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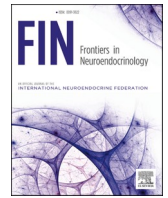
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# Sex differences in bipolar disorder: The dorsolateral prefrontal cortex as an etiopathogenic region

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## ABSTRACT

Bipolar disorder (BD) is worldwide a prevalent mental illness and a leading risk factor for suicide. Over the past three decades, it has been discovered that sex differences exist throughout the entire panorama of BD, but the etiologic regions and mechanisms that generate such differences remain poorly characterized. Available evidence indicates that the dorsolateral prefrontal cortex (DLPFC), a critical region that controls higher-order cognitive processing and mood, exhibits biological disparities between male and female patients with psychiatric disorders, which are highly correlated with the co-occurrence of psychotic symptoms. This review addresses the sex differences in BD concerning epidemiology, cognitive impairments, clinical manifestations, neuroimaging, and laboratory abnormalities. It also provides strong evidence linking DLPFC to the etiopathogenesis of these sex differences. We emphasize the importance of identifying gene signatures using human brain transcriptomics, which can depict sexually different variations, explain sex-biased symptomatic features, and provide novel targets for sex-specific therapeutics.

## 1. Introduction

Bipolar disorder (BD) is a severe mood disorder that is categorized by extreme mood swings that include emotional highs (mania or hypomania) and lows (depression). According to the intensity of mood elevation, two major forms of BD are distinguished: bipolar I disorder (with mania) and bipolar II disorder (with hypomania). In 2019, more than 40 million people experienced BD worldwide (Kakhramonovich, 2022). Approximately half to 70% of BD patients develop psychotic features during their lifetime (Van Bergen et al., 2019). A history of psychotic features has been associated with earlier onset of BD, more frequent hospitalizations, severer cognitive impairments, lower response to lithium, and worse psychosocial prognosis, particularly for manic episodes (Van Bergen et al., 2019; Maj, 2003; Glahn et al., 2007; Maj et al., 2002). As a major hazard of psychiatric illnesses, life expectancy in patients with BD has been reported to be decreased by 10–20 years, with suicide serving as the primary culprit (Kessing et al., 2015). Suicidal behaviors are prevalent among patients with BD, as 20–60% of them attempt suicide at least once in their lifetime (Dome et al., 2019). The incidence of suicide death among patients with BD can be more than 20 times higher than in the general population, particularly when

untreated (Grande et al., 2016). In addition, the lethal index, a parameter defined as the ratio of suicidal attempts to suicide completion, is more than 10 times lower for BD patients (3:1) than for the general population (35:1) (Dome et al., 2019).

A distinct feature that underpins the high suicidality in BD is its sex difference. Among bipolar patients, suicide attempters were 35% more frequent in females than in males, regardless of the diagnostic subtypes (Tondo et al., 2016). When patients had manic episodes, females were 2.4 times more likely to die by suicide than males (Bhattacharya et al., 2011). This sex-related suicide rate was up to 3 times higher in female patients with a first-episode psychosis than in male counterparts, but suicidality can be better remitted by therapeutic interventions in female than in males (Chang et al., 2011; Tseliou et al., 2017). These data suggest that the manic episodes and psychotic features are major risk factors for suicide. The higher prevalence of suicide rate in females with BD, and the observation that suicidality increased with the development of psychotic symptoms and was reduced after medical care, have led to the idea that unraveling the neurobiological basis of sex differences in BD, particularly in patients with comorbid psychosis (bipolar psychosis), may provide novel therapeutic targets for extending the lifespan of BD populations.

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An immune/inflammatory-mediated alteration in neurotransmitter signaling involving the limbic network is considered to be an important pathophysiological mechanism underlying BD (Magioncalda and Martino, 2022). The limbic circuits are, therefore, key loci to search for biological evidence for sex differences underpinning BD. This review explores the literature on sex differences in BD with respect to epidemiology, clinical presentations, and brain region-specific genetics. As major specifiers of BD, the sex differences in psychotic features were also discussed. Of note, literature concerning psychotic features in schizophrenia is excluded in this review, in order to keep biological homogeneity in the topic psychosis. Supported by these human studies, we conclude that the dorsolateral prefrontal cortex (DLPFC) is a central brain region with respect to the pathophysiological context in BD.

