For a better understanding of pathogenesis of bipolar disorders and more targeted interventions

Biomarkers and vulnerability to bipolar disorders

Camille Piguet[a,c], Alexandre Dayer[b,c], Jean-Michel Aubry[b,d]

[a] Unité de psychiatrie du jeune adulte, Service de psychiatrie générale, département de Santé Mentale et Psychiatrie, Hôpitaux Universitaires de Genève
[b] Unité des troubles de l'humeur, Service des spécialités psychiatriques, département de Santé Mentale et Psychiatrie, Hôpitaux Universitaires de Genève
[c] Département de Neurosciences Fondamentales, Faculté de Médecine, Université de Genève
[d] Département de Psychiatrie, Faculté de Médecine, Université de Genève

Summary

Bipolar spectrum disorders are common and severe psychiatric diseases, with an important personal and societal burden. Current psychiatric neuroscience research combines different approaches in order to unravel the pathophysiology of the disease, and focuses on vulnerability factors. Here we review the main biological findings regarding trait markers of bipolar disorders, and how they can be considered as vulnerability factors in high-risk subjects, or biomarkers of illness progression or treatment response.

Key words: biomarker; bipolar disorder; highrisk offspring; imaging

Introduction

The fifth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) reports a combined prevalence rate for bipolar disorder (BD), namely BD-I, BD-II and other types of BD of 1.8% in the USA and non-USA community samples, with a typical age of onset in late adolescence or young adulthood. Recently, the lifetime prevalence of bipolar spectrum disorder in 11 countries taken together has been estimated to be around 2.4% [1], and the prevalence of bipolar spectrum disorder in the United States is sometimes estimated as up to 4.4% [2]. BD prevalence is higher in unemployed/disabled individuals [2, 3]. In Switzerland, prevalence of BD in young adults has been estimated as up to 11% with the use of a relatively broad spectrum definition [4]. A recent study using DSM-5 criteria in a community sample in Lausanne found slightly lower prevalence rates, ranging from 1.0% for BD-I, 0.8% for BD-II, 1.0% for "other specified bipolar and related disorders" to 3% for hyperthymic personality [5].

According to The Global Burden of Disease (2004 update), BD constitutes the 12th leading disabling disease, among all other diseases, irrespective of the age of patients and the economic power of their country [6]. Indeed, bipolar disorder represents an important economic and emotional burden for the patients, their relatives and the society [7]. Moreover, despite its relatively low prevalence compared with major depressive disorder (MDD), which ranges from 11.9 to 14.6% depending on the country [8], BD patients represent a total cost per subject twice as high as unipolar depressive patients [9]. This could be explained by the pronounced functional impairment of BD patients at all levels (e.g., cognitive, physical, personal, social and professional) compared with major depressive patients and healthy subjects [10]. Bipolar depression in particular is more widespread than hypomanic/manic symptoms, and leads to higher indirect costs owing to impaired work productivity and increased rates of disability, as well as a greater burden for caregivers [11].

Studying vulnerability factors in bipolar disorder

BD is considered to have a higher heritability than MDD, estimated at above 80% based on twin and family studies [12], although it might be lower. For example, heritability was estimated at 59% by Liechtenstein et al. [13].

The aetiology of BD is thought to be multifactorial, and to result from complex gene-environment interactions. However, despite numerous candidate gene studies reporting genetic associations with BD, attempts to replicate these results have been mostly inconsistent [14]. The same pattern of nonreplication of candidate gene association studies has been observed in the field of schizophrenia [15]. Although monozygotic concordance is high (40–70%) in BD, it still remains less than 100%, pointing to the importance of nongenetic factors in the pathophysiology of BD [16]. Recently, psychiatric neuroscience research has focused on endophenotypes, defined as intermediate phenotypes that fill the gap between genetic risk factors and complex multidimensional symptoms observable at the clinical level [17]. By definition, endophenotypes have to be associated with the disease, heritable, state-independent, and found in healthy relatives at a higher rate than in the general population

Table 1: Peripherical potential markers of bipolar disorder.

	Genes	Epigenetics	Immune markers	Stress markers	Sleep
Studies in patient	**BDNF, FKBP5, 5HTTLPR, CACNA1C,** ANK3, ADCY2, ODZ4 overall >30 SNP (Psychiatric GWAS Consortium Bipolar disorder Working Group, 2011 [166])	**FKBP5,** NR3C1, **microRNA**	**IL-4, IL-6, IL-10, TNFα;** CRP (?) insulin resistance	↑ Basal morning cortisol ↑ **Cortisol metabolism** ↑ α-amylase ↓ Cortisol after dexamethasone	**Evening type** ↑ Sleep-wake cycle variability ↑ Sensitivity of melatonin to light ↓ Melatonin overnight
Studies in high-risk subjects	Polygenic risk score	?	Monocyte expression	↑ Basal morning cortisol ↑ Daily cortisol ↑ Cortisol after dexamethasone	↑ Sleep-wake cycle variability ↑ Sensitivity of melatonin to light

Bold type indicates the most promising biomarkers.
CRP = C-reactive protein; IL = interleukin; SNP = single-nucleotide polymorphism; TNFα = tumour necrosis factor-alpha
Genes coding for: 5HTTLPR = serotonin-transporter-linked polymorphic region; ADCY2 = encodes for a protein involved in cAMP signalling; ANK3 = ankyrin 3 – membrane protein involved in sodium regulation; BDNF = brain-derived neurotrophic factor; CACNA1C = subunit of L-type voltage gated calcium channels; FKBP5 = co-chaperone of glucocorticoid receptor; ODZ4 = also known as TENM4 or teneurin transmembrane protein [38–41]

[18]. Currently, BD endophenotypes corresponding to these criteria have not been validated. Current streams of research focus on combining structural and functional neuroimaging data with genetic and biological biomarkers to identify vulnerability factors in BD [19, 20, for a review see 21].

One approach to the study of vulnerability factors in BD is to focus on relatives of patients with BD and, in particular, high-risk offspring. Indeed, several longitudinal cohort studies have revealed that offspring of patients with BD have an increased risk of developing a spectrum of psychiatric disorders, in particular mood and anxiety disorders [22–24]. For example, in the Dutch study, 72% of the offspring of bipolar parents developed a psychiatric disorder, 54% a mood disorder, and 13% a bipolar spectrum disorder, with only 3% who had BD-I disorder [23]. Comparable numbers were found in the Swiss study, with a more than 50% chance to develop a psychiatric disorder. More precisely, 34.5% of the offspring of patients with BD developed a mood disorder, and 42.5% an anxiety disorder [24]. Only 2.3% of the offspring developed a BD, which is low compared with North American studies [e.g., 22], but probably a result of more strict diagnostic criteria. Interestingly, risks for BD are greater when both parents are affected with the disease [24], which is comparable to offspring of schizophrenia patients (cumulative risk of schizophrenia 27.3% if two parents have schizophrenia and 7% if one parent has it); for offspring of bipolar patients the risks for BD are 24.9% and 4.4%, respectively [25]. In addition, some recent studies indicate that the two dimensions of BD, mania and depression, are differentially transmitted to relatives of BD patients [1]. As the risk of developing BD might be ten-fold higher in high-risk offspring, multimodal imaging studies are being used in these individuals to identify alterations in neural circuits that underlie vulnerability to BD. When identified, these circuit alterations will need to be linked to specific clinical dimensions and genetic factors associated to BD [26, 27]. Unmasking vulnerability factors in high-risk patients will thus help to better understand the pathophysiology of the disease and potentially to prevent its onset (see fig. 1).

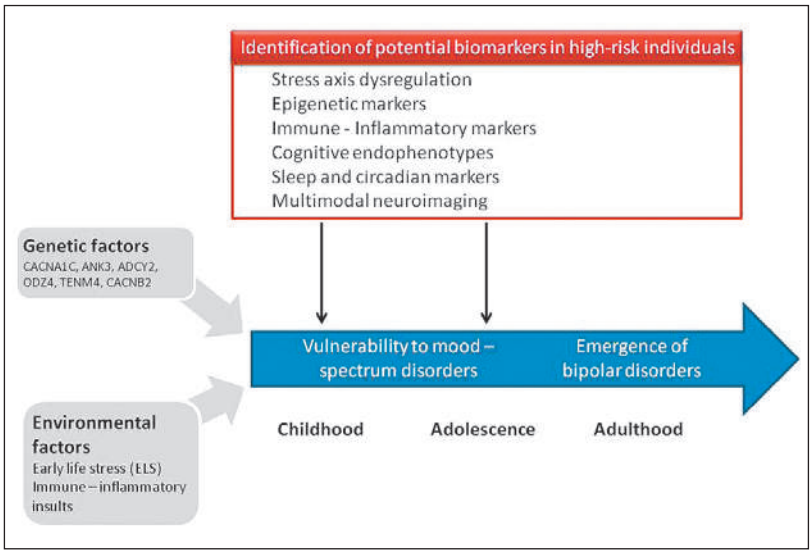

Figure 1: Interaction between adverse environmental factors and genetic risk variants which can lead to the emergence of vulnerability to mood spectrum disorders. Current research aims at identifying peripheral and brain biomarkers in high-risk individuals.

Genetic factors

Historically, candidate gene association studies in BD have been performed in small sample sizes and have led to a large amount of results that have been difficult to replicate [14]. In a similar manner, the large majority of historical candidate genes associated with schizophrenia have not been replicated in large scale genome-wide association studies (GWAS), suggesting that earlier studies may have given rise to false

positive results [15]. Among pre-GWAS risk variants, *BDNF* (brain-derived neurotrophic factor) [28–30], *FKBP5* (a gene encoding for a cochaperone of hsp90 involved in the regulation of the sensitivity of glucocorticoid receptors) [31, 32] and *5HTTLPR* (a serotonin transporter) [33] have been associated with BD. These genes are worth mentioning as they interact with early life adversity, regulate the hypothalamic-pituitary-adrenal (HPA) axis involved in the stress response, and increase the risk for affective disorders [34–37].

More recently, GWAS have led to the identification of several risk genes for BD (table 1) [38–41]. Among them, *CACNA1C* (calcium channel, voltage-dependent, L type, alpha 1C subunit) variants have been found to be associated with schizophrenia and BD in several independent large-scale replication GWAS [40, 42, 43]. Importantly, in one of the largest GWAS performed in the field of psychiatry on 27 888 controls and 32 332 cases of patients with autism spectrum disorder, schizophrenia, BD, attention deficit-hyperactivity disorder and MDD, only four loci surpassed the cutoff for genome-wide significance, among which were variants in the *CACNA1C* gene [38]. Furthermore, *CACNA1C* variants have been shown to affect brain circuitries related to mental disorders in healthy subjects in several functional magnetic resonance imaging (fMRI) tasks [44]. Finally, rare mutations in *CACNA1C* lead to the Timothy syndrome, which comprises autism spectrum symptoms and in rare cases BD [45]. Another recent study aimed at combining GWAS data with gene expression data from prefrontal cortex (PFC) to identify pathways involved in the genetic predisposition to BD [46]. This approach led to the identifications of risk genes involved in hormonal regulation, calcium channels, second messenger systems, and glutamate signalling, as well as neuronal development pathways [46]. However, the predictive risk of each of these risk variants is still individually too small to be of clinical use [16]. Therefore, genetic risk variants need to be combined with multimodal imaging data and other biomarkers to define a vulnerability phenotype in BD.

Environmental risk factor: early-life stress and vulnerability to bipolar disorder

Epidemiological studies have established that early-life stress (ELS, sexual/physical abuse, neglect, loss of a parent) is frequently associated with BD [47]. Early-life adversity is clearly not a specific risk factor for BD since it has been associated with other psychiatric disorders such as anxiety disorders, unipolar depression and borderline personality disorder [48]. Severe physical and sexual abuses during childhood are present in about 40–60% of BD patients [49–52]. Up to 80% of patients presenting a first manic episode went through stressful events in their youth [53]. An increased frequency of severe emotional neglect (16% in BD patients compared with 7% in controls) and of severe emotional abuse (15% in BD patients, 2% in controls) has also been documented [54].

