipolar disorder (BD): Identification of new therapeutic targets. Pharmacol Res 2021, 163: 105325.
67. Magioncalda P, Martino M. A unified model of the pathophysiology of bipolar disorder. Mol Psychiatry 2022, 27: 202–211.
68. Mesman E, Hillegers MH, Ambree O, Arolt V, Nolen WA, Drexhage HA. Monocyte activation, brain-derived neurotrophic factor (BDNF), and S100B in bipolar offspring: A follow-up study from adolescence into adulthood. Bipolar Disord 2015, 17: 39–49.
69. Snijders G, Mesman E, de Wit H, Wijkhuijs A, Nolen WA, Drexhage HA, *et al*. Immune dysregulation in offspring of a bipolar parent. Altered serum levels of immune growth factors at adolescent age. Brain Behav Immun 2017, 64: 116–123.
70. Slusher AL, Mischo AB, Acevedo EO. Pentraxin 3 is an anti-inflammatory protein associated with lipid-induced interleukin 10 *in vitro*. Cytokine 2016, 86: 36–40.
71. Camps J, Rodríguez-Gallego E, García-Heredia A, Triguero I, Riera-Borrull M, Hernández-Aguilera A, *et al*. Paraoxonases and chemokine (C–C motif) ligand-2 in noncommunicable diseases. Adv Clin Chem 2014, 63: 247–308.
72. Scola G, Andreazza AC. The role of neurotrophins in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2015, 56: 122–128.
73. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer 2008, 8: 915–928.
74. Lin K, Shao R, Wang R, Lu W, Zou W, Chen K, *et al*. Inflammation, brain structure and cognition interrelations among individuals with differential risks for bipolar disorder. Brain Behav Immun 2020, 83: 192–199.
75. Duffy A, Horrocks J, Doucette S, Keown-Stoneman C, Grof P, Andreazza A, *et al*. Immunological and neurotrophic markers of risk status and illness development in high-risk youth: Understanding the neurobiological underpinnings of bipolar disorder. Int J Bipolar Disord 2014, 2: 29.
76. Rosenberg-Hasson Y, Hansmann L, Liedtke M, Herschmann I, Maecker HT. Effects of serum and plasma matrices on multiplex immunoassays. Immunol Res 2014, 58: 224–233.
77. Carroll BJ, Curtis GC. Neuroendocrine identification of depressed patients. Aust N Z J Psychiatry 1976, 10: 13–20.
78. Perini G, Fava G, Morphy M, Carson S, Molnar G, Jusko W. The metyrapone test in manic patients and healthy subjects. Pharmacopsychiatry 1984, 17: 94–97.
79. Mukherjee D, Weissenkampen JD, Wasserman E, Krishnamurthy VB, Millett CE, Conway S, *et al*. Dysregulated diurnal cortisol pattern and heightened night-time cortisol in individuals with bipolar disorder. Neuropsychobiology 2022, 81: 51–59.
80. Watson S, Gallagher P, Ritchie JC, Ferrier IN, Young AH. Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. Br J Psychiatry 2004, 184: 496–502.
81. Belvederi Murri M, Prestia D, Mondelli V, Pariante C, Patti S, Olivieri B, *et al*. The HPA axis in bipolar disorder: Systematic review and meta-analysis. Psychoneuroendocrinology 2016, 63: 327–342.
82. Melo MCA, Garcia RF, Linhares Neto VB, Sá MB, de Mesquita LMF, de Araújo CFC, *et al*. Sleep and circadian alterations in people at risk for bipolar disorder: A systematic review. J Psychiatr Res 2016, 83: 211–219.
83. Ellenbogen MA, Hodgins S, Walker CD. High levels of cortisol among adolescent offspring of parents with bipolar disorder: A pilot study. Psychoneuroendocrinology 2004, 29: 99–106.
84. Ellenbogen MA, Hodgins S, Walker CD, Couture S, Adam S. Daytime cortisol and stress reactivity in the offspring of parents with bipolar disorder. Psychoneuroendocrinology 2006, 31: 1164–1180.
85. Ellenbogen MA, Santo JB, Linnen AM, Walker CD, Hodgins S. High cortisol levels in the offspring of parents with bipolar disorder during two weeks of daily sampling. Bipolar Disord 2010, 12: 77–86.
