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Research article

Unearthing the hidden links: Investigating the functional connectivity between amygdala subregions and brain networks in bipolar disorder through resting-state fMRI

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ABSTRACT

Introduction: Bipolar disorder is a multifaceted psychiatric condition characterized by fluctuating activity levels and dysfunctional mood states, oscillating between manic and depressive episodes. These mood disturbances are accompanied by persistent functional and cognitive impairments, even during periods of euthymia. Prior studies have underscored the critical role of amygdala activity in the pathophysiology of bipolar disorder. This research aims to utilize resting-state functional Magnetic Resonance Imaging (rs-fMRI) to explore the functional modifications in the six sub-regions that compose the amygdala of individuals diagnosed with bipolar disorder.

Method: The study encompassed 80 participants, bifurcated into two groups: 40 individuals with bipolar disorder and 40 healthy controls. Each group comprised an equal gender distribution of 20 females and 20 males, ranging in age from 21 to 50 years. Using rs-fMRI, we examined the functional connectivity within six amygdala sub-regions across eight regional functional networks.

Results: Comparative analysis between the control group and the bipolar patients revealed that all six amygdala sub-regions demonstrated connectivity with the eight functional brain networks. Notable similarities and disparities were observed in the connectivity patterns between the bipolar group and controls, particularly within the amygdala's sub-regions and other brain networks. The most significant functional connectivity alterations were found with the salience network and the default mode network. Additionally, alterations in the functional connectivity between the amygdala, sensory-motor, and visual networks were noted in bipolar patients.

Conclusion: The study's findings highlight the distinct patterns of resting-state functional connectivity of the amygdala and various brain networks in differentiating bipolar patients from

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healthy controls. These variations suggest the existence of multiple pathophysiological mechanisms contributing to emotional dysregulation in bipolar disorder.

1. Introduction

Bipolar disorder (BD) is a common mental health condition that disrupts neural function and can alter brain structures [1]. Characterized by alternating periods of depression and mania, it often involves functional and cognitive deficits persisting into periods of euthymia [2]. While the onset of the first manic or depressive episode typically occurs during adolescence or early adulthood [3], the exact etiology remains elusive, with a tendency towards familial inheritance [3]. Manic episodes are marked by social and occupational impairments, heightened energy, and an excessively elevated mood. Conversely, depressive episodes are primarily characterized by a pervasive low mood, sleep disturbances, and a decline in social functioning [2]. Euthymia in BD is described as a stable mental state, free from the extremes of mania and depression, with patients spending approximately 50 % of their lives in this phase [2]. However, even during euthymia, significant neurocognitive deficits are observed, impacting psychomotor speed, executive control, verbal memory, and sustained attention, thereby affecting socio-occupational functioning [2]. The underlying mechanisms of the euthymic phase are not well understood [4]. The incidence of BD is as high as 4–5% in the population, and around 90 % of patients with these disorders will experience a relapse or recurrence of their symptoms over time [5].

BD is associated with increased mortality rates due to both natural and unnatural causes, including suicide [6]. Early diagnosis and treatment are crucial in reducing these mortality rates [6]. Neuroimaging techniques such as PET, MRI, fMRI, and MRS have been instrumental in investigating the neuroanatomy and function of BD, leading to significant insights into its neural underpinnings [7]. Morphometric neuroimaging, in particular, helps identify specific neuroanatomic abnormalities that may differentiate BD patients from healthy individuals and those with other psychiatric conditions [7]. Despite the recognition of BD's neurological basis, its neurobiological mechanisms remain partially understood, posing challenges to developing new treatments [2].