Interestingly, exposure to severe ELS is also associated with more severe forms of unipolar and bipolar disorders. For example, BD patients with ELS have more severe depressive and manic episodes, more frequent manic episodes, as well as more rapid cycles [49, 52, 55]. They also present a younger age of onset [52, 55]. ELS is also associated with more frequent hospitalisations [52] and more problems with the justice system [53]. Clinically, patients with ELS also show a lower level of premorbid functioning [53] and more cognitive impairments [56]. Moreover, in BD, ELS increases the risk for developing psychotic symptoms, mainly auditory and visual hallucinations (but not delusions) [57, 58]. Finally, patients are at increased risk of developing a more chronic form of BD [47, 59]. At a biological level, ELS has been associated with dysfunction of the HPA axis [60, 61]. It has been proposed that HPA axis dysregulation induced by ELS could mediate the relationship between genetic vulnerability, stress vulnerability later in life, and the emergence of depressive episodes [62, 63]. This hypothesis remains to be tested in the case of BD.

Biological biomarkers in patients

Epigenetics

Epigenetic markers could be a useful method to delineate stages in the progression of BD [64]. Indeed, environmental risk factors such as early-life adversity induce long-lasting epigenetic changes such as DNA methylation modifications in a variety of genes including the glucocorticoid receptor *NR3C1* [65], *FKBP5* [66], microRNAs [67] and many other genes involved in the stress response [68]. Although this field is still in its infancy for BD, a few studies have emerged. Using a candidate gene approach, a recent study showed that a blunted glucocorticoid response, defined by salivary cortisol level after dexamethasone challenge in BD patients, might be linked to epigenetic modulation of the *FKBP5* gene [69]. However, epigenetic markers in peripheral blood DNA are tissue-specific and do not reflect brain-specific methylation changes. To begin to address this question, a genome-wide methylome approach on brain tissue revealed widespread hypomethylation of genes in the frontal cortex of both schizophrenia and BD patients compared with controls. In contrast, hypermethylation of genes in the anterior cingulate cortex (ACC) was observed in schizo-

phrenia and BD patients compared with controls [70]. These results thus suggest region-specific aberrant DNA methylation patterns in BD, which need to be further confirmed in subsequent studies.

Stress axis

Persistent HPA dysregulation is observed in BD patients in remission and correlates with increased risk for recurrence of mood episodes [71, 72]. As a marker of HPA function, the cortisol level has been under study with inconsistent results. A recent meta-analysis of morning cortisol levels in both schizophrenic and bipolar patients found a moderate increase in both groups compared with healthy controls, but the effect was stronger for outpatients and non-manic participants [73]. Increased cortisol metabolism, measured as increased enzymatic activity of 5β-reductase, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and 5α-reductase, was also found in BD subjects, although to a lesser extent than in schizophrenic subjects [74]. A recent study found a blunted salivary cortisol response and increased autonomic stress response after social stress in euthymic BD-I patients; however the difference in endocrine response was potentially attributable to antipsychotic medication [75]. Another study using electrical stimulation as a stressor resulted in increased salivary α-amylase in patients compared with healthy controls, more in female than men, with no difference in salivary cortisol [76]. Finally, another recent study speaks in favour of decreased responsiveness of glucorticoids receptors in BD patients, especially in the late stage of the disorder, since the authors found increased postdexamethasone salivary cortisol levels when compared to controls [69].

"Body markers": immune markers and insulin resistance

Recently, a seminal paper proposed that BD should be viewed as a multisystem inflammatory disease [77]. The immune system strongly interacts with the HPA axis at different levels and it has been shown that proinflammatory cytokines can induce a state of resistance to glucocorticoids and lead to overactivation of the HPA axis. Data suggest that cytokines levels such as interleukin (IL)-6, tumour necrosis factor-α (TNFα), and IL-10 could be altered in early phase of BD [78, 79]. IL-6 and TNFα levels are increased both in BD during mood episodes and in cardiovascular diseases [80]. Additionally, IL-6 appears associated with illness progression [81]. Inflammatory processes could explain, better than side effects of treatment, why BD is frequently associated with metabolic and/or cardiovascular disease [79, 82, 83]. On the other hand, some studies found that the association of increased C-reactive protein levels and mood disorder does not survive statistically when more covariables, such as comorbidities and treatment, are taken into account [84]. Therefore, much confirmatory work needs to be done in this emerging field [78].

The same is true for insulin resistance and type 2 diabetes, which are more and more frequently associated with BD. Both might actually be risk factors for brain alterations in BD [85] and might represent an important factor in treatment resistance [86]. For example, a recent article showed that global DNA methylation is influenced by insulin resistance and antipsychotic use [87]. Further research is needed to distinguish the effects of medication or BD disease states on inflammatory and metabolic markers.

Sleep and circadian markers

Recent studies show that polysomnography might constitute an interesting tool to investigate biomarkers for BD [20, 88]. Patients show a dysregulation of the wake-sleep cycle, both during a mood episode and in-between [88]. Sleep patterns in BD patients, even euthymic, resemble those of insomniac patients [88, 89]. Persistence of sleep disturbances in euthymic states is associated with rapid cycling, neuroticism and ELS [90]. Furthermore, sleep alterations might be associated with cognitive deficits found in euthymic BD patients [91] and could thus represent an important target for interventions [92]. Finally, circadian phenotypes such as lifestyle irregularity, higher sleep-wake variability, evening type and melatonin secretion changes have repeatedly been associated with BD, and might also represent interesting vulnerability factors for BD [93, 94]. A recent review emphasises that evening preference and actigraphic variables are relatively consistent across studies and that genetic association studies have implicated several circadian genes such as *CLOCK, ARNTL2, GSK3beta, PER3* and *NR1D1* [95].

Neuroimaging biomarker

– *Structural and connectivity:* Consistent changes in grey matter volumes have been difficult to identify in BD compared with healthy controls or even with schizophrenia patients. Although the ENIGMA-Bipolar Disorder Working group found significant reductions in the bilateral thalamus, hippocampus, and amygdala of 1022 patients compared with 1415 controls [96], there was a high variability inside the sample and the analyses are still ongoing. In contrast, white matter changes have been more strongly associated with the disease [97]. Structural connectivity seems to be altered, and many diffu-

Table 2: Central potential markers of bipolar disorder.

	Cognitive dysfunctions	Structural volume changes	Structural connectivity changes	Functional changes
Studies in patients	**Memory:** *working memory,* verbal memory, visual memory **Sustained attention / processing speed** **executive functions:** planning, task initiation, *task switching, inhibition,* interference resolution + fine motor dexterity, verbal learning	↓ Thalamus bilateral ↓ Hippocampus ↓ Amygdala	↓ FA left cingulum ↓ FA anterior cingulate ↓ FA uncinate fasciculus	↓ *vlPFC/IFG and dlPFC* ↓ ACC ↓ Precuneus ↑ *PHG and amygdala*
Studies in high-risk subjects	**Memory:** working memory, verbal memory, verbal fluency **Executive functions:** task initiation, task switching, inhibition + verbal learning	↓ Thalamus left ↓ Hippocampus/PHG ↑ Insula, IFG	(see Lee et al. 2014 [124])	↓↑ vlPFC/IFG ↑ Amygdala

Italic text indicates the most promising biomarkers. Arrows show direction of volume/activity changes.
ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; FA = fractional anisotropy; IFG = inferior frontal gyrus; PHG = parahippocampal gyrus; vlPFC = ventrolateral prefrontal cortex

sion tensor imaging studies have been performed. BD patients do show altered fractional anisotropy (FA), index of water molecule diffusion along white matter fibers, compared with controls. A meta-analysis found involvement of all major tracts, but in particular decreased FA in the left cingulum and anterior cingulate white matter tracts, as well as decreased FA in the right posterior white matter, likely involving long association tracts [98, 99]. Tracts involved in emotion regulation are thought to be altered, such as white matter tracts interconnecting the amygdala, hypothalamus, striatum, and the subdivisions of the frontal cortex [100]. However, results remain hard to interpret given the dissimilarities between studies and lack of reproducibility, both in region of interest and whole-brain approaches.

– *Functional:* Brain imaging studies consistently reported alterations in circuits implicated in emotional reactivity and regulation in BD patients, such as limbic hyperactivity and frontal hypoactivity [101–104]. Overall, reduced activation in prefrontal areas could explain deficit in cognitive control, coupled with overactivation in regions involved in emotional arousal [105]. A meta-analysis of fMRI studies using whole-brain analysis of emotional paradigms in patients found decrease activation in ventrolateral PFC, dorsolateral PFC, ACC and precuneus coupled with increase activation of parahippocampal gyrus extending in the amygdala for example [106]. Regarding the combination of structural and functional connectivity, common findings include deficit in prefrontal-limbic coupling, in regions such as uncinate fasciculus, amygdala, parahippocampal cortex, cingulate cortex and corpus callosum [107]. To conclude, three main processes are probably altered in BD: emotion processing emotion regulation, involving cognitive control and inhibitory processes, and reward processing [64].

Cognitive biomarkers

Cognitive deficits are found even in euthymic or remitted patients [108–110], although it might concern only a defined subgroup [111]. It has a direct clinical impact since it is a significant predictor of psychosocial functioning and disability in BD [112–114]. Langenecker et al. initially proposed as intermediate cognitive phenotypes processing speed with interference resolution, visual memory, and fine motor dexterity [115]. Others have proposed that the domains of learning and memory, sustained attention, and executive skills (planning, task initiation and switching, inhibition) are consistently impaired in BD patients compared with healthy controls [88]. Finally, impairments in verbal learning and verbal memory, as well as response inhibition, have been proposed as potential cognitive endophenotypes for BD [116–118]. However, even domains such as executive function / working memory, verbal learning and verbal memory, which are the most compatible with the endophenotype definition, lack specificity [118]. We summarise the main cognitive domains associated with BD in table 2.

In a recent study, a large sample of BD and MDD patients was tested for sustained attention and processing speed (Parametric Go Task). These results showed similar attentional impairment for both disorders outside the scanner. However, inside the scanner, BD patients showed increased difficulty and related hypoactivation [119]. Dysfunction in working memory tasks such as demanding n-back tasks are reliably observed in BD [120] and this has been linked to reduced ventrolateral and medial PFC activity in patients, consistent with interference in cognitive control of brain regions involved in emotional processing [121]. Cognitive deficits do not appear to be explained by variations in

mood, but are considered as rather stable [122] and might be linked to personality traits such as openness to ideas [123]. The longitudinal course of these cognitive deficits is still debated, although a recent article showed that the longitudinal course of specific neuropsychological performance might predict functional outcome, albeit in a transdiagnostic approach [124].

Potential vulnerability markers in high-risk populations

Epigenetics

To our knowledge, no research in this promising area has been published yet that includes relatives of BD patients.

Stress axis

In high-risk BD offspring, subtle changes in HPA function have been reported but need to be confirmed [78, 125–127]. For example, a recent study showed increased awakening and daily cortisol levels in offspring of bipolar patients compared with offspring with no family history of affective disorders, but only in those with high interpersonal chronic stress [128]. Interestingly, style of parenting (in this case structure) may interact with genetic vulnerability regarding cortisol elevated response to stress of bipolar offspring [129]. High-risk subjects having a met allele for BDNF Val66Met polymorphism also showed higher whole blood BDNF and evening cortisol level [130]. Most of these data though-come from the same group and need to be replicated, since the literature is not consistent. Indeed, one study did not find a blunted cortisol response in healthy relatives of BD patients, contrary to the affected subjects [75].

"Body markers": immune markers, insulin resistance, circadian biomarkers

Data from studies in high-risk individuals indicate that subtle neuroendocrine and immune alterations may precede the emergence of mood disorders and may thus be informative as biological indicators of vulnerability to BD [78]. However, data are still too sparse to allow any definitive conclusion.

Sleep disorders also seem to precede the onset of BD in high-risk subjects, and could represent a marker of vulnerability [131, 132]. In depression as well, sleep disorders have been found in high-risk subjects, suggesting that these problems appear early before the emergence of syndromic depression [133, 134]. Circadian model theory is a promising framework for research on vulnerability and potential therapeutic interventions [93, 95]. These data suggest that preventive rhythm-focus therapy in high-risk adolescents [135] could constitute an early intervention that may decrease the risk for BD.

Neuroimaging biomarker

- *Structural and connectivity:* A recent review of grey matter changes in first-degree relatives of BD patients found few replicated findings [136]. The most consistent results were larger insular cortex volumes [137] and right inferior frontal gyrus [e.g., 138]. Other findings included decreased gray matter density or volume in the left thalamus, the left hippocampus and the parahippocampal gyrus, and some studies found no evidence of differences [136]. For example subgenual ACC, striatum and pituary volumes were not different between first-degree relatives and controls [139–141]. Regarding structural connectivity and diffusion tensor imaging, a recent review highlighted the current lack of consistent conclusion with this technique for relatives of BD patients [142].
- *Functional:* Few reviews of imaging data are available for high-risk BD offspring [143, 144]. Globally, the pattern of results indicates the involvement of the same type of regions found altered in BD patients, although the pattern is sometimes reversed owing to compensatory mechanisms. Amygdala activation was increased in relatives of BD patients both during emotional processing [145] and with level of difficulty [146]. The inferior frontal gyrus also showed an altered pattern, in different directions [147–149]. A study using an n-back task with emotional faces as distracters to investigate the role of cognitive control on emotional processing found decreased ventrolateral PFC modulation of the amygdala to both happy and fearful face distracters [150].

Cognitive biomarkers

Cognitive deficits are also found in healthy relatives in regards to some executive functions [151, 152]. Some studies support familial aggregation of neurocognitive traits, with performance of siblings of bipolar patients being intermediate between patients and healthy controls, especially regarding verbal memory, verbal fluency, set-shifting and inhibition [116]. A systematic review on neurocognition in relatives of BD patients concluded that verbal learning, verbal memory and verbal working memory were the best potential candidates for cognitive endophenotypes [153]. In 66 high-risk offspring of schizophrenia and BD patients, Berthelot et al. found that those exposed to ELS had a lower IQ and showed impairments in visual episodic memory and executive functions of initiation [154].

Although results were still sparse and heterogeneous a few years ago [153], it is a rapidly expanding literature. Another recent review confirms that executive functioning and verbal memory impairments are consistently found in relatives of BD patients and could represent proper endophenotypes; however, findings again lack specificity and should be compared with other patient groups [118].

Clinical staging and prevention for at-risk subjects

Recently, major research efforts have aimed at identifying vulnerability factors in high-risk offspring of BD patients in order to better define prevention targets. A recent review of prospective studies in the general population found that precursors of BD include mood lability, subsyndromal and major depression (with or without psychotic symptoms), subsyndromal hypomanic symptoms, and cyclothymia. More specifically, BD was also predicted by early onset of major depression, as well as frequency and loading of hypomanic or depressive symptoms [155]. In at-risk subjects (defined as parents or siblings suffering from BD), Perich et al. found higher rates of depressive, anxiety and behavioural disorders compared with controls. They also included a group of BD patients, and showed that prior behavioural disorders increased the risk to develop mood disorders [156]. Axelson et al. found similar results; subthreshold manic or hypomanic episode, depressive episode and disruptive behavior disorders were risk factors of emergent bipolarity [157].

Different groups working on longitudinal studies for more than a decade found that in offspring of BD patients, episodes of depression, anxiety and perturbation of chronotype are the most consistent predictors of development of BD [158–161]. Anxiety disorder can appear years before BD and be considered as an early risk syndrome rather than a prodrome, as it is also predictor of ADHD, for example [161]. Risk of substance abuse is also increased. Finally, temperament can also be viewed as a vulnerability trait. For example, mood instability is common in remission and might be an indicator of vulnerability. In high-risk offspring, Doucette et al. [162] showed psychological predictors of mood disorder such as perceived neglect from mother and emotionality. Another vulnerability trait might be the response style, since high-risk offspring show increased tendency to ruminate [163]. On the other hand, severe and nonepisodic irritability in children, often viewed as associated with BD, might actually predict anxiety and depression rather than mania [164].

Conclusion

This short review is not exhaustive, since, for example, we have not included electroencephalography or spectroscopy data. Although no biological biomarker has currently the power to help diagnosis and/or treatment stratification [165], current research frameworks combining clinical DSM categories with dimensional and multimodal approaches should translate into the definition of more homogeneous forms of bipolarity. Peripherical markers such as immune markers or circadian markers are promising, both as vulnerability markers of BD and biomarkers that can help stratifying subtypes and might even lead to novel therapeutic approaches. Cognitive and neural markers push further our understanding of the development of this disease. This will ultimately lead the field to a better understanding of the pathogenesis of bipolar disorders, and will hopefully allow more preventive and stage-specific targeted interventions.

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Correspondence:
Professeur
Jean-Michel Aubry, M.D.
Service des spécialités psychiatriques
Département de Santé Mentale et Psychiatrie
Hôpitaux Universitaires de Genève
Rue de Lausanne 20bis
CH-1201 Genève
jean-michel.aubry [at]hcuge.ch

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