86. Ellenbogen MA, Hodgins S, Linnen AM, Ostiguy CS. Elevated daytime cortisol levels: A biomarker of subsequent major affective disorder? J Affect Disord 2011, 132: 265–269.
87. Ostiguy CS, Ellenbogen MA, Walker CD, Walker EF, Hodgins S. Sensitivity to stress among the offspring of parents with bipolar disorder: A study of daytime cortisol levels. Psychol Med 2011, 41: 2447–2457.
88. Coello K, Munkholm K, Nielsen F, Vinberg M, Kessing LV. Hair cortisol in newly diagnosed bipolar disorder and unaffected first-degree relatives. Psychoneuroendocrinology 2019, 99: 183–190.
89. Deshauer D, Duffy A, Meaney M, Sharma S, Grof P. Salivary cortisol secretion in remitted bipolar patients and offspring of bipolar parents. Bipolar Disord 2006, 8: 345–349.
90. Goodday SM, Horrocks J, Keown-Stoneman C, Grof P, Duffy A. Repeated salivary daytime cortisol and onset of mood episodes in offspring of bipolar parents. Int J Bipolar Disord 2016, 4: 12.
91. Ghaziuddin N, Shamseddeen W, Bertram H, McInnis M, Wilcox HC, Mitchell PB, *et al*. Salivary melatonin onset in youth at familial risk for bipolar disorder. Psychiatry Res 2019, 274: 49–57.
92. Brandt JM, Hemager N, Ellersgaard D, Gregersen M, Søndergaard A, Ohland J, *et al*. Hair cortisol concentrations and daily life stress in 7-year-old children at familial high-risk of schizophrenia or bipolar disorder. The Danish high risk and resilience study—VIA 7. Prog Neuropsychopharmacol Biol Psychiatry 2023, 125: 110750.
93. Schreuder MM, Vinkers CH, Mesman E, Claes S, Nolen WA, Hillegers MHJ. Childhood trauma and HPA axis functionality in offspring of bipolar parents. Psychoneuroendocrinology 2016, 74: 316–323.

94. Vandeleur CL, Strippoli MPF, Castelao E, Gholam-Rezaee M, Ferrero F, Marquet P, *et al*. The Lausanne–Geneva cohort study of offspring of parents with mood disorders: Methodology, findings, current sample characteristics, and perspectives. Soc Psychiatry Psychiatr Epidemiol 2017, 52: 1041–1058.
95. Post RM. Role of BDNF in bipolar and unipolar disorder: Clinical and theoretical implications. J Psychiatr Res 2007, 41: 979–990.
96. Munkholm K, Vinberg M, Kessing LV. Peripheral blood brain-derived neurotrophic factor in bipolar disorder: A comprehensive systematic review and meta-analysis. Mol Psychiatry 2016, 21: 216–228.
97. Vega-Núñez A, Gómez-Sánchez-Lafuente C, Mayoral-Cleries F, Bordallo A, Rodríguez der F F, Suárez J, *et al*. Clinical value of inflammatory and neurotrophic biomarkers in bipolar disorder: A systematic review and meta-analysis. Biomedicines 2022, 10: 1368.
98. Bauer IE, Pascoe MC, Wollenhaupt-Aguiar B, Kapczinski F, Soares JC. Inflammatory mediators of cognitive impairment in bipolar disorder. J Psychiatr Res 2014, 56: 18–27.
99. Mora E, Portella MJ, Piñol-Ripoll G, López R, Cuadras D, Forcada I, *et al*. High BDNF serum levels are associated to good cognitive functioning in bipolar disorder. Eur Psychiatry 2019, 60: 97–107.
100. Mansur RB, Brietzke E, McIntyre RS, Cao B, Lee Y, Japiassú L, *et al*. BDNF and BMI effects on brain structures of bipolar offspring: Results from the global mood and brain science initiative. Acta Psychiatr Scand 2017, 136: 607–614.
101. Vasconcelos-Moreno MP, Fries GR, Gubert C, Dos Santos BTMQ, Fijtman A, Sartori J, *et al*. Telomere length, oxidative stress, inflammation and BDNF levels in siblings of patients with bipolar disorder: Implications for accelerated cellular aging. Int J Neuropsychopharmacol 2017, 20: 445–454.