## 2. Sex differences in the epidemiology of bipolar disorder

Sex differences in BD displayed distinct patterns in terms of the incidence and the longitudinal course of the disease. According to epidemiologic and clinical studies, the prevalence of BD is approximately equal between the sexes in the general population but is about two times higher amongst female as amongst male adolescents (Mitchell et al., 2018). Seasonality is also a well-documented feature. A population-based study has shown that, in admissions, the seasonality in BD was significant in females for depressive episodes that peaked in winter, and in males for manic episodes that peaked in spring and summer (Yang et al., 2013). The same study also presented data showing that young adults displayed a higher degree of seasonality for acute admissions than middle-aged adults, which indicates that age-related sex hormone changes might act on the pathogenesis of seasonality in BD (Yang et al., 2013). Compared to female patients, male patients experience the onset of symptoms earlier, including the development of mood, mania, and hospitalization (Mitchell et al., 2020; Kennedy et al., 2005). It is likely that female adolescents are more vulnerable to BD than their male counterparts, while male adolescents with BD have more severe clinical manifestations than female adolescent patients.

The sex difference in epidemiological vulnerability can be further complicated when specific psychiatric conditions, such as psychotic features or early life adversity, are comorbid. For example, a meta-analysis that included 33 reports has shown that, compared to patients with non-affective disorders, females with mood disorders had a nearly two times higher incidence of psychosis than male counterparts (Castillejos et al., 2018). Conversely, among patients with psychotic features, the incidence of BD among females was 6.6-fold lower than among males (Scully et al., 2002). This evidence indicates that females with a pre-existing diagnosis of BD are more prone to develop psychotic symptoms than males, but not vice versa.

## 3. Sex differences in the cognitive impairment in bipolar disorder

Cognitive deficits are strongly associated with a worse course and outcome in BD, while these deficits present with complicated variabilities in relation to sex. When compared to healthy controls, BD patients exhibit three main forms of sex-biased cognitive dysfunctions. First, BD may disrupt sex-related neurocognitive variations as they are present in healthy controls. For example, clinical analyses of the neurocognitive variables have shown that healthy females outperformed healthy males in the emotional and affective aspects of social cognition, a sex difference that was absent in BD patients (Navarra-Ventura et al., 2021). On the other hand, male controls were significantly better at performing spatial working memory tasks than female controls, a sex difference that also disappeared as BD progressed (Barrett et al., 2008; Solé et al., 2022; Tournikioti et al., 2018). Second, BD has specific sex-related variations in neurocognitive deficits. In the early phase of BD, for example in first-diagnosed and drug-naïve patients, males had worse cognitive dysfunctions compared to females in verbal learning, attention, and

immediate and delayed memory (Solé et al., 2022; Xu et al., 2021; Carrus et al., 2010). Third, in single-sex comparisons, BD patients have significantly more cognitive disturbances compared to the controls of the same sex, which is absent in the other sex. It has been reported that male BD patients had poorer spatial working memory scores than male controls, a difference that was insignificant in female patients (Suwalska and Łojko, 2014). In addition, the presence of sex-biased cognitive deficiencies may be strongly associated with the development and prognosis of mania. It has been shown that cognitive deficits, such as worse attention and delayed memory performance, were correlated with mania severity only in BD males (Xu et al., 2021). Following their recovery from mania, these patients may regain the sex differences in cognitive functions that are shown in non-psychiatric controls (Bücker et al., 2014). Taken together, among non-psychiatric controls, male controls were significantly better at performing spatial working memory tasks than female controls. This sex difference was not present when male patients with BD were compared to female patients with BD. The cognitive deficits in male patients were associated with the severity of manic symptoms. However, the cognitive dysfunctions that are prevalent in male patients are not statistically significant in female patients (Suwalska and Łojko, 2014).

Cognitive impairment is also a key feature of psychosis and is expected to be a treatment target in early interventions. Individuals who are at a high-risk mental state for psychosis have already developed sex-biased differences in cognitive functions. For example, males at ultra-high risk for developing a psychotic disorder exhibited significantly poorer social functioning and higher levels of negative symptoms than females at ultra-high risk (Willhite et al., 2008). At the early phase of psychosis, patients can still retain some sex-related cognitive abilities as they occur in control populations. Large-cohort cognitive functioning analyses have shown that, from healthy control subjects to patients with first-episode psychosis, females generally performed better in verbal learning and memory than males (Ittig et al., 2015). However, some sex-associated cognitive functions, such as better auditory attention as observed in control females compared to control males, can be disrupted by the aggravation of psychotic symptoms (Ruiz-Veguilla et al., 2017). Early life adversity also plays a negative role in cognitive deterioration in male patients. In the first episode and early-onset psychosis, males had greater impairments of their cognitive functioning, as the experience of emotional abuse in their childhood could account for impaired global functioning in adulthood (Fresan et al., 2003; Pruessner et al., 2019; Smelror et al., 2021; Good et al., 2007). Similar relations between early life adversity and cognitive impairments were not observed in female patients.

Compared to male patients, cognitive impairments in female psychotic patients are mainly focused on perceptual functions. Clinical observations have reported more severe psychotic symptoms in females than males, especially in perceptual abnormalities and lowered self-certainty (Hu et al., 2022; Penney et al., 2020). Among adult-onset psychosis patients, females reported a significantly higher emotional reactivity to daily life stress compared to males, which consists of both, an increase in negative affect and a decrease in positive affect (Myin-Germeys et al., 2004). Females also underwent more profound deterioration in personal identity than males, including higher dejection-related emotions and lower facial emotion recognition (Andric Petrovic et al., 2019; García-Mieres et al., 2020). In bipolar psychosis, the aforementioned sex differences became more complicated. Among these patients, males were more likely than females to exhibit suicidal ideations and hallucinatory behaviors, which was the opposite when psychotic symptoms were absent (Dell'Osso et al., 2021).

## 4. Sex differences in the clinical manifestations of bipolar disorder

### 4.1. Sex differences in the onset and clinical type of bipolar disorder

The clinical features of BD are characterized by differences between the sexes. Males and females with BD differed in the episodes at the onset. The first episode in males was mostly mania, whereas the majority of females had a first episode of depression (Pillai et al., 2021). Throughout their lifespan, the number of manic episodes was significantly higher in BD males, while female patients presented a higher rate of rapid cycling, depressive polarity, mixed episodes, and suicide attempts (Dell'Osso et al., 2021; Pillai et al., 2021). Therefore, bipolar II disorder, which is predominated by depressive episodes, also appears to be more common in females than in males (Arnold, 2003). Interestingly, the occurrence of depression and mixed symptoms were associated with the presence and severity of hypomania in females (Suppes et al., 2005).

### 4.2. Sex differences in the comorbidities of bipolar disorder

In addition, the two sexes differ in the type of comorbid illnesses. Female patients with BD have a much higher burden of medical comorbidity and hazard of recurrence than male patients. With respect to physical diseases, female patients with BD had higher odds of comorbid metabolic disorders and inflammatory diseases than males (Patel et al., 2018). One exception is the prevalence of hyperhomocysteinemia, which is higher in male than in female patients (Mu et al., 2020). In view of psychiatric disorders, males were more likely to present with obsessive-compulsive disorder, substance abuse, pathological gambling, and conduct disorder (Benedetti et al., 2007; Kawa et al., 2005). Subsequently, more male than female patients had a history of legal problems (Baldassano et al., 2005). Fewer female than male patients develop substance use disorder. However, the heavy load of some long-term substance abuse, such as cannabis intake, had worsened the quality of life in BD females, particularly on bodily pain and mental health subscales, which did not significantly affect male patients (de La Fuente-Tomas et al., 2020). However, female patients had a much higher likelihood of combining post-traumatic stress disorder, panic disorder, and anxiety disorders compared to males (Patel et al., 2018; Benedetti et al., 2007). Female BD patients were older than males at clinical intake but had more frequent psychiatric visits, longer inpatient length, and more inpatient episodes (Mitchell et al., 2020; Ragazan et al., 2019; Buoli et al., 2019; Fellinger et al., 2018).

Sex differences in the clinical features of psychosis already appear when people are at high risk or experiencing subclinical psychosis (Schultze-Lutter et al., 2020; Stainton et al., 2021). Research suggests that males at the stage of clinical high risk for psychosis displayed more pronounced negative symptoms, higher rates of past substance abuse disorders, and higher deficits in social functioning than females (Rietschel et al., 2017). Such male-biased sex differences persist throughout the process of psychosis. In general, males have an earlier onset of psychotic symptoms than females. In first episode psychosis, more female patients have affective and positive symptoms and past suicide attempts, but they have higher levels of cognitive functioning than males (Chang et al., 2011; Pruessner et al., 2019). Childhood trauma is strongly associated with sex differences in the clinical manifestations of first episode psychosis in both sexes. Drastic early life trauma has been related to severe depressive symptoms with a reduced age of onset in females and to the presence of psychotic symptoms in males (Pruessner et al., 2019; Comacchio et al., 2019). Particularly in male patients, emotional abuse predicted positive symptom severity and impaired global functioning, while emotional neglect predicted more severe negative symptoms (Pruessner et al., 2019). Patients with early onset psychosis presented with similar sex differences as in first-episode psychosis in adults (Carter et al., 2022; Garcia et al., 2016). In adult-onset psychotic features, females manifested a greater mixture of symptoms

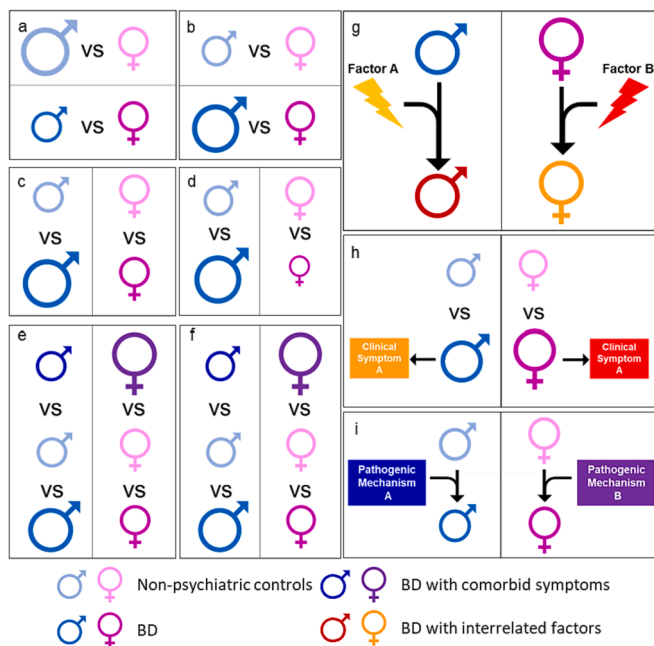
than males, especially concerning mixed affective symptoms and less aggressive behaviors (Copolov et al., 1990; Baccetti et al., 2020). Compared to depressive episodes, there seems to be a sex-biased connection between manic episodes and psychosis. Among individuals in a pure manic episode, males had significantly more and worse psychotic symptoms than females (Miquel et al., 2011). However, in BD patients with acute manic episodes, females exhibited a specific pattern of psychotic features, appearing to be associated with greater severity of the acute episode, more mixed states, and a more severe course of BD (Bräuning et al., 2009). A specific molecular basis may have underpinned these sex differences among bipolar patients who develop psychotic symptoms.

## 5. Hormonal origins of sex differences in bipolar disorder

The higher prevalence of bipolar II/hypomania, rapid cycling, and mixed episodes in females than males during the reproductive years is thought to result from the differential effects of genetic influences and gonadal hormones. In addition to genetic factors, epigenetic modifications establish and maintain sex differences. A study has examined the association of more than 14,000 X-chromosome single nucleotide polymorphisms (SNPs) with sex-associated BD traits in almost 2,000 samples and discovered that the X-chromosome variant rs5932307 is associated with BD with a stronger effect in females than males (Jons et al., 2019). Gonadal steroid hormones may also determine sex differences. Evidence has been accumulating to support the relationship between hormonal oscillations due to menstrual cycle; reproduction, and menopause and the course of BD (Gogos et al., 2019). Therefore, a link between female sex hormones (progesterone and estrogens) and the pathways of neuroprotection/neurodegeneration/neuroinflammation may be implicated in the psychobiological mechanisms of BD in females (Frey and Dias, 2014). It has been reported that euthymic BD females had increased circulating progesterone and allopregnanolone (an active metabolite of progesterone) during the luteal phase of the menstrual cycle (Hardoy et al., 2006). A small clinical trial also highlighted the efficacy of using synthetic progesterone for the treatment of acute mania (Kulkarni et al., 2014).

As a major product of progesterone, cortisol, one of the key stress hormones, has distinctly different responses in BD between the sexes. Systemic cortisol metabolism that influences blood cortisol levels and HPA axis functioning was found increased in BD (Steen et al., 2011). However, the increase correlated to sex-different clinical manifestations in BD. In males, the release of cortisol after mental challenges was blunted in BD patients compared to non-psychiatric controls, while in female patients, cortisol fluctuations were associated with the number of depressive episodes (Steen et al., 2011). Since the immune system response to stress can be suppressed by cortisol, inflammatory cell components in peripheral blood have also presented sex differences. For example, the neutrophil-to-lymphocyte ratio appeared to be a peripheral biomarker of (hypo)mania exclusive to males, while blood platelet counts appeared to be similarly exclusive to females (Fusar-Poli et al., 2021). In response to inflammation, the C-reactive protein further showed sex-specific associations with modulating cognition and real-world functioning. In males with BD, the C-reactive protein level in peripheral blood was related to psychosocial dysfunction (interpersonal relationships and financial functioning), while in their female counterparts, it was correlated with cognitive performance (immediate and delayed verbal learning, and verbal fluency) (Sanchez-Autet et al., 2018).

The potential associations between corticosteroids, gonadal hormones, and sex differences in psychotic features are worth further discussion. In the psychosis-risk period, males, but not females, who carried the catechol-O-methyltransferase (COMT) polymorphism rs4680 are more prone to develop psychotic-like symptoms (de Castro-Catala et al., 2015). It has been found that the COMT polymorphisms may alter the HPA axis function and cortisol secretion (Oswald et al., 2004). Male



**Fig. 1. Major patterns of sex differences between patients with bipolar disorder and controls within and across sex.** Nine possible forms of sex differences are summarized as follows: **a** Physical sex differences that are present in non-psychiatric controls but disappear in individuals with BD. **b** Sex differences that are present in BD but are absent in non-psychiatric controls. **c** Only one sex shows alterations in biological hallmarks between patients with BD and the controls. **d** The two sexes show opposite alterations in one biological symbol between patients with BD and the controls. **e** and **f** Pre-existing sex differences in BD can be reversed when a particular comorbid symptom, such as psychotic symptoms, emerge. **g** Two interrelated factors are altered in both sexes in BD, but their sequence of occurrence is switched between the two sexes. This example is referring to the biased preferences in the occurrence and consequence of BD and psychotic features in two sexes. **h** When compared to controls, both sexes display the same molecular changes in BD, but these changes were linked to different clinical symptoms in each sex (i.e., an elevated systemic cortisol metabolism was present in BD, but the release of cortisol after mental challenges was blunted in male BD patients, while cortisol fluctuations were associated with the number of depressive episodes in female patients). **i** Both sexes display the same alteration in BD, but they were driven by different pathogenic mechanisms.

patients with first-episode psychosis showed significantly lower cortisol awakening response (CAR) compared to male controls and female patients, which was related to the presence of positive symptoms and functional deficits (Pruessner et al., 2015). On the other hand, females with early psychosis had an increased CAR, which was related to poorer cognitive performance such as processing speed and verbal memory (Labad et al., 2016).

Elevated plasma prolactin in psychosis is another biological marker that shows sex-dependent characteristics in clinical symptoms. In female patients with emerging psychosis, the increased prolactin level was related to enhanced stress reactivity and higher vulnerability to developing psychotic features, possibly due to the modulation of progesterone and estradiol (Ittig et al., 2017; Camilletti et al., 2019). The incidence of hyperprolactinemia, an adverse drug event during psychosis treatments, was more frequent in females than in males (Sorup et al., 2020). Compared to female patients who presented prolactin fluctuations in the emerging phase, males with first episode early psychosis had higher prolactin levels and experienced more severe symptoms, impaired cognitive processing, and more intensive treatments (Hidalgo-Figueroa et al., 2022; Montalvo et al., 2018). The biological connections of cortisol and prolactin to psychosis displayed two sex-specific patterns, suggesting that psychotic features might drive distinct molecular

systems depending on sex (Montalvo et al., 2018).

## 6. Major patterns of sex differences in bipolar disorder

Sex influences every pathophysiological aspect of BD. As summed up in previous literature, theoretically, two main categories of sex differences in BD became apparent (Fig. 1). It should be noted that other psychiatric disorders may potentially display comparable patterns. One is the diagnosis-based divergences between sexes, such as physiological sex differences that were present in non-psychiatric controls and that disappeared in individuals with BD, or vice versa (Fig. 1a and b). The second type shows sex-based divergences between BD and controls, which can be divided into six subsets. First, only one sex shows alterations in biological hallmarks in BD compared to the controls (Fig. 1c). Second, the two sexes show opposite alterations in one biological symbol in BD compared to the controls (Fig. 1d). Third, with the emergence of a particular comorbid symptom, pre-existing sex differences in BD can be reversed (Fig. 1e and f). Fourth, two interrelated factors were altered in both sexes in BD, but their sequences of occurrence are switched between the two sexes (Fig. 1g). Fifth, when compared to controls, both sexes displayed the same changes in BD, but these changes were linked to different clinical symptoms in each sex (Fig. 1h). Sixth, both sexes displayed the same alterations in BD, but they might be driven by different pathogenic mechanisms (Fig. 1i). However, the molecular mechanisms behind the different types of sex differences in BD stem from etiological cell types, circuits and key brain regions that are largely unknown. Such information is important since it provides essential evidence for divergent therapeutic strategies between sexes.

## 7. Dorsolateral prefrontal cortex: A sex-dependent etiopathogenic region in bipolar disorder

Sex-associated cognitive and other clinical alterations in psychiatric disorders have their biological fingerprints in the human brain. Structural and functional neuroimaging studies have proposed that the DLPFC is a promising region involved in the etiopathogenesis of sex differences in BD (Mitchell et al., 2018; Jiang et al., 2021; Jogia et al., 2012). Recent studies have investigated individuals with BD by functional magnetic resonance imaging (fMRI), focusing on sex-by-diagnosis interactions on patterns of brain activation obtained during tasks for working memory, incentive decision-making, and facial affect processing (Jogia et al., 2012). They demonstrated that the prefrontal regions, which were integrated into the neurocircuits that regulated emotion and reward, were implicated in the crosstalk between sex and diagnosis in BD (Jogia et al., 2012). In addition, by structural MRI measuring gray matter volume, it is shown that BD may disrupt the inherent sex differences in brain structures involved in the prefrontal network as generally seen in non-psychiatric control subjects (Mitchell et al., 2018). A resting-state fMRI study further discovered that, so far, the DLPFC was the only cerebral structure that had a major effect on sex-by-diagnosis interactions involved in the dysfunction of the cortico-limbic neural system in BD (Jiang et al., 2021). The specific role of the DLPFC seems to be preserved even when psychotic features are comorbid. Structural neuroimaging studies of voxel-based morphometry have detected significant reductions in the gray matter of fronto-temporo-limbic structures in subjects at vulnerable states for psychosis, as well as the role of prefrontal abnormalities in relation to early risk and subsequent disease transition (Koutsouleris et al., 2009); which has been shown to be more pronounced in male patients than female patients (Rapado-Castro et al., 2015).

A related line of evidence supports the relationship between sex and BD therapies. In clinical practice, treatment with repetitive transcranial magnetic stimulation (rTMS) over the DLPFC is becoming a promising option for patients with BD. A meta-analysis of 54 sham-controlled studies published across 16 years has shown that the antidepressant properties of rTMS may depend on sex (Kedzior et al., 2014). Recent

studies further investigated the clinical and neuroimaging biomarkers associated with responsiveness to high-frequency rTMS over the DLPFC in a large cohort of patients with treatment-resistant depression, showing that more females than males, and patients with BD rather than patients with major depressive disorder (MDD) respond better (Harika-Germaneau et al., 2022). More evidence also indicated that these region-specific sex differences may be more obvious in BD than in MDD or schizophrenia (Zhang et al., 2021; Maniam et al., 2020; Huber et al., 2003; Zhang et al., 2020). A possible explanation could be that high levels of estradiol may facilitate cortical excitability (Hanlon and McCalley, 2022). A large-scale clinical study reported that serum estradiol levels in female patients with BD of reproductive age were two times higher than in male patients of the same age, irrespective of the mood episodes (Lyu et al., 2023). A clinical trial further showed that a greater neuroplastic response to TMS over the DLPFC is seen in females when estrogen is at its highest level compared to males, suggesting that endogenous estrogen levels contribute to variability in response to TMS (Chung et al., 2019). Therefore, the treatment response may be more effective in females with BD.

Another obvious explanation for the sex differences mentioned above is the role of sex-specific genetic factors underlying DLPFC function of BD patients. In the largest genome-wide genotype-by-sex analysis of mood and psychotic disorders to date, significant sex-dependent effects were found to be enriched for genes related to immune processes, neuronal development, and vascular functions in BD (Blokland et al., 2022). Our transcriptional analysis additionally validated this hypothesis by measuring the expression of glial genes in the DLPFC of BD versus the controls (Zhang et al., 2020). A remarkable sex difference was observed: most glial genes were expressed at significantly higher levels in male BD patients than in female patients. This applied to all three glial cell types (astrocyte, microglia, and oligodendrocyte) that were involved in a wide range of biomechanisms. A subset analysis additionally showed that the sex differences in glia genes were closely correlated with the presence of psychotic features. In addition, evidence also indicated that significant glial markers were related to suicide death, even independent of confounding factors. These findings implied that dysfunctional genomics in the DLPFC are stronger in males than females with BD, which may explain the clinically well-known sex differences.

Existing publications have provided substantial evidence supporting the molecular basis of sex differences in the DLPFC of BD patients, including but not limited to serotonin and dopamine transmission (aldehyde dehydrogenase 1 family member L1, *ALDH1L1*), purine (purinergic receptor *P2RY12*) and lipid metabolism (triggering receptor expressed on myeloid cells 2, *TREM2*, proteolipid protein, *PLP*), and cell proliferation. In addition, prolactin may be a pleiotropic factor in distinguishing BD males from females on glial expression, especially when psychotic features are comorbid. It has been shown that prolactin modulates glial cell proliferation by acting on its prolactin receptors expressed in glia (Anagnostou et al., 2018; Gregg et al., 2007; Ramos-Martinez et al., 2021). The higher level of prolactin in male versus female psychotic patients suggests its effect on a general upregulation of glial cells in the DLPFC.

In mechanistic genomics, we compiled a number of scenarios that contributed to these sex differences. For example, the risk for BD has sex-specific associations with the *serotonin transporter-linked polymorphic region* gene (*5-HTTLPR*), depending on its specific variants. In males with BD, only the ll (S+) polymorphism was found to be associated with the *dopamine D2 receptor* variant (Wang et al., 2014), while in female counterparts, the ss genotype was associated with higher impulsivity severity (Boscutti et al., 2022). Compared to the ll genotype which can express sufficient serotonin transporters (5HT-T), it has been shown that the ss genotype expresses less 5HT-T on the presynaptic site (Shinozaki, 2012). Consequently, excess extracellular serotonin may have been absorbed by glial cells in BD females that may mediate programmed glial cell death (Shinozaki, 2012; Persico et al., 2003). In addition,

linkage and association studies have implicated that the dopamine transporter gene *DAT1* in the etiopathophysiology of BD is specific to males, indicating sex differences with respect to predisposing polymorphic alleles and susceptibility to affection (Ohadi et al., 2007).

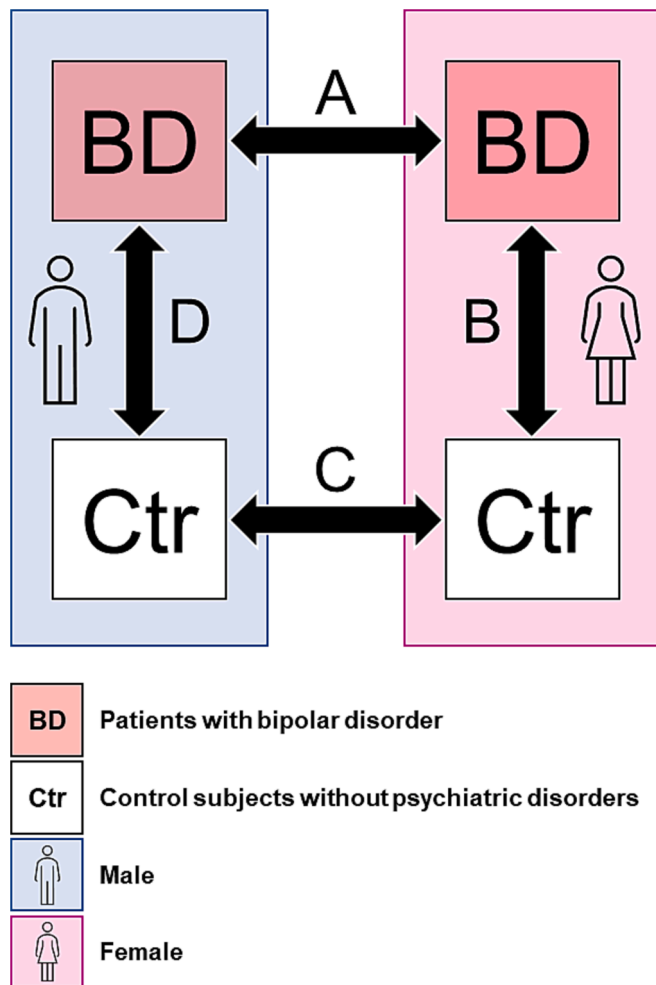
Available evidence suggests a special involvement of purinergic metabolism in sex differences in bipolar patients. A nuclear magnetic resonance-based metabolomic study has measured the urinary metabolite biomarkers of BD patients versus non-psychiatric controls and found that male and female BD patients have distinct biomarkers in urine, e.g., choline and formate in males versus oxalacetate and acetone in females (Chen et al., 2014). Such increased anabolism of choline and formate in male patients may elevate the concentration of tetrahydrofolate for purine synthesis, which is consistent with our finding in individuals with BD that the microglia-expressing purinergic receptor *P2RY12* has a higher expression in the DLPFC of males versus females (Zhang et al., 2020; Lamarre et al., 2013). Additional evidence refers to a large cohort genotyping study that the effects of purinergic receptor *P2RX7* variants (rs1621388 and rs2230912) on BD may be sex-specific, with increased *P2X7* activity substantially elevating the risk for BD only in females (Winham et al., 2019).

Cognitive impairments in female patients with BD have been related to GABAergic deficits. It has been suggested that low plasma GABA was a trait-related feature in episodes of BD (Petty et al., 1995). A clinical observation discovered that pretreatment plasma GABA was negatively correlated with the severity of manic symptoms, a relation that was stronger in females (Swann et al., 1999). As a major component that is strongly expressed in GABAergic interneurons, Reelin expression is decreased in the prefrontal cortex of BD (Torrey et al., 2005; Vilchez-Acosta et al., 2022). Genotyping analyses have provided preliminary support that genetic variation in Reelin is associated with susceptibility to BD and, in particular, to BD in females (F. Goes, V. Willour, P. Zandi, P. Belmonte, D. MacKinnon, F. Mondimore, B. Schweizer, N.I.o.M.H.G.I. B.D. Consortium, J. DePaulo Jr, and E. Gershon, 2010). The major types of glial cells are known to express functional metabotropic and ionotropic GABA receptors (Fraser et al., 1994; Liu et al., 2016; Serrano-Regal et al., 2020). Such an overall decrease in GABAergic signaling in neuron-glia interaction may be linked to the lower expression of glia-related genes in female patients with BD.

Clinical symptoms and peripheral biomarkers of people with BD differ by sex, yet there are discrepancies. As opposed to female patients who are more susceptible to concomitant metabolic diseases, males with BD have shown overall altered biosignatures in peripheral blood toward metabolic risks. A sex-specific genetic association has been found between polymorphisms of D-element binding protein, which is a candidate genetic marker for metabolic risk, and the severity of metabolic syndrome or obesity in male patients with BD (Kim et al., 2016). Plasma profiles of lipids have shown that in patients with BD, compared to females, males have a higher prevalence of disturbed lipid metabolism, also indicating a metabolic involvement underlying the BD etiology (Vemuri et al., 2011). Similarly, this relationship between metabolic factors and psychiatric symptoms in individuals with first-episode psychosis was sex-dependent, as a female-specific negative correlation was found between serum high-density lipoprotein levels and negative symptoms (Gjerde et al., 2021). The peripheral biosignatures of oxidative stress, which were implicated as both causative and consequential to concurrent metabolic disorders in adults with BD, are found to be significantly higher in BD males than in their female counterparts (Bengesser et al., 2015). Further evidence is needed to determine whether these sex-related changes were brain-derived.

## 8. A future perspective

Evidently, current limited knowledge merely provides a glimmer of explanation for the existing sex-dependent impact on bipolar patients, particularly on bipolar psychosis patients. An observation of the gene expression patterns and their interaction networks at the cellular and



**Fig. 2.** Divergent transcriptomes in the dorsolateral prefrontal cortex in males and females with BD. Differential gene expression results are dually compared: BD versus Ctr or male versus female: (A) BD-biased genes diverge between males and females. (B) Female-biased genes diverge between BD and Ctr. (C) Ctr-biased genes diverge between males and females. (D) Male-biased genes diverge between BD and Ctr.

subcellular level is essential for in-depth sex-directing cell biology in BD. Only a few studies have found transcriptional or proteomic signatures for sex differences and affective pathways with respect to human samples from donors with psychiatric disorders, with the majority of the findings being related to MDD or schizophrenia (Maitra et al., 2022; Lobentanzer et al., 2019; Tiuhonen et al., 2019; Talishinsky et al., 2022). Our previous findings have strongly indicated that the pathophysiology of BD differs between males and females, emphasizing the necessity to gain more basic knowledge of specific molecular changes. Given recent technical innovations, sex-related cerebral transcriptomics resulting from BD-perturbed biological networks can be captured with advanced measurement techniques such as bulk RNA sequencing (bulk RNA-seq) and single-nucleus RNA sequencing (snRNA-seq). However, there is no one-size-fits-all approach due to the low sensitivity of snRNA-seq data and the reduced specificity of bulk RNA-seq (Barrett et al., 2022).

Earlier bulk RNA-seq analysis of DLPFC specimens from BD patients has put forward dysregulation of neuroplasticity, circadian rhythms, and GTPase binding as putative target pathways for therapeutic interventions (Akula et al., 2014). Yet, such tissue-level approaches do not provide insights into the putatively differential involvement of distinct cellular (sub)populations in these observations. Moreover, altered cell type composition may impact the observed gene expression changes between BD and control individuals (Ramaker et al., 2017). Employing

snRNA-seq, significant associations with BD genetic risk were recently reported in excitatory, layer-specific DLPFC subpopulations, providing initial proof-of-concept that distinct cell type-specific molecular signatures may differentially contribute to BD pathophysiology (Tran et al., 2021). Of note, none of the studies described here has assessed the dependency of these findings on sex-specific variables; reversely, female subjects have been even underrepresented (Ramaker et al., 2017). Following such strategies, the differential expression patterns of sex-related transcripts in the DLPFC of BD patients and their matched controls can be profiled and analyzed (Fig. 2). Apart from the promising sex differences to be reported between males and females with BD, other three types of differential gene expression can be examined (Fig. 2).

## 9. Conclusions

Due to the asymmetry in research intensity between the clinical and biological literature that has controlled for sex, at present, we could merely provide our speculative explanation for the origin of sex disparities in clinical symptoms and cognitive impairments in BD. While there are highly promising preliminary findings, research on the pathophysiology of BD has yet to fully analyze the confounding factors, particularly psychotic features, and suicide in relation to sex. Transcriptomic approaches to study the neurobiology of BD in both sexes have been discussed. These techniques place a strong emphasis on discovering the key cells and molecules across psychiatric diagnoses as well as comorbidities based on diverse clusters of symptoms.

Despite the fact that the effect of female sex hormones and neurosteroids on BD is beginning to be understood, studies should evaluate treatments in terms of female hormonal fluctuations, such as entering puberty, menstrual cycle stage, menopausal stage, or use of hormonal contraception. There should be clinical and laboratorial consensus that, in BD research at multi-dimensional levels, data are analyzed including sex as a confounder.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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