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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 over-activated 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 (β = − 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.
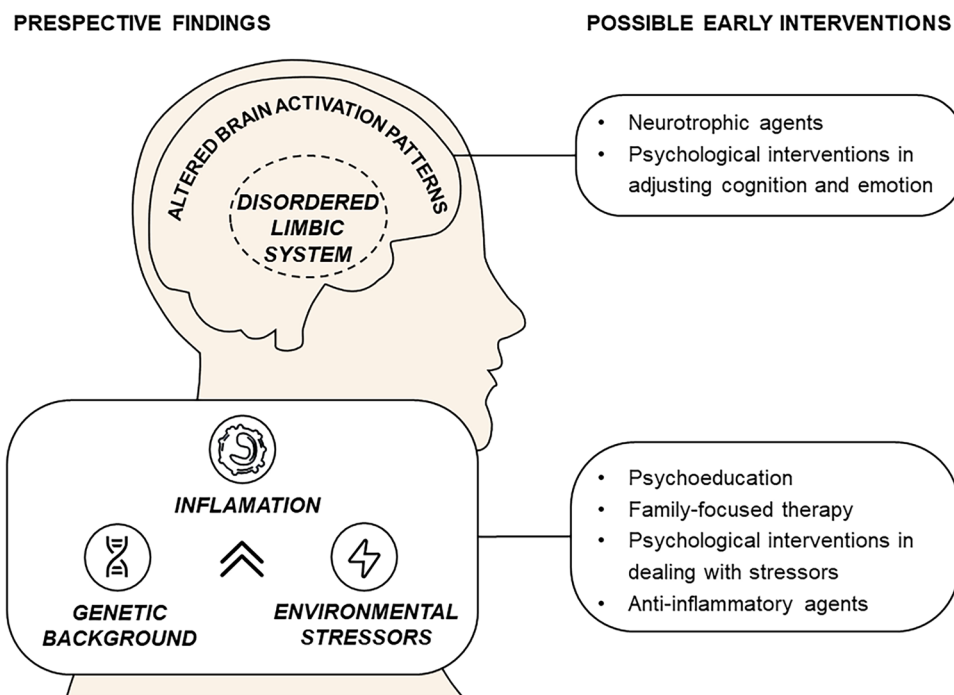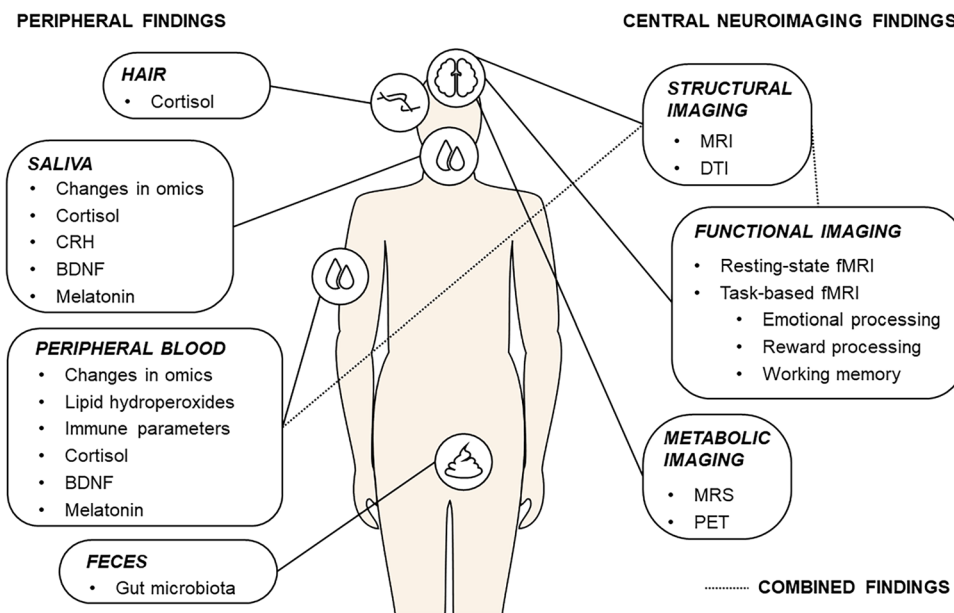

Fig. 2 The landscape of sample sources in at-risk youth in finding early biomarkers. *CRH* Corticotropin-releasing hormone, *BDNF* Brain-derived neurotrophic factor, *MRI* Magnetic resonance imaging, *DTI* Diffusion tensor imaging, *MRS* Magnetic resonance spectroscopy, *PET* Positron emission tomography.

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].

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

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