102. Gershon A, Kaufmann CN, Depp CA, Miller S, Do D, Zeitzer JM, *et al*. Subjective versus objective evening chronotypes in bipolar disorder. J Affect Disord 2018, 225: 342–349.
103. Seleem MA, Merranko JA, Goldstein TR, Goldstein BI, Axelson DA, Brent DA, *et al*. The longitudinal course of sleep timing and circadian preferences in adults with bipolar disorder. Bipolar Disord 2015, 17: 392–402.
104. Kim KL, Weissman AB, Puzia ME, Cushman GK, Seymour KE, Wegbreit E, *et al*. Circadian phase preference in pediatric bipolar disorder. J Clin Med 2014, 3: 255–266.
105. Dallaspezia S, Benedetti F. Melatonin, circadian rhythms, and the clock genes in bipolar disorder. Curr Psychiatry Rep 2009, 11: 488–493.
106. Nováková M, Praško J, Látalová K, Sládek M, Sumová A. The circadian system of patients with bipolar disorder differs in episodes of mania and depression. Bipolar Disord 2015, 17: 303–314.
107. Robillard R, Naismith SL, Rogers NL, Scott EM, Ip TKC, Hermens DF, *et al*. Sleep–wake cycle and melatonin rhythms in adolescents and young adults with mood disorders: Comparison of unipolar and bipolar phenotypes. Eur Psychiatry 2013, 28: 412–416.
108. Nurnberger JI Jr, Berrettini W, Tamarkin L, Hamovit J, Norton J, Gershon E. Supersensitivity to melatonin suppression by light in young people at high risk for affective disorder. A preliminary report. Neuropsychopharmacology 1988, 1: 217–223.
109. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol 2021, 19: 55–71.
110. Sani G, Manchia M, Simonetti A, Janiri D, Paribello P, Pinna F, *et al*. The role of gut microbiota in the high-risk construct of severe mental disorders: A mini review. Front Psychiatry 2021, 11: 585769.
111. Tang Q, Jin G, Wang G, Liu T, Liu X, Wang B, *et al*. Current sampling methods for gut microbiota: A call for more precise devices. Front Cell Infect Microbiol 2020, 10: 151.
112. Coello K, Hansen TH, Sørensen N, Munkholm K, Kessing LV, Pedersen O, *et al*. Gut microbiota composition in patients with newly diagnosed bipolar disorder and their unaffected first-degree relatives. Brain Behav Immun 2019, 75: 112–118.
113. Coello K, Hansen TH, Sørensen N, Ottesen NM, Miskowiak KW, Pedersen O, *et al*. Affective disorders impact prevalence of *Flavonifractor* and abundance of Christensenellaceae in gut microbiota. Prog Neuropsychopharmacol Biol Psychiatry 2021, 110: 110300.
114. Vinberg M, Ottesen NM, Meluken I, Sørensen N, Pedersen O, Kessing LV, *et al*. Remitted affective disorders and high familial risk of affective disorders associate with aberrant intestinal microbiota. Acta Psychiatr Scand 2019, 139: 174–184.
115. Yousaf T, Dervenoulas G, Politis M. Advances in MRI methodology. Int Rev Neurobiol 2018, 141: 31–76.
116. Bertocci MA, Hanford L, Manelis A, Iyengar S, Youngstrom EA, Gill MK, *et al*. Clinical, cortical thickness and neural activity predictors of future affective lability in youth at risk for bipolar disorder: Initial discovery and independent sample replication. Mol Psychiatry 2019, 24: 1856–1867.
117. van Haren NEM, Setiaman N, Koevoets MGJC, Baalbergen H, Kahn RS, Hillegers MHJ. Brain structure, IQ, and psychopathology in young offspring of patients with schizophrenia or bipolar disorder. Eur Psychiatry 2020, 63: e5.
118. de Zwarte SMC, Brouwer RM, Agartz I, Alda M, Aleman A, Alpert KI, *et al*. The association between familial risk and brain abnormalities is disease specific: An ENIGMA-relatives study of schizophrenia and bipolar disorder. Biol Psychiatry 2019, 86: 545–556.
119. Mikolas P, Bröckel K, Vogelbacher C, Müller DK, Marxen M, Berndt C, *et al*. Individuals at increased risk for development of bipolar disorder display structural alterations similar to people with manifest disease. Transl Psychiatry 2021, 11: 485.