Task-based fMRI and resting-state functional connectivity (rsFC) studies consistently reveal abnormal activity in brain regions associated with cognitive and emotional processing in BD patients [8]. Research indicates that BD is characterized by morphological and functional connectivity changes in various brain regions, such as the amygdala, prefrontal cortex, and striatum [9]. The amygdala, vital for emotional processing, is a key structure in studying BD pathophysiology [10], with abnormal amygdala activation significantly influencing BD [2] Furthermore, meta-analyses provide robust evidence supporting these findings. A comprehensive meta-analysis by Chen et al. (2022) examined both functional and structural brain differences in BD, revealing increased resting-state functional activity in regions such as the left middle frontal gyrus, right inferior frontal gyrus (IFG) extending to the right insula, right superior frontal gyrus, and bilateral striatum. Decreased activity was observed in the left middle temporal gyrus extending to the left superior temporal gyrus and post-central gyrus, left cerebellum, and bilateral precuneus. Additionally, voxel-based morphometry (VBM) meta-analyses showed decreased VBM in regions including the right IFG extending to the right insula, temporal pole and superior temporal gyrus, anterior cingulate cortex, left superior frontal gyrus (medial prefrontal cortex), left thalamus, and right fusiform gyrus. These findings suggest that BD exhibits similar patterns of aberrant brain activity and structure in the insula extending to the temporal cortex, fronto-striatal-thalamic, and default-mode network regions, providing valuable insights into the underlying pathophysiology of BD [11]. Furthermore, meta-analyses provide robust evidence supporting these findings. A comprehensive meta-analysis by Chen et al. (2022) examined both functional and structural brain differences in BD, revealing increased resting-state functional activity in regions such as the left middle frontal gyrus, right inferior frontal gyrus (IFG) extending to the right insula, right superior frontal gyrus, and bilateral striatum. Decreased activity was observed in the left middle temporal gyrus extending to the left superior temporal gyrus and post-central gyrus, left cerebellum, and bilateral precuneus. Additionally, voxel-based morphometry (VBM) meta-analyses showed decreased VBM in regions including the right IFG extending to the right insula, temporal pole and superior temporal gyrus, anterior cingulate cortex, left superior frontal gyrus (medial prefrontal cortex), left thalamus, and right fusiform gyrus. These findings suggest that BD exhibits similar patterns of aberrant brain activity and structure in the insula extending to the temporal cortex, fronto-striatal-thalamic, and default-mode network regions, providing valuable insights into the underlying pathophysiology of BD [11].

The amygdala is a small, almond-shaped structure located within the cerebral hemisphere of all vertebrates. Traditionally, most studies have focused on the amygdala as a single region, but recent research highlights the need to examine its sub-regions separately due to distinct anatomical and functional characteristics. The amygdala is composed of multiple distinct sub-regions or nuclei, each involved in various specific functions, such as perceiving and processing sensory information, regulating emotions, cognitive processing, and generating behaviors adapted to environmental conditions. Understanding the physiology and functional role of these sub-regions is crucial given their involvement in both normal brain function and the pathogenesis of specific neurological and psychiatric diseases [11–13]. This study classifies the amygdala, based on The JuBrain Anatomy Toolbox [14–17]. Into six sub-regions: Centro-medial complex (CM), Intermedia fiber (IF), Latero-basal (LB), Medial fiber (MF), Superficial (SF), and Ventromedial (VTM). Each of these sub-regions within the amygdala have distinct locations, structures.

The brain networks are groups of regions in the brain that have correlated activity at rest or during task performance. In recent studies, the pathophysiological mechanisms of bipolar disorder (BD) were investigated by building functional brain networks and looking for abnormal communication between them. Due to the neurobiological nature of BD, it is essential to investigate the disease-associated structural and functional brain changes. The investigated networks are: The default mode network (DMN): The global DMN is involved in a variety of cognitive and affective processes, including emotional processing, self-referential mental activity, mind

wandering, and experience recall. It may also play a modulatory role during attention-demanding tasks [13,18]. The salience network (SN): The salience network, comprising specific brain regions, detects and prioritizes significant environmental stimuli. It directs attention to both external (e.g., loud noises, sudden movements) and internal (e.g., hunger, pain) events, while integrating sensory inputs, emotional responses, and cognitive processes. This prioritization aids decision-making and behavior control [12,18]. The fronto-parietal network (FPN): Regions of the brain play a pivotal role in various functions, encompassing motor control, cognitive processing, language production and comprehension, sensory perception, and visuospatial integration. Specifically, the prefrontal cortex handles advanced cognitive tasks like decision-making and problem-solving, whereas the parietal lobe manages sensory data integration, spatial awareness, attention, and aids in language comprehension [5,19]. The cerebellar network (CN): This network is critical for coordinating and fine-tuning motions, balance, and posture. It receives data from sensory systems such as the vestibular system and proprioceptive receptors and integrates it to aid in smooth and coordinated movement [20]. The language network (LN): This network incorporates a bunch of cerebrum districts critical for different language-related capabilities, including discourse creation, cognizance, and semantic handling [21]. The dorsal attention network (DAN): The main role of this network is to guide attention towards external stimuli and organize goal-oriented actions. It specializes in top-down attentional processes, where attention is consciously directed according to task requirements or objectives. By filtering out distractions and sharpening the focus on pertinent information, the DAN aids in effective task execution [22,23]. The visual network (VN): The brain's visual network processes information from the eyes, enabling us to perceive and understand our surroundings. It comprises various brain regions collaborating to analyze visual stimuli. One vital function is object recognition, where objects and shapes are identified and categorized based on visual features, helping us recognize familiar items like faces and animals [24]. Finally, the sensorimotor network (SMN): This network integrates sensory input and orchestrates motor responses. Comprising diverse brain regions, it processes external stimuli (sensory information) and generates suitable motor actions, crucial for tasks like movement, balance, and engaging with the environment [25].

The amygdala, central to emotional regulation, shows hyperactivity during manic episodes, possibly contributing to symptoms. The study findings indicate that altered connectivity within amygdala sub-regions is crucial in bipolar disorder (BD) pathophysiology, highlighting fundamental differences compared to control subjects [26]. Significant disruptions were noted in bilateral CM-VTM connectivity, with BP showing a loss of the typical strong connection between right VTM and right CM, and weaker left VTM-right CM connectivity compared to controls and that suggesting dysregulation affecting emotional reactivity and cognitive control [26]. Additionally, alterations in default mode network (DMN) functioning, particularly during depressive episodes, are implicated in the pathophysiology of bipolar disorder (BD), affecting cognition and emotion processing [24,27]. Dysregulation in the sensorimotor network (SMN) and visual network (VN) is observed, impacting motor control, attention, and visual processing ([28,29]. The salience network (SN) dysfunction, especially during mood episodes, affects behavior regulation [30,31]. Lastly, disruptions in frontoparietal regions, crucial for various functions including motor control and language comprehension, are associated with BD, potentially contributing to its cognitive impairments. These findings emphasize the complex neural alterations underlying BD, highlighting the involvement of multiple brain networks in its pathophysiology. The heterogeneity of neuroimaging methods and the resulting findings underscore the need for standardization in the field to better translate these insights into consensual biological markers of disease.

This study aims to examine the functional connectivity changes in the amygdala's sub-regions and their association with other brain networks, to understand the diverse pathophysiological pathways underlying emotional dysfunction in BD. Specifically, this study will classify the amygdala into six sub-regions: Centro-medial complex (CM), Intermedia fiber (IF), Latero-basal (LB), Medial fiber (MF), Superficial (SF), and Ventromedial (VTM), and investigate their functional connectivity with eight related functional networks are the default mode network, the salience network, the language network, the fronto-parietal network, the dorsal attention network, the sensorimotor network, the visual network, and the cerebellar network.

2. Materials and methods

2.1. Subject selection and scanning

The data were sourced from the Open fMRI database (https://openfmri.org/dataset/ds000030/, UCLA Consortium for Neuropsychiatric Phenomics LA5c Study), with the dataset identifier *ds000030 and version 1.0.2*. This dataset is known for its open accessibility, public availability, and lack of usage restrictions. The study encompassed *80* participants, divided into two cohorts: *40* individuals diagnosed with bipolar disorder and *40* healthy controls (HC). Each group was balanced in terms of gender, comprising *20* females and *20* males, aged between *21* and *50* years.

The researchers recruited participants for the study through community advertisements in the Los Angeles area. The participants underwent extensive neuropsychological testing as well as functional MRI (fMRI) scans. To be eligible for inclusion in the study, individuals had to self-identify as either "White, Not of Hispanic or Latino Origin" or "Hispanic or Latino, of Any Race" based on the racial/ethnic categories defined by the National Institutes of Health (NIH). Participants were also required to have at least *8* years of education, as other racial/ethnic groups were excluded from the study in order to reduce potential confounding factors for the planned genetic analyses. For bilingual participants, the language used for the testing procedures was determined based on an assessment of their verbal fluency. Participants went through a thorough screening process to exclude those with certain medical and psychiatric conditions. Individuals were screened out if they had any neurological diseases, a history of head injuries, current use of psychoactive medications, recent substance dependence, a history of major mental illness or ADHD, or current mood or anxiety disorders. The researchers verified self-reported psychiatric history using the Structured Clinical Interview for DSM-IV (SCID-IV), and also conducted drug screening via urinalysis to exclude anyone who tested positive for substances like cannabis, amphetamines, opioids, cocaine, or benzodiazepines. For the fMRI portion of the study, participants had to have successfully completed all previous testing and also meet

additional exclusion criteria. This included having no significant medical illnesses, no MRI contraindications, not using any mood-altering medications on the scan day, having no vision issues that would prevent them from seeing the task stimuli, and not being left-handed [32,33,34].

Imaging was conducted using a Siemens *3-T Trio scanner. Parameters for T1-weighted MPRAGE - BWM images included a repetition time (TR) of 2.53 s, echo time (TE) of 3.31s, a matrix size of 256 × 256, a flip angle of 7°, a total scan time of 363s, and 255 phase encoding steps. For the resting-state fMRI (BOLD–RESTING) sequence, the acquisition parameters were TR = 2.0 s, TE = 3s, matrix size 64 × 64, flip angle 90°, total scan time 312s, and 63 phase encoding steps.*

2.2. Pre-processing & statistical analysis

Pre-processing and statistical analyses were conducted using CONN and Cytoarchitecture atlases [14–17]. The rsfMRI imaging volumes underwent standard pre-processing steps: slice timing corrections, realignment of functional volumes, normalization to an MNI template using structural data, outlier detection using ART tools in CONN, and smoothing with an 8-mm kernel. Temporal processing and data denoising were also performed to eliminate artifacts and confounds from the BOLD signal, such as those arising from white matter, CSF signals, motion, and scrubbing parameters.

2.3. Region of interest selection

The study focused on six amygdala sub-regions, divided into right and left hemispheres: Centro-medial complex (CM), Intermedia fiber (IF), Latero-basal (LB), Medial fiber (MF), Superficial (SF), and Ventromedial (VTM), as depicted in Fig. 1. These regions were identified using the SPM anatomy toolbox. The major collections of functional networks targeted in this study, defined in CONN, included the default mode, sensorimotor, visual, salience, dorsal attention, frontoparietal, language, and cerebellar networks.

3. Statistical analysis

This study implemented a two-level statistical analysis for each participant. At the first level (individual level), weighted general linear bivariate correlation models were used to generate connectivity matrices. These matrices were based on Fisher-transformed bivariate correlation coefficients between time series data from pre-defined regions of interest (ROIs). The analysis then progressed to the second level (group level), where functional connectivity measures were calculated and compared. This comparison utilized group-level statistical methods, such as T-tests and F-tests, as deemed appropriate.

Additionally, the study identified and compared rsfMRI network connections associated with each amygdala sub-region at the group level. To maintain rigorous statistical standards, a corrected false discovery rate (FDR) of $p < 0.05$ was employed (using multivariate statistics parametric (MVPA) omnibus tests). Cluster-level inferences were drawn using multivariate parametric statistical inferences, which considered the functional network connectivity in relation to grouped ROIs or networks. The analysis encompassed a comprehensive examination of all connections between the ROIs, both within individual networks and across multiple networks. This approach facilitated an efficient multivariate parametric generalized linear model analysis across the entirety of the connectivity data.

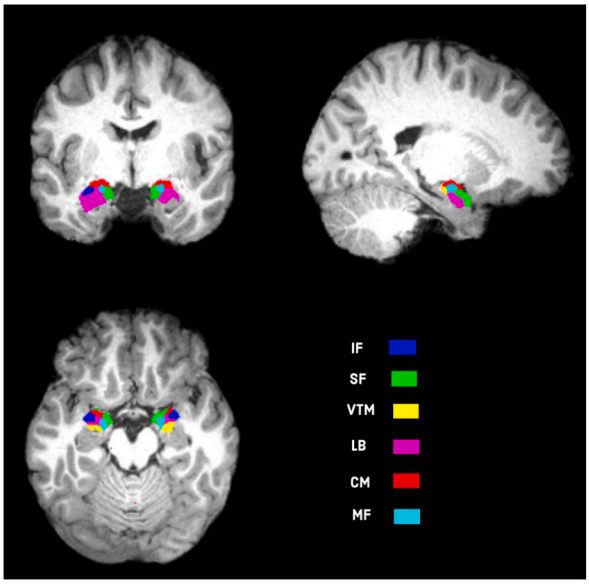

Fig. 1. Illustrations of the six sub-regions of amygdala.

4. Results

Figs. 2 and 3 reveal how sub-regions are connected. Additionally, the statistically distinct strength of each connection is exhibited in the figures. Positive connectivity is indicated by the red lines of the connections, whose colors are proportional to their statistical strength. All the sub-regions have positive connectivity. Nevertheless, there are differences in strength, either strong or weak connections between control and bipolar patients.

Bipolar patients exhibit altered functional connectivity compared to healthy controls across sub-regions of amygdala. The right IF shows stronger connectivity with left MF, left LB, and right VTM, as well as bilateral SF. The left IF has stronger connectivity with the left SF, but weaker connectivity with right LB, right CM, right MF, and bilateral VTM. The right SF shows stronger connectivity with right IF, left MF, and left VTM, but weaker connectivity with right MF, right LB, and right VTM. The left SF demonstrates stronger connectivity with right and left IF, left MF, right LB, and left VTM, but weaker connectivity with right MF and bilateral CM. The right VTM has stronger connectivity with right IF and right CM, but weaker connectivity with right SF, left IF, right and left MF, and bilateral LB. Bipolar patients also exhibit a loss of connectivity between right VTM and left CM. The left VTM shows stronger connectivity with left MF, bilateral SF, and bilateral LB, but weaker connectivity with left IF and right CM. The bilateral LB, as well as the bilateral CM, demonstrate a mix of stronger and weaker connectivity patterns in bipolar patients compared to controls.

The positive and negative connections of the amygdala and other brain networks are exhibited in Figs. 4 and 5. The results indicate several key differences in functional connectivity between the IF and other brain networks in control subjects versus bipolar patients. In the right IF region, control subjects showed positive connectivity with the right and left lateral sensorimotor network, the right salience insula, the default mode MPFC, and the right language pSTG, while bipolar patients had positive connections with the left salience insula, the right default mode LP, the right and left language pSTG, and the cerebral anterior. Additionally, control subjects had negative connections between the right IF and right LPFC, right PPC, and left PPC in the fronto-parietal network, which were absent in bipolar patients. Similarities were found in positive connectivity between the left IF and the bilateral lateral sensorimotor network across both groups. However, differences emerged in the left IF connectivity with the salience, language, and default mode networks. Control subjects exhibited positive connections with the right salience insula, the right language IFG, and the default mode MPFC, whereas bipolar patients showed positive connections with the left salience insula and SMG, the left language IFG and right pSTG. Interestingly, bipolar patients also displayed a negative connection between the left IF and the visual occipital network, which was not observed in controls (see Fig. 6).

The analysis of functional connectivity in the right SF reveals both similarities and differences between control subjects and bipolar patients. Positive connectivity was similar between the groups in the bilateral lateral sensorimotor network as well as the right language pSTG. However, differences emerged in connectivity with the default mode network, where control subjects showed positive connections with the MPFC and right LP, while bipolar patients had connections with the MPFC and bilateral LP. Notably, control subjects exhibited positive connectivity with the right salience insula, which was absent in the bipolar group. Both groups have negative connectivity with the cerebellar posterior. Additionally, control subjects demonstrated negative connections between the right SF and the bilateral fronto-parietal LPFC and PPC, which were lost in the bipolar patients. In left SF, positive similarities were found in connectivity with the default mode MPFC and left LP. However, differences arose in connections with the language network, where control subjects connected the left SF to the bilateral language IFG, while bipolar patients connected it to the bilateral language IFG as well as the right and left pSTG. The groups also differed in positive connections with the salience network, in control subjects show connection to the bilateral salience insula, left SMG, and ACC, compared to bipolar patients who only exhibited connections with the left salience insula and SMG. Similarly, control subjects have positive connections between the left SF and bilateral lateral

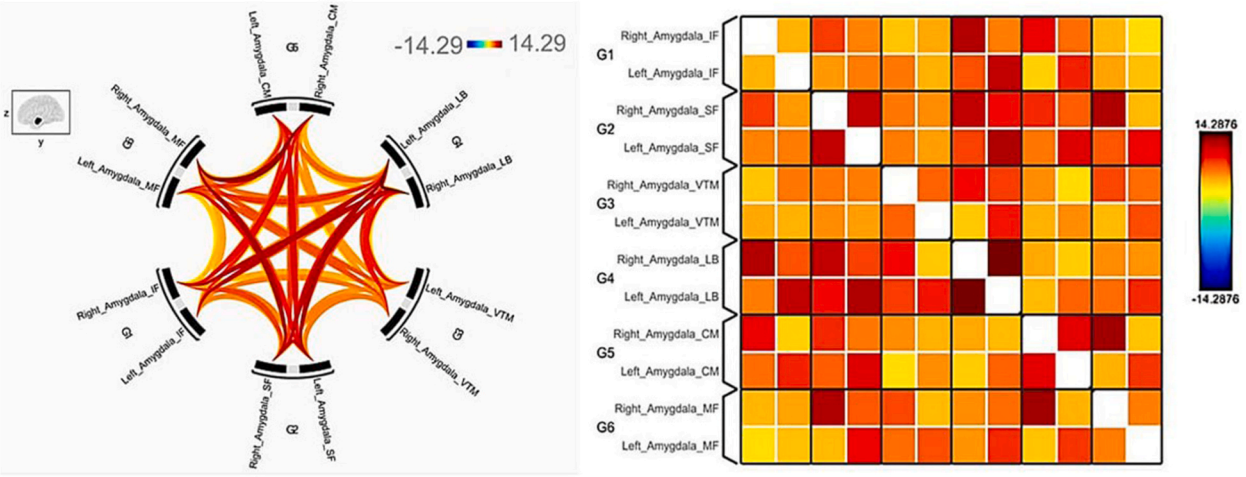

Fig. 2. The functional connectivity between the six sub-regions of the amygdala is exhibited in control subjects. The cluster threshold was set at $p < 0.05$ p-FDR corrected, and the connection threshold was set at $p < 0.05$ p-uncorrected.

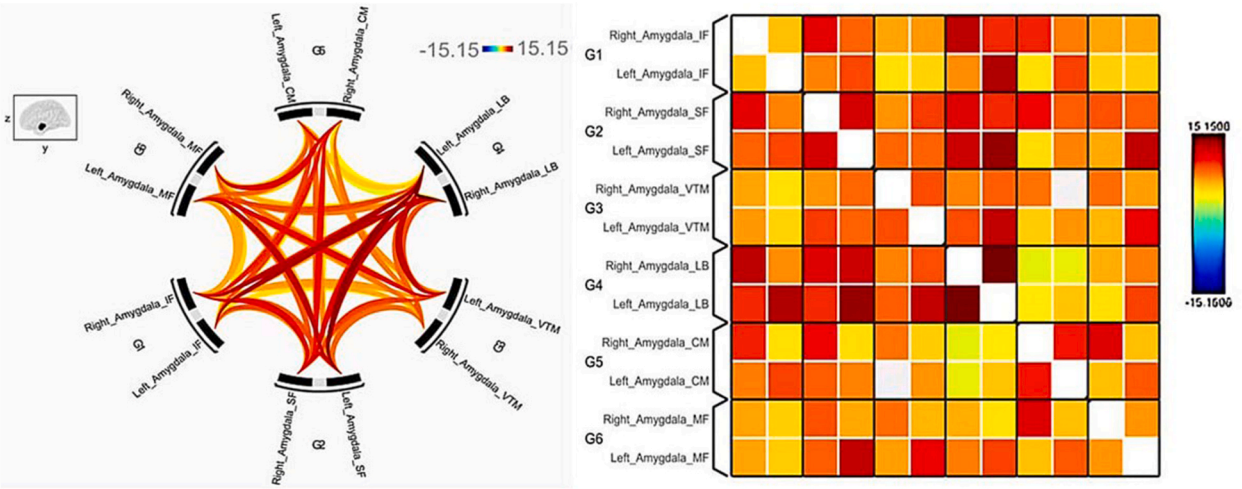

Fig. 3. The functional connectivity between the six sub-regions of the amygdala is exhibited in bipolar patients. The cluster threshold was set at $p < 0.05$ p-FDR corrected, and the connection threshold was set at $p < 0.05$ p-uncorrected.

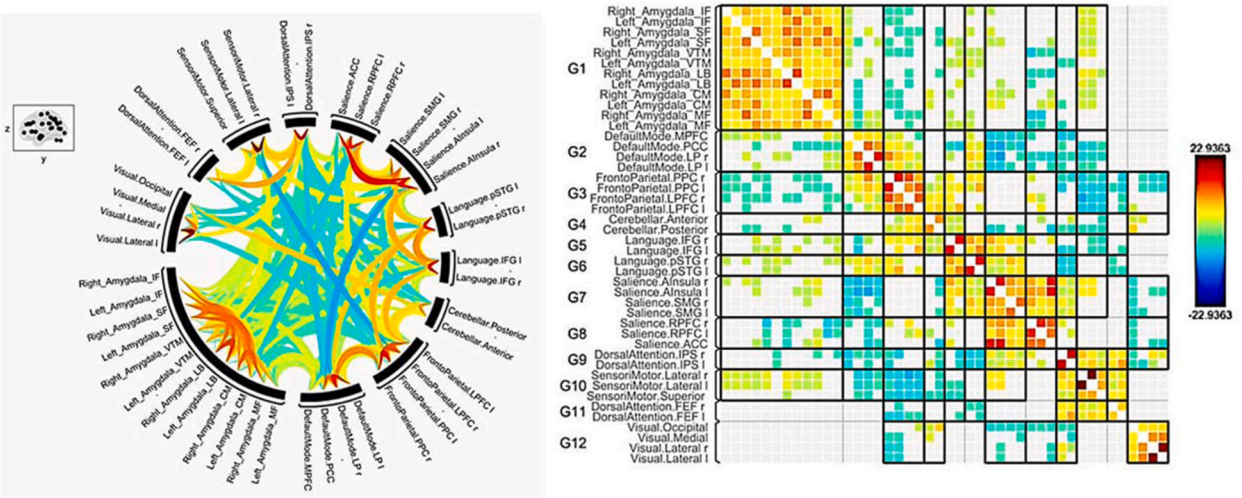

Fig. 4. The positive and negative connections of the amygdala and other brain networks are exhibited in control subjects. The cluster threshold was set at $p < 0.05$ p-FDR corrected, and the connection threshold was set at $p < 0.05$ p-uncorrected.

sensorimotor network, whereas bipolar patients only showed a connection with the left lateral sensorimotor. Negative similarities were observed in connectivity with the cerebellar posterior. Lastly, control subjects displayed negative connections between the left SF and the right fronto-parietal LPFC and PPC, the right salience PRFC, and the default mode PCC, which were absent in the bipolar group. Interestingly, bipolar patients exhibited a negative connection between the left SF and the visual medial network, which was not seen in controls.

The functional connectivity in the right VTM reveals differences between control subjects and bipolar patients. While both groups showed positive connectivity with the default mode network, control subjects had connections with the MPFC whereas bipolar patients had connections with the MPFC and bilateral LP. Differences also emerged in positive connectivity with the language network, control subjects connected with the left language IFG and bilateral pSTG while bipolar patients connected with the bilateral language IFG and right pSTG. Notably, control subjects exhibited positive connections between the right VTM and the bilateral lateral sensorimotor and superior sensorimotor networks, which were absent in bipolar patients. Additionally, controls demonstrated negative connectivity between the right VTM and regions like the default mode PCC, bilateral fronto-parietal LPFC and PPC, bilateral salience ACC and RPFC, and bilateral dorsal attention IPS this connections were entirely lost in the bipolar group. In contrast, bipolar patients showed negative connectivity between the right VTM and the visual medial network, which was not seen in control subjects. The left VTM region show that the control subjects connected to the left VTM to the default mode MPFC and bilateral LP, while bipolar patients only connected to the MPFC. Positive connectivity was seen with language network, in control subjects connected the left VTM to the bilateral language IFG and bilateral pSTG, whereas bipolar patients connected it to the left language IFG and bilateral pSTG. Notably, bipolar patients

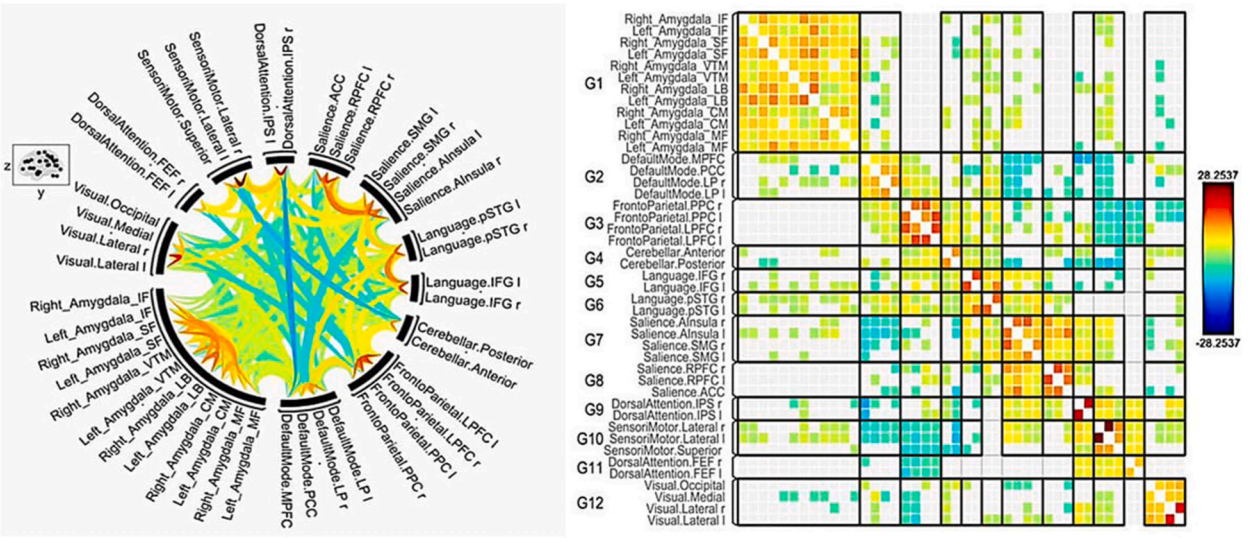

Fig. 5. The positive and negative connections of the amygdala and other brain networks are exhibited in bipolar patients. The cluster threshold was set at $p < 0.05$ p-FDR corrected, and the connection threshold was set at $p < 0.05$ p-uncorrected.

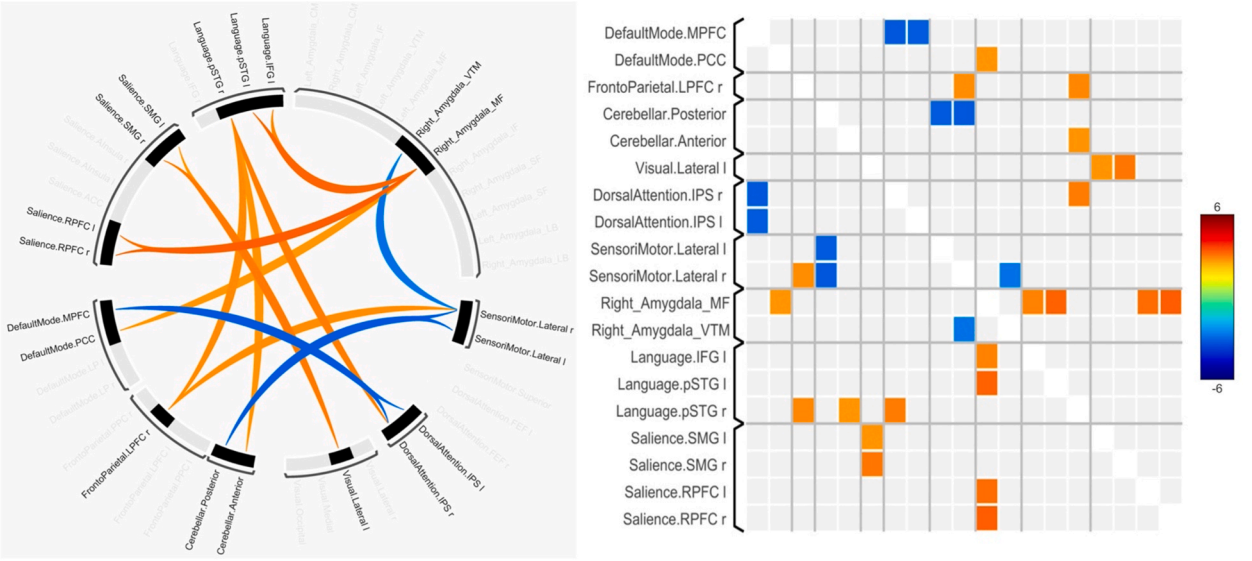

Fig. 6. Shows the comparison between bipolar patients and control subjects. The red color shows the higher connectivity in bipolar patients compared to control subjects as a direct comparison while the blue is vice versa. The cluster threshold was set at $p < 0.5$ p-FDR corrected, and the connection threshold was set at $p < 0.05$.

exhibited positive connections between the left VTM and the left lateral sensorimotor and left salience insula, which were absent in control subjects. The groups further diverged in their negative connectivity patterns, the control subjects show connections between the left VTM and the bilateral dorsal attention IPS, and the left fronto-parietal PPC this connection were lost in bipolar patients. Conversely, bipolar patients demonstrated negative connectivity between the left VTM and the visual medial, visual lateral, and default mode PCC networks, which were not observed in the control group.

The functional connectivity in the right and left LB reveals both similarities and differences between control subjects and bipolar patients. In the right LB, both groups showed positive connectivity with the right default mode LP. However, differences emerged in their positive connections to the language network, control subjects show a connection to the right language pSTG, whereas bipolar patients connected with the right language IFG and bilateral pSTG. Distinctions were also observed in positive connection with the sensorimotor network. Control subjects exhibited connections between the right LB and the bilateral lateral and superior sensorimotor regions, while bipolar patients only showed links to the bilateral lateral sensorimotor areas. Interestingly, bipolar patients demonstrated positive connections between the right LB and regions like the left salience SMG, bilateral dorsal attention IPS, and right visual

lateral, which were completely absent in the control group. Additionally, control subjects have negative connections between the right LB and areas such as the right fronto-parietal LPFC and PPC, cerebellar posterior, salience ACC and RPFC, but these connections were lost in bipolar patients. In the left LB the only positive similarity between the two groups was in connectivity with the left salience insula. Differences were evident in their positive language network connections control subjects connected the left LB to the bilateral language IFG and bilateral pSTG, while bipolar patients connected it to the bilateral language IFG and right pSTG. Regarding the sensorimotor network, control subjects showed positive connections with the bilateral lateral sensorimotor regions, whereas bipolar patients only connected to the left lateral sensorimotor area. Uniquely, bipolar patