Neural connectivity in youth at-risk for bipolar disorder: a review of functional magnetic resonance imaging studies

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REVIEW

Neural connectivity in youth at-risk for bipolar disorder: a review of functional magnetic resonance imaging studies

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Abstract

Background: Delayed diagnosis of bipolar disorder (BD) is common in adolescents and young adults and the search for biomarkers to help in early diagnosis in BD at-risk populations is an important goal of neuroimaging research. Functional connectivity studies in BD patients suggests that anomalous connectivity between prefrontal and limbic regions could be risk biomarkers for BD. The aim of this review is to provide an overview of the neuroimaging literature that employed functional connectivity techniques in adolescents and young adults at-risk for BD.

Methods: A literature search was conducted using PubMed and EMBASE databases, to identify fMRI studies that employed a measure of functional or effective connectivity or network based statistics and included individuals at-risk for BD who were in the age range of early-mid adolescence (13–18 years old) and/or young adulthood (19–25 years old).

Results: Ten studies focusing on 4 functional imaging domains were identified, namely emotion processing, affective cognition, reward processing and resting-state. Altered functional connectivity between amygdala and ventrolateral prefrontal cortex (PFC); amygdala and anterior cingulate cortex and between anterior cingulate cortex, ventrolateral PFC and dorsolateral PFC emerged as putative risk biomarkers. Heterogeneity in BD at-risk samples, tasks and connectivity analysis methods has been identified.

Conclusions: Youth at-risk for BD have altered functional connectivity in prefrontal-limbic networks supporting emotion regulation that might underlie emotion lability and mood dysregulation predisposing to BD. Future longitudinal studies in adolescents and young adults with Bipolar At-Risk criteria are important to establish functional connectivity measures as risk biomarkers.

Keywords: Bipolar Disorder, At-Risk, Functional Connectivity, fMRI.

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Introduction

Bipolar disorder (BD) is a lifelong illness, characterized by recurrent episodes of depressed, elevated and mixed mood states interpolated by euthymic periods [1]. It is a disabling illness due to its early onset, severity and chronicity [2], with around 75% patients having a first mood episode in adolescence or early adulthood [3]. This early onset and the associated level of disability places BD as the 4th leading cause of global disease burden in adolescents and young adults [4].

Efficacious psychopharmacological and psychosocial treatments are available [5], but delayed diagnosis is common [6]. Mental health services are increasingly adopting a strategy to diagnose and treat BD as early as possible [7,8], in order to prevent poor outcomes such as social and occupational disability and premature mortality from suicide and medical comorbidities [9-11]. However, the current approach to identify individuals at risk for BD, with an emphasis on clinical features, temperamental traits and family history, has insufficient predictive validity, with only a minority of 'at risk' individuals making the transition to BD [8,12,13]. The identification of biomarkers, a key goal of BD neuroimaging research, could increase the confidence of early diagnosis in adolescents and young adults [14].

Technical advances in neuroimaging methods have led to the conceptualization of the brain as a network of functionally connected and constantly interacting regions, requiring a focus on understanding patterns of connectivity as well as localized activation [15]. Task based connectivity analysis aims to assess changes in the strength of correlated activity among brain regions of interest when comparing different task conditions. In these analyses, it is important to distinguish undirected associations between brain regions (functional connectivity) from directed and causal relationships (effective connectivity) [16]. Resting-state functional connectivity studies are based on the collection of blood oxygenation level-dependent (BOLD) signal time-series in the absence of any task demands. The analysis of these data can take several forms, but all exploit the fact that brain regions with strong anatomical connections typically show organized spontaneous correlations in their functional activity over time [17]. A powerful tool for the study of functional brain networks is graph theory. Graph theory model the brain as a network comprised of nodes (voxels or brain regions) and edges (connections between nodes). This enables the analysis of functional interactions between every possible brain region, known as the functional connectome. Graph-theory metrics can be used to study the topological properties of such network. Network based statistics such as clustering-coefficient, characteristic path length, centrality, efficiency, modularity, among others, provide insights about functional integration, segregation, resilience or organization of the network as a whole or of its individual nodes [18,19].

Findings indicate a variety of different patterns of abnormal functional connectivity in individuals with BD, suggesting corticolimbic dysconnectivity as a possible biomarker [20]. Functional connectivity studies have focused predominantly on the amygdala and striatal-prefrontal cortical networks during emotional processing, emotional regulation, reward-processing and cognitive control tasks [21]. Several of these studies have shown, in individuals with BD, both abnormally increased positive functional connectivity between the amygdala and ventrolateral prefrontal cortex (PFC) or abnormally decreased inverse functional connectivity between these regions. Similar findings of enhanced connectivity have been observed using resting-state fMRI. Connectivity between the amygdala and medial prefrontal regions and between medial and lateral regions within the PFC has also been implicated in BD, but the direction of findings is less consistent. Recent studies have also demonstrated altered connectivity in reward-related networks, particularly the ventral striatum (VS) and its interactions with medial PFC [21].

However, studies in patients with BD do not allow the distinction of alterations linked to disease vulnerability from those associated with the clinical course, treatment and psychiatric comorbidities. Thus, one of the steps that is needed to elucidate neural network functional connectivity abnormalities in BD, include examination of the development of functional brain networks in youth at risk for BD, before the emergence of full-blown disorder. To our knowledge only one review reported results of functional connectivity analysis in relatives of patients with BD [22]. In this systematic review of 29 fMRI studies, the authors included 2 BD offspring studies that employed connectivity analyses (Psychophysiological Interaction – PPI). The authors concluded that first-degree relatives of BD patients showed changes in the same brain regions implicated in the pathophysiology of the disease in studies with BD patients, such as the inferior frontal gyrus (IFG), the medial PFC, the insula, the amygdala and the parietal lobe. However, this review focused in fMRI activation data and the authors considered the great heterogeneity of age range of the samples as a limitation of their study To date, there are no systematic reviews focused in fMRI connectivity data in at-risk populations at the peak age of incidence of BD.

The aim of this review is to provide an overview of the literature regarding findings from neuroimaging studies that employed functional connectivity techniques in samples with adolescents and young adults at-risk for BD.

Methods

Literature search

A computerized advanced search using the databases PubMed and EMBASE for articles published until 31 August 2017 was conducted using the following key search terms: "bipolar disorder" AND (at-risk OR high risk OR genetic risk OR offspring) AND "connectivity". The ref-

erence lists of articles meeting the inclusion criteria were also searched manually for relevant articles.

Study selection

Studies were included if they: (i) used fMRI (task based and/or resting state); (ii) employed a measure of functional or effective connectivity or network based statistics; (iii) included individuals in the age range of early-mid adolescence (13–18 years old), and/or young adulthood (19–25 years old); (iv) included a group of individuals with genetic or clinical risk for BD (offspring of patients with BD; youth with Bipolar at-risk criteria) and a comparison group; and (v) were published in English in a peer-review journal. We did not exclude studies where overlapping samples (i.e., the same cohort of patients) were used, although these will be identified as such when reviewed below.

Results

Figure 1 summarizes the review process. The search identified 127 studies. After removal of duplicates, screening and assessment for eligibility, 10 articles met the inclusion criteria and were selected for review. No additional article was found in the manual search. Most of the studies were conducted in adolescents [23-30] with only two studies conducted in young adults [31,32]. The samples of subjects at-risk for BD were comprised of healthy offspring of bipolar patients [25,28,29], healthy and symptomatic offspring of bipolar patients [24,26,27,30], symptomatic offspring of bipolar patients [23] and healthy and symptomatic offspring or siblings of bipolar patients [31,32]. Some studies were conducted by the same research groups, with partially overlapping samples [23,26,27,30][25,28,29][31,32].
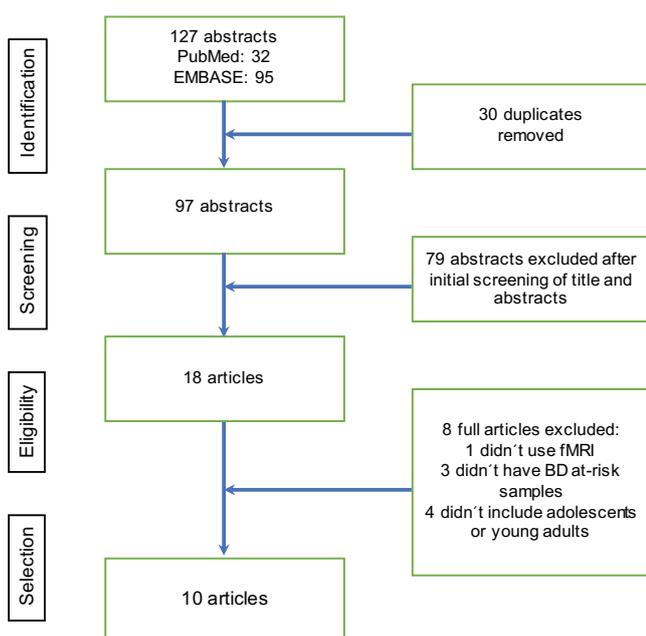
Figure 1. Flowchart of review process and study selection.

The studies focused in 4 functional imaging domains: 2 studies employed an emotion processing task [23,26]; 2 studies employed a cognitive-affective task [25,31]; 3 studies employed a reward processing task [27,28,30] and 3 were resting state fMRI studies [24,29,32]. **Table 1** resume the main methodological characteristics and results of the selected studies.

Emotion processing

Manelis and colleagues [26] performed a fMRI study with an implicit facial emotion processing paradigm, 'the dynamic faces task' [33]. The authors compared the functional connectivity between offspring of parents with BD, offspring of non-bipolar parents and controls, employing psychophysiological interaction (PPI) analysis. The seed region was the right amygdala and target regions comprise the anterior cingulate cortex, orbitofrontal cortex and ventrolateral PFC. They found that the offspring of parents with BD showed significantly more negative right amygdala-anterior cingulate cortex functional connectivity to emotional faces versus shapes, but significantly more positive right amygdala-left ventrolateral PFC functional connectivity to happy faces than the offspring of non-bipolar parents and controls.

In a recent study, Chang and colleagues [23] compared functional connectivity between symptomatic offspring of parents with BD and controls, using an explicit facial emotion processing task. Using psychophysiological interaction (PPI) analysis with the amygdala as the seed region and the rest of the brain as target regions, the authors found that the offspring of parents with BD, compared to the control group, had significantly greater connectivity between the amygdala and visual cortex and between the amygdala and right ventrolateral PFC.

Affective cognition

Ladoucer and colleagues [25] also employed psychophysiological interaction (PPI) analysis to measure functional connectivity in healthy offspring of parents with BD and controls, using ventrolateral PFC as seed region and the amygdala and dorsolateral PFC as target regions. An fMRI with an emotional working memory paradigm, 'the emotional face N-Back task' [34], was performed in both groups. With fearful face distracters, offspring of parents with BD, compared to the control group, had significantly reduced ventrolateral PFC modulation of the right amygdala. With happy face distracters, offspring of parents with BD had significantly reduced ventrolateral PFC modulation of the left amygdala and less functional connectivity between right ventrolateral PFC and left dorsolateral PFC.

Breakspear and colleagues [31] used a different method of connectivity analysis, dynamic causal modelling, to infer patterns of effective connectivity underlying the interaction of motor inhibition and fear perception. Using an emotional face go-no go task, the authors compared

Table 1. Main methods and results of functional connectivity studies in individuals at-Risk for BD.

First Author, Year	Participants (number, mean age)	Paradigm	Connectivity Analysis	Results in At-Risk BD
Breakspear, 2015 [31]	41 At-Risk BD (24,4) 55 BD (25,0) 45 HC (23,3)	Emotional face Go/No-Go task	Dynamic causal modeling	Marked difference in the hierarchical influence of the ACC from the DLPFC to the IFG
Chang, 2017 [23]	50 At-Risk BD (13,5) 29 HC (13,6)	Explicit facial emotion processing task	Psychophysiological interaction	Greater connectivity between the amygdala and 1) visual cortex and 2) right VLPFC
Collin, 2017 [24]	60 At-Risk BD (14,2) 28 At-Risk SZ (13,1) 23 HC (12,7)	Resting state	Graph theory analysis	No connectivity deficits of the brain's central rich club system. Increased coupling between structural and functional connectivity (SC-FC coupling) of long-distance connections
Ladoucer, 2013 [25]	16 At-Risk BD (14,2) 15 HC (13,8)	Emotional working memory task	Psychophysiological interaction	Reduced connectivity between VLPFC and the right amygdala with fearful face distracters and reduced connectivity between 1) VLPFC and the left amygdala and 2) right VLPFC and left DLPFC with happy face distracters
Manelis, 2015 [26]	29 At-Risk BD (13,8) 29 NBO (13,8) 23 HC (13,7)	Implicit facial emotion processing task	Psychophysiological interaction	More negative right amygdala-ACC functional connectivity to emotional faces versus shapes, but more positive right amygdala-left VLPFC functional connectivity to happy faces
Manelis, 2016 [27]	29 At-Risk BD (13,8) 29 NBO (13,8) 23 HC (13,7)	Card number guessing game	Psychophysiological interaction	Greater negative functional connectivity between the bilateral VS and the right VLPFC
Roberts, 2017 [32]	71 At-Risk BD (24,4) 49 BD (25,0) 80 HC (23,3)	Resting state	Graph theory analysis	Weaker functional connectivity between IFG and insular regions and the ACC
Singh, 2014 [28]	20 At-Risk BD (12,7) 29 HC (11,8)	Monetary incentive delay task	Psychophysiological interaction	Weaker functional connectivity between the pregenual ACC and the right VLPFC while anticipating rewards but stronger connectivity between these regions while anticipating losses
Singh, 2014 [29]	24 At-Risk BD (12,2) 23 HC (13,7)	Resting state	Independent component analysis (ICA) and region of interest (ROI) based intrinsic connectivity	ICA: increased connectivity in the VLPFC sub-region of the left ECN. ROI-based analyses: decreased connectivity between 1) the left amygdala and pregenual ACC, 2) the subgenual ACC and supplementary motor cortex, and 3) the left VLPFC and left caudate.
Sohener, 2016 [30]	25 At-Risk BD (13,8) 21 NBO (13,8)	Card number guessing game	Psychophysiological interaction	More VS-left posterior insula connectivity. Increased VS-left posterior insula connectivity and VS-left anterior insula/VLPFC connectivity were associated with greater mood dysregulation

ACC: Anterior Cingulate Cortex; BD: Bipolar Disorder; DLPFC: Dorsolateral Prefrontal Cortex; ECN: Executive Control Network; HC: Healthy Controls; ICA: Independent Component Analysis; IFG: Inferior Frontal Gyrus; NBO: Non-Bipolar Offspring; ROI: Region of Interest; SZ: Schizophrenia; VLPFC: Ventrolateral Prefrontal Cortex; VS: Ventral Striatum

four bilinear and four non-linear models of the effective connectivity between the nodes specified by the model: left fusiform gyrus and primary visual cortex for stimulus input, left anterior cingulate cortex for the effect of fear, left dorsolateral PFC for the effect of motor inhibition and left inferior frontal gyrus (IFG) for the interaction of fear and inhibition. The authors reported a marked difference in the hierarchical influence of the anterior cingulate on the effective connectivity from the dorsolateral PFC to the inferior frontal gyrus that is unique to the at-risk cohort, suggesting distinct brain network mechanisms for the integration of cognitive control and emotion perception in these clinical population.

The first study [28] that compared functional connectivity data between healthy offspring of parents with BD and controls using a reward processing task ('the monetary incentive delay task') employed psychophysiological interaction (PPI) analysis. The seed region was the pregenual cingulate and the target regions the bilateral amygdalae, insula, nucleus accumbens and ventrolateral PFC. Offspring of parents with BP had weaker functional connectivity between the pregenual cingulate and the right ventrolateral PFC while anticipating rewards than did controls but had a stronger connectivity between these regions while anticipating losses.

Manelis and colleagues [27] compared the functional connectivity between offspring of parents with BD, offspring of non-bipolar parents and controls, employing psychophysiological interaction (PPI) analysis to data of an fMRI study with a reward processing paradigm, 'the card number-guessing game' [35]. The seed region was bilateral ventral striatum and the target regions comprised bilateral

anterior cingulate cortex, medial PFC, orbitofrontal cortex, ventrolateral PFC and insula. There was a significant main effect of group on functional connectivity between the bilateral ventral striatum and the right ventrolateral prefrontal cortex, with the offspring of parents with BD showing significantly greater negative functional connectivity than other participants.

Using the same reward processing paradigm and the same method of functional connectivity analysis, Soehner and colleagues [30] compared the offspring of parents with BD with the offspring of non-bipolar parents and correlated the functional connectivity results with sleeping and mood dysregulation data obtained from psychometric instruments. The authors found that the offspring of parents with BD showed significantly more ventral striatum-left posterior insula connectivity than offspring of non-bipolar parents. Sleep duration and ventral striatum-left anterior insula/ventrolateral PFC connectivity were negatively related in the offspring of parents with BD, but positively related in the offspring of non-bipolar parents. Additionally, increased ventral striatum-left posterior insula connectivity and ventral striatum-left anterior insula/ventrolateral PFC connectivity were associated with greater mood dysregulation only in the offspring of parents with BD.

Resting state fMRI

Singh and colleagues [29] compared resting state fMRI data between the offspring of parents with BD, offspring of non-bipolar parents and controls, using two connectivity analysis methods: data-driven independent component analysis (ICA) and hypothesis-driven region-of-interest (ROI) based intrinsic connectivity. In the ROI analysis, the authors have selected neural circuits that underlie emotional and inhibitory control: the left and right amygdala, the left and right ventrolateral PFC, and the subgenual anterior cingulate. Four out of the 25 group functional networks, including the dorsal and ventral default mode (DMN) and the executive control (ECN) networks, were selected a priori. ICA revealed that, relative to low-risk youth, high-risk youth showed increased connectivity in the ventrolateral PFC subregion of the left executive control network (ECN), which includes frontoparietal regions important for emotion regulation. ROI-based analyses revealed that high-risk versus low-risk youth had decreased connectivity between the left amygdala and pregenual cingulate, the subgenual cingulate and supplementary motor cortex, and between the left ventrolateral PFC and left caudate.

Roberts and colleagues [32] performed between-group analyses of the left IFG functional connectivity and used graph theory to study its local functional network topology. Machine learning was used to study classification based solely upon the functional connectivity of the IFG. In BD patients, the left IFG was functionally disconnected from a network of regions including bilateral insula, ventrolateral prefrontal gyri, superior temporal gyri and the putamen. A small network incorporating neighboring insular regions

and the anterior cingulate cortex showed weaker functional connectivity in at-risk for BD subjects when compared to controls. These regions overlapped with frontolimbic regions which a machine learning classifier selected as predicting group membership with an accuracy significantly greater than chance.

In a recent multimodal imaging study, Collin and colleagues [32] performed resting state fMRI and diffusion-weighted MRI scans to compare the structural and functional connectome in offspring of bipolar patients, offspring of schizophrenia (SZ) patients and controls. Anatomical and functional brain networks were reconstructed and examined using graph theoretical analysis to study anatomical connectome topology, rich club organization and functional communities. The authors also analyzed structural-functional coupling between at-risk groups and controls. The SZ offspring were found to show connectivity deficits of the brain's central rich club system relative to both controls and the BD offspring. The disruption in anatomical rich club connectivity in SZ offspring was associated with increased modularity of the functional connectome. In addition, increased coupling between structural and functional connectivity (SC-FC coupling) of long-distance connections was observed in both SZ and BD offspring. The finding of no rich club deficits in the offspring of BD patients suggest a differential effect of genetic predisposition for schizophrenia versus bipolar disorder on the developmental formation of the connectome.

Discussion

In this article, we have systematically reviewed the available fMRI functional and effective connectivity studies in adolescents and young adults at-risk for BD, to provide a comprehensive account of the literature to date. Collectively, the literature provides evidence for a role of frontolimbic network anomalous connection patterns in the development of BD. The findings are consistent with reviews of functional connectivity neuroimaging research in patients with BD [20,21] which suggests that alterations of functional connectivity are putative risk biomarkers for the disorder.

Altered functional connectivity between prefrontal regions, including the ventrolateral PFC, dorsolateral PFC and anterior cingulate cortex (ACC), as well as closely related subcortical areas including the amygdala, ventral striatum and insula, were present during tasks of emotional processing, affective cognition, reward-based decision-making and resting-state conditions in samples with healthy and symptomatic offspring of parents with BD. These results are compatible with the consensus model of the functional neuroanatomy of BD [36] which hypothesized that the disease arises from dysfunction of brain networks that modulate emotional behavior. In this model, two ventral prefrontal networks are similarly organized to form iterative feedback loops that process information and modulate the amygdala

and other limbic brain areas. One network originates in the ventrolateral PFC and modulate emotion states generated by external emotional cues, such as with affective face tasks. The other network originates in the ventromedial PFC (orbitofrontal cortex) and modulate emotional states generated by stimuli that arise from internal feeling states, such as paradigms that involve inducing an emotional response to personalized events. Additionally, different voluntary and automatic emotion regulation subprocesses have been identified, centered on the ventrolateral and ventromedial prefrontal cortices, respectively.

Despite the variability of results related to heterogeneity of the samples, connectivity analysis techniques and tasks, three frontolimbic dysconnectivity patterns emerged: altered connectivity between the ventrolateral PFC and the amygdala, altered connectivity between the ACC and the amygdala and altered connectivity between the ventrolateral PFC, dorsolateral PFC and ACC. Altered connectivity between the ventrolateral PFC and the amygdala, with individuals at-risk for BD showing more functional connectivity between these regions during emotion processing tasks [23,26] and less functional connectivity during affective cognitive tasks [25], partially overlaps with findings of abnormally heightened functional connectivity between the amygdala and ventrolateral PFC during rest or emotional processing in BD patients [21]. Abnormally high connectivity between the amygdala and ventrolateral PFC may represent a lack of flexibility to incorporate feedback from other neocortical areas, such as the dorsolateral PFC and ACC, that may predispose youths to the development of mood dysregulation and eventually BD [37]. This is also compatible with findings in BD at-risk subjects of more negative right amygdala—ACC functional connectivity during emotional processing tasks [26], decreased connectivity between the left amygdala and pregenual cingulate [29] in resting state and prefrontal dysconnectivity patterns during emotional cognition tasks [25,31] and resting state [29,32].

Ventrolateral PFC (and the partial overlapping region of Inferior Frontal Gyrus) emerged as an important node of the frontolimbic networks showing functional connectivity alterations in adolescents and young adults at-risk for BD, with reports of altered functional connectivity in studies of all functional domains (emotional processing, affective cognition, reward processing and resting state studies). The ventrolateral PFC is implicated in psychological processes of emotion self-regulation [38] and social regulation of emotion [39]. Emotion regulation can be conceptualized in terms of multiple valuation mechanisms and is initiated by a second-order valuation system that assigns value to the emotional feelings that were generated by a first-order valuation system [38]. In this model, emotion generation results from an initial perception-valuation-action (PVA) cycle, and emotion regulation results from a second PVA cycle that takes the initial emotion as the target of perception that is itself evaluated. When there is a discrepancy between desired and actual emotions, specific emotion regulation strategies (situation selection or modification; attentional deployment; reappraisal; response modulation) are then evaluated to determine which to implement. Ventrolateral PFC may contribute to these high-level appraisal mechanisms that assign value to ongoing emotional states and to emotion regulatory strategies [40] and anomalous patterns of functional connectivity with other cortical and subcortical brain regions could be a neural substrate of emotional lability and mood dysregulation in BD at-risk individuals.

One important limitation of the studies included in this review is that some subcortical and prefrontal regions were analyzed as a single brain region, despite important subdivisions with different functions and connectivity profiles. The amygdala has distinct subregions with structurally and functionally distinct nuclei. The primary nuclei complexes— basolateral (BL) and centromedial (CM)— have been found to have different patterns of connectivity with prefrontal and subcortical networks during the processing of emotional material, with the CM complex typically connecting with sensory and autonomic areas and the BL complex connecting with motor and prefrontal areas [41]. Similarly, the ACC has important subdivisions, with different profiles of functional connectivity and functional specialization [40]. Subgenular ACC is important for the appraisal of viscero-motor signals based on anticipated interaction with the environment and drives changes in physiological arousal while the pregenular ACC is relatively specialized in the appraisal of viscero-sensory signals based on conceptual meaning and implications for self, contributing to subjective feelings of pleasure and displeasure. The dorsal ACC appears to be preferentially in appraisal of actions based on expected outcomes, motor costs, task context and social goals [40]. Future functional neuroimaging connectivity studies in BD at-risk populations should take into account these different subdivisions in order to provide a more detailed understanding of the developmental trajectory of functional connectivity anomalies predisposing to BD.

Another limitation found in this review is the absence of studies in high-risk clinical populations without family history of BD. Although BD has a high heritability [42,43], the presence of a positive family history does not have a good clinical utility for case finding in adolescents and young adults with a history of depressive episodes, due to their low prevalence in general psychiatric samples and because a significant proportion of the offspring of BD patients will continue to suffer from depressive disorder. Other temperamental characteristics, such as cyclothymia, have a better clinical utility for case finding in depressed youth at-risk of early transition for BD [13]. Neuroimaging studies in adolescents and young adults with a history of depressive episodes, assessed with dimensional measures of cyclothymia and categorical Depression Bipolar At-Risk (BAR-D) criteria, are an important future research avenue to find functional connectivity risk markers that predict future conversion to BD.

There is also a clear need for longitudinal studies, with cohorts of adolescents and young adults with BAR-D criteria, integrating functional connectivity data from neuroimaging studies with clinical information and data from peripheral blood-based and smartphone-based electronic biomarkers [44]. Machine learning techniques may also be used to assess individuals at risk for BD, transforming data into applicable information about the individual risk for conversion to BD. In this sense, machine learning may allow to develop personalized interventions to prevent the transition from at-risk states to full-blown illness [45].

Conclusion

In summary, the findings of this qualitative systematic review in youth at-risk for BD are compatible with the consensus model of the functional neuroanatomy of BD [36] and are also consistent with reviews of functional connectivity neuroimaging research in patients with BD [20,21] which suggests that alterations of functional connectivity are putative risk biomarkers for the disorder. Ventrolateral PFC emerged as an important node of the frontolimbic networks showing functional connectivity alterations in adolescents and young adults at-risk for BD. The ventrolateral PFC role in high-level appraisal mechanisms that assign value to ongoing emotional states and to emotion regulatory strategies could be impaired due to anomalous patterns of functional connectivity with other cortical and subcortical brain regions, underlying the emotional lability and mood dysregulation predisposing to BD in at-risk adolescents and young adults.

Abbreviations

ACC: Anterior Cingulate Cortex; BAR-D Bipolar At-Risk Depression; BD: Bipolar Disorder; BL: Basolateral; BOLD: Blood Oxigenation Level Dependent; CM: Centromedial; DMN: Default Mode Network; ECN: Executive Control Network; fMRI: Functional Magnetic Resonance Imaging; ICA: Independent Component Analysis; IFG: Inferior Frontal Gyrus; MRI: Magnetic Resonance Imaging; PFC: Prefrontal Cortex; PPI: Psychophysiological Interaction; PVA: Perception-Valuation-Action; ROI: Region-of-Interest; SC-FC: Structural-Functional; SZ: Schizophrenia; VS: Ventral Striatum

Competing interests

The authors declare no conflict of interest.

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