120. Huth F, Tozzi L, Marxen M, Riedel P, Bröckel K, Martini J, *et al*. Machine learning prediction of estimated risk for bipolar disorders using hippocampal subfield and amygdala nuclei volumes. Brain Sci 2023, 13: 870.
121. Mikolas P, Marxen M, Riedel P, Bröckel K, Martini J, Huth F, *et al*. Prediction of estimated risk for bipolar disorder using machine learning and structural MRI features. Psychol Med 2024, 54: 278–288.
122. Birmaher B, Axelson D, Goldstein B, Monk K, Kalas C, Obreja M, *et al*. Psychiatric disorders in preschool offspring of parents with bipolar disorder: The Pittsburgh bipolar offspring study (BIOS). Am J Psychiatry 2010, 167: 321–330.
123. Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, *et al*. Diffusion tensor imaging: Concepts and applications. J Magn Reson Imaging 2001, 13: 534–546.
124. Parker GJM. Analysis of MR diffusion weighted images. Br J Radiol 2004, 77(2): S176-185. https://doi.org/10.1259/bjr/81090732.
125. Ching CRK, Hibar DP, Gurholt TP, Nunes A, Thomopoulos SI, Abé C, *et al*. What we learn about bipolar disorder from large-scale neuroimaging: Findings and future directions from the *ENIGMA* Bipolar Disorder Working Group. Hum Brain Mapp 2022, 43: 56–82.
126. Hu R, Stavish C, Leibenluft E, Linke JO. White matter microstructure in individuals with and At risk for bipolar disorder: Evidence for an endophenotype from a voxel-based meta-analysis. Biol Psychiatry Cogn Neurosci Neuroimaging 2020, 5: 1104–1113.
127. Li X, Lu W, Zhang R, Zou W, Gao Y, Chen K, *et al*. Integrity of the uncinate fasciculus is associated with the onset of

bipolar disorder: A 6-year followed-up study. Transl Psychiatry 2021, 11: 111.
128. Hou L, Lam BYH, Wong NML, Lu W, Zhang R, Ning Y, *et al*. Integrity of cerebellar tracts associated with the risk of bipolar disorder. Transl Psychiatry 2022, 12: 335.
129. Liégeois F, Elward R (2020) Chapter 19—Functional magnetic resonance imaging. In: Gallagher A *et al* (eds) Handb Clin Neurol, vol 174, Elsevier, pp 265–275.
130. Acuff HE, Versace A, Bertocci MA, Hanford LC, Ladouceur CD, Manelis A, *et al*. White matter—emotion processing activity relationships in youth offspring of bipolar parents. J Affect Disord 2019, 243: 153–164.
131. Li CT, Tu PC, Hsieh JC, Lee HC, Bai YM, Tsai CF, *et al*. Functional dysconnection in the prefrontal-amygdala circuitry in unaffected siblings of patients with bipolar I disorder. Bipolar Disord 2015, 17: 626–635.
132. Lin K, Shao R, Lu R, Chen K, Lu W, Li T, *et al*. Resting-state fMRI signals in offspring of parents with bipolar disorder at the high-risk and ultra-high-risk stages and their relations with cognitive function. J Psychiatr Res 2018, 98: 99–106.
133. Cattarinussi G, Bellani M, Maggioni E, Sambataro F, Brambilla P, Delvecchio G. Resting-state functional connectivity and spontaneous brain activity in early-onset bipolar disorder: A review of functional magnetic resonance imaging studies. J Affect Disord 2022, 311: 463–471.
134. Singh MK, Leslie SM, Bhattacharjee K, Gross M, Weisman EF, Soudi LM, *et al*. Vulnerabilities in sequencing and task switching in healthy youth offspring of parents with mood disorders. J Clin Exp Neuropsychol 2018, 40: 606–618.
135. Davey CG, Harrison BJ, Yücel M, Allen NB. Regionally specific alterations in functional connectivity of the anterior cingulate cortex in major depressive disorder. Psychol Med 2012, 42: 2071–2081.
136. Zou W, Song P, Lu W, Shao R, Zhang R, Yau SY, *et al*. Global hippocampus functional connectivity as a predictive neural marker for conversion to future mood disorder in unaffected offspring of bipolar disorder parents. Asian J Psychiatr 2022, 78: 103307.
137. Fischer AS, Holt-Gosselin B, Hagan KE, Fleming SL, Nimarko AF, Gotlib IH, *et al*. Intrinsic connectivity and family dynamics: Striatolimbic markers of risk and resilience in youth at familial risk for mood disorders. Biol Psychiatry Cogn Neurosci Neuroimaging 2022, 7: 855–866.
138. Maheshwari M, Deshmukh T, Leuthardt EC, Shimony JS. Task-based and resting state functional MRI in children. Magn Reson Imaging Clin N Am 2021, 29: 527–541.
139. Mesbah R, Koenders MA, van der Wee NJA, Giltay EJ, van Hemert AM, de Leeuw M. Association between the Frontolimbic network and cognitive and emotional functioning in individuals with bipolar disorder: A systematic review and meta-analysis. JAMA Psychiatry 2023, 80: 432–440.
140. Mercer L, Becerra R. A unique emotional processing profile of euthymic bipolar disorder? A critical review. J Affect Disord 2013, 146: 295–309.
141. Acuff HE, Versace A, Bertocci MA, Ladouceur CD, Hanford LC, Manelis A, *et al*. Association of neuroimaging measures of emotion processing and regulation neural circuitries with symptoms of bipolar disorder in offspring at risk for bipolar disorder. JAMA Psychiatry 2018, 75: 1241–1251.
142. Chang K, Garrett A, Kelley R, Howe M, Sanders EM, Acquaye T, *et al*. Anomalous prefrontal-limbic activation and connectivity in youth at high-risk for bipolar disorder. J Affect Disord 2017, 222: 7–13.
143. Manelis A, Ladouceur CD, Graur S, Monk K, Bonar LK, Hickey MB, *et al*. Altered amygdala-prefrontal response to facial emotion in offspring of parents with bipolar disorder. Brain 2015, 138: 2777–2790.
144. Olsavsky AK, Brotman MA, Rutenberg JG, Muhrer EJ, Deveney CM, Fromm SJ, *et al*. Amygdala hyperactivation during face emotion processing in unaffected youth at risk for bipolar disorder. J Am Acad Child Adolesc Psychiatry 2012, 51: 294–303.
145. Tseng WL, Bones BL, Kayser RR, Olsavsky AK, Fromm SJ, Pine DS, *et al*. An fMRI study of emotional face encoding in youth at risk for bipolar disorder. Eur Psychiatry 2015, 30: 94–98.
146. Wiggins JL, Brotman MA, Adleman NE, Kim P, Wambach CG, Reynolds RC, *et al*. Neural markers in pediatric bipolar disorder and familial risk for bipolar disorder. J Am Acad Child Adolesc Psychiatry 2017, 56: 67–78.
147. Pan N, Qin K, Patino LR, Tallman MJ, Lei D, Lu L, *et al*. Aberrant brain network topology in youth with a familial risk for bipolar disorder: A task-based fMRI connectome study. J Child Psychol Psychiatry 2024, https://doi.org/10.1111/jcpp.13946.
148. Brotman MA, Deveney CM, Thomas LA, Hinton KE, Yi JY, Pine DS, *et al*. Parametric modulation of neural activity during face emotion processing in unaffected youth at familial risk for bipolar disorder. Bipolar Disord 2014, 16: 756–763.
149. Ladouceur CD, Diwadkar VA, White R, Bass J, Birmaher B, Axelson DA, *et al*. Fronto-limbic function in unaffected offspring at familial risk for bipolar disorder during an emotional working memory paradigm. Dev Cogn Neurosci 2013, 5: 185–196.
150. Acuff HE, Versace A, Bertocci MA, Ladouceur CD, Hanford LC, Manelis A, *et al*. Baseline and follow-up activity and functional connectivity in reward neural circuitries in offspring at risk for bipolar disorder. Neuropsychopharmacology 2019, 44: 1570–1578.
151. Singh MK, Kelley RG, Howe ME, Reiss AL, Gotlib IH, Chang KD. Reward processing in healthy offspring of parents with bipolar disorder. JAMA Psychiatry 2014, 71: 1148–1156.
152. Soehner AM, Bertocci MA, Manelis A, Bebko G, Ladouceur CD, Graur S, *et al*. Preliminary investigation of the relationships between sleep duration, reward circuitry function, and mood dysregulation in youth offspring of parents with bipolar disorder. J Affect Disord 2016, 205: 144–153.
153. Nimarko AF, Gorelik AJ, Carta KE, Gorelik MG, Singh MK. Neural correlates of reward processing distinguish healthy youth at familial risk for bipolar disorder from youth at familial risk for major depressive disorder. Transl Psychiatry 2022, 12: 31.
154. Thermenos HW, Makris N, Whitfield-Gabrieli S, Brown AB, Giuliano AJ, Lee EH, *et al*. A functional MRI study of working memory in adolescents and young adults at genetic risk for bipolar disorder: Preliminary findings. Bipolar Disord 2011, 13: 272–286.
155. Nimarko AF, Fischer AS, Hagan KE, Gorelik AJ, Lu Y, Young CJ, *et al*. Neural correlates of positive emotion processing that distinguish healthy youths at familial risk for bipolar versus major depressive disorder. J Am Acad Child Adolesc Psychiatry 2021, 60: 887–901.
156. Hafeman DM, Merranko J, Goldstein TR, Axelson D, Goldstein BI, Monk K, *et al*. Assessment of a person-level risk calculator to predict new-onset bipolar spectrum disorder in youth at familial risk. JAMA Psychiatry 2017, 74: 841–847.
157. Hanford LC, Eckstrand K, Manelis A, Hafeman DM, Merranko J, Ladouceur CD, *et al*. The impact of familial risk and early life adversity on emotion and reward processing networks in youth at-risk for bipolar disorder. PLoS One 2019, 14: e0226135.
158. Eva M. Serrao, Avnesh S. Thakor, Vicky Goh, Ferdia A. Gallagher. Functional and Molecular Imaging for Personalized Medicine in Oncology. Grainger & Allison's Diagnostic Radiology, 7th Ed., 2021, Elsevier Limited. 1752–1765.
159. Vecera CM, Chong AC, Ruiz AC, Rong C, Jones G, Machado-Vieira R, *et al*. Magnetic resonance spectroscopy in bipolar

disorder. Biomark Bipolar Disord 2022, https://doi.org/10.1016/B978-0-12-821398-8.00030-8.
160. Scotti-Muzzi E, Chile T, Moreno R, Pastorello BF, da Costa Leite C, Henning A, *et al*. ACC Glu/GABA ratio is decreased in euthymic bipolar disorder I patients: Possible *in vivo* neurometabolite explanation for mood stabilization. Eur Arch Psychiatry Clin Neurosci 2021, 271: 537–547.
161. Chouinard VA, Kim SY, Valeri L, Yuksel C, Ryan KP, Chouinard G, *et al*. Brain bioenergetics and redox state measured by ^{31}P magnetic resonance spectroscopy in unaffected siblings of patients with psychotic disorders. Schizophr Res 2017, 187: 11–16.
162. Nery FG, Weber WA, Blom TJ, Welge J, Patino LR, Strawn JR, *et al*. Longitudinal proton spectroscopy study of the prefrontal cortex in youth at risk for bipolar disorder before and after their first mood episode. Bipolar Disord 2019, 21: 330–341.
163. Singh MK, Spielman D, Libby A, Adams E, Acquaye T, Howe M, *et al*. Neurochemical deficits in the cerebellar vermis in child offspring of parents with bipolar disorder. Bipolar Disord 2011, 13: 189–197.
164. Cecil KM, DelBello MP, Sellars MC, Strakowski SM. Proton magnetic resonance spectroscopy of the frontal lobe and cerebellar vermis in children with a mood disorder and a familial risk for bipolar disorders. J Child Adolesc Psychopharmacol 2003, 13: 545–555.
165. Gallelli KA, Wagner CM, Karchemskiy A, Howe M, Spielman D, Reiss A, *et al*. N-acetylaspartate levels in bipolar offspring with and at high-risk for bipolar disorder. Bipolar Disord 2005, 7: 589–597.
166. Hajek T, Bernier D, Slaney C, Propper L, Schmidt M, Carrey N, *et al*. A comparison of affected and unaffected relatives of patients with bipolar disorder using proton magnetic resonance spectroscopy. J Psychiatry Neurosci 2008, 33: 531–540.
167. Singh M, Spielman D, Adleman N, Alegria D, Howe M, Reiss A, *et al*. Brain glutamatergic characteristics of pediatric offspring of parents with bipolar disorder. Psychiatry Res 2010, 182: 165–171.
168. Singh MK, Jo B, Adleman NE, Howe M, Bararpour L, Kelley RG, *et al*. Prospective neurochemical characterization of child offspring of parents with bipolar disorder. Psychiatry Res 2013, 214: 153–160.
169. Béard E, Braissant O. Synthesis and transport of creatine in the CNS: Importance for cerebral functions. J Neurochem 2010, 115: 297–313.
170. Moghbel M, Newberg A, Alavi A. Positron emission tomography: Ligand imaging. Handb Clin Neurol 2016, 135: 229–240.
171. Teixeira AL, Colpo GD, Fries GR, Bauer IE, Selvaraj S. Biomarkers for bipolar disorder: Current status and challenges ahead. Expert Rev Neurother 2019, 19: 67–81.
172. Hu B, Cha J, Fullerton JM, Hesam-Shariati S, Nakamura K, Nurnberger JI, *et al*. Genetic and environment effects on structural neuroimaging endophenotype for bipolar disorder: A novel molecular approach. Transl Psychiatry 2022, 12: 137.
173. Meyers JL, Chorlian DB, Bigdeli TB, Johnson EC, Aliev F, Agrawal A, *et al*. The association of polygenic risk for schizophrenia, bipolar disorder, and depression with neural connectivity in adolescents and young adults: Examining developmental and sex differences. Transl Psychiatry 2021, 11: 54.
174. Poletti S, Aggio V, Hoogenboezem TA, Ambrée O, de Wit H, Wijkhuijs AJM, *et al*. Brain-derived Neurotrophic Factor (BDNF) and gray matter volume in bipolar disorder. Eur Psychiatry 2017, 40: 33–37.
175. Collin G, Scholtens LH, Kahn RS, Hillegers MHJ, van den Heuvel MP. Affected anatomical rich club and structural-functional coupling in young offspring of schizophrenia and bipolar disorder patients. Biol Psychiatry 2017, 82: 746–755.
176. van den Heuvel MP, Sporns O, Collin G, Scheewe T, Mandl RCW, Cahn W, *et al*. Abnormal rich club organization and functional brain dynamics in schizophrenia. JAMA Psychiatry 2013, 70: 783–792.
177. Yu Q, Sui J, Liu J, Plis SM, Kiehl KA, Pearlson G, *et al*. Disrupted correlation between low frequency power and connectivity strength of resting state brain networks in schizophrenia. Schizophr Res 2013, 143: 165–171.
178. Jan Z, Ai-Ansari N, Mousa O, Abd-Alrazaq A, Ahmed A, Alam T, *et al*. The role of machine learning in diagnosing bipolar disorder: Scoping review. J Med Internet Res 2021, 23: e29749.
179. Librenza-Garcia D, Kotzian BJ, Yang J, Mwangi B, Cao B, Pereira Lima LN, *et al*. The impact of machine learning techniques in the study of bipolar disorder: A systematic review. Neurosci Biobehav Rev 2017, 80: 538–554.
180. Dickstein DP. Editorial: It's difficult to make predictions, especially about the future: Risk calculators come of age in child psychiatry. J Am Acad Child Adolesc Psychiatry 2021, 60: 950–951.
181. Sathyanarayanan A, Mueller TT, Moni MA, Schueler K, Baune BT, Lio P, Mehta D, Baune BT, Dierssen M, Ebert B, Fabbri C. Multi-omics data integration methods and their applications in psychiatric disorders. Eur Neuropsychopharmacol 2023, 1(69): 26–46.
182. Shi W, Fan L, Jiang T. Developing neuroimaging biomarker for brain diseases with a machine learning framework and the brainnetome atlas. Neurosci Bull 2021, 37: 1523–1525.
183. Kraguljac NV, McDonald WM, Widge AS, Rodriguez CI, Tohen M, Nemeroff CB. Neuroimaging biomarkers in schizophrenia. Am J Psychiatry 2021, 178: 509–521.
184. Hu X, Yu C, Dong T, Yang Z, Fang Y, Jiang Z. Biomarkers and detection methods of bipolar disorder. Biosens Bioelectron 2023, 220: 114842.
185. Goldstein BI, Shamseddeen W, Axelson DA, Kalas C, Monk K, Brent DA, *et al*. Clinical, demographic, and familial correlates of bipolar spectrum disorders among offspring of parents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2010, 49: 388–396.
186. Bertocci MA, Bebko G, Olino T, Fournier J, Hinze AK, Bonar L, *et al*. Behavioral and emotional dysregulation trajectories marked by prefrontal-amygdala function in symptomatic youth. Psychol Med 2014, 44: 2603–2615.
187. Bebko G, Bertocci MA, Fournier JC, Hinze AK, Bonar L, Almeida JRC, *et al*. Parsing dimensional vs diagnostic category-related patterns of reward circuitry function in behaviorally and emotionally dysregulated youth in the Longitudinal Assessment of Manic Symptoms study. JAMA Psychiatry 2014, 71: 71–80.
188. Perlman SB, Fournier JC, Bebko G, Bertocci MA, Hinze AK, Bonar L, *et al*. Emotional face processing in pediatric bipolar disorder: Evidence for functional impairments in the fusiform gyrus. J Am Acad Child Adolesc Psychiatry 2013, 52: 1314-1325.e3.
189. Lin K, Xu G, Wong NML, Wu H, Li T, Lu W, *et al*. A multidimensional and integrative approach to examining the high-risk and ultra-high-risk stages of bipolar disorder. EBioMedicine 2015, 2: 919–928.
190. Ellersgaard D, Jessica Plessen K, Richardt Jepsen J, Soeborg Spang K, Hemager N, Klee Burton B, *et al*. Psychopathology in 7-year-old children with familial high risk of developing schizophrenia spectrum psychosis or bipolar disorder. The Danish high risk and resilience study—VIA 7, a population-based cohort study. World Psychiatry 2018, 17: 210–219.
191. Holz NE, Berhe O, Sacu S, Schwarz E, Tesarz J, Heim CM, *et al*. Early social adversity, altered brain functional connectivity, and mental health. Biol Psychiatry 2023, 93: 430–441.

192. Holz NE, Zabihi M, Kia SM, Monninger M, Aggensteiner PM, Siehl S, *et al*. A stable and replicable neural signature of lifespan adversity in the adult brain. Nat Neurosci 2023, 26: 1603–1612.
193. Andersen SL. Neuroinflammation, early-life adversity, and brain development. Harv Rev Psychiatry 2022, 30: 24–39.
194. Kim EY, Miklowitz DJ, Biuckians A, Mullen K. Life stress and the course of early-onset bipolar disorder. J Affect Disord 2007, 99: 37–44.
195. Koenders MA, Giltay EJ, Spijker AT, Hoencamp E, Spinhoven P, Elzinga BM. Stressful life events in bipolar I and II disorder: Cause or consequence of mood symptoms? J Affect Disord 2014, 161: 55–64.
196. Kemner SM, van Haren NE, Bootsman F, Eijkemans MJ, Vonk R, van der Schot AC, *et al*. The influence of life events on first and recurrent admissions in bipolar disorder. Int J Bipolar Disord 2015, 3: 6.
197. Johnson KC, Brennan PA, Stowe ZN, Leibenluft E, Newport DJ. Physiological regulation in infants of women with a mood disorder: Examining associations with maternal symptoms and stress. J Child Psychol Psychiatry 2014, 55: 191–198.
198. Pfennig A, Leopold K, Martini J, Boehme A, Lambert M, Stamm T, *et al*. Improving early recognition and intervention in people at increased risk for the development of bipolar disorder: Study protocol of a prospective-longitudinal, naturalistic cohort study (Early-BipoLife). Int J Bipolar Disord 2020, 8: 22.
199. Vogelbacher C, Sommer J, Schuster V, Bopp MHA, Falkenberg I, Ritter PS, *et al*. The German research consortium for the study of bipolar disorder (BipoLife): A magnetic resonance imaging study protocol. Int J Bipolar Disord 2021, 9: 37.
200. Lee Y, Mansur RB, Brietzke E, Kapogiannis D, Delgado-Peraza F, Boutilier JJ, *et al*. Peripheral inflammatory biomarkers define biotypes of bipolar depression. Mol Psychiatry 2021, 26: 3395–3406.
201. Ivleva EI, Clementz BA, Dutcher AM, Arnold SJM, Jeon-Slaughter H, Aslan S, *et al*. Brain structure biomarkers in the psychosis biotypes: Findings from the bipolar-schizophrenia network for intermediate phenotypes. Biol Psychiatry 2017, 82: 26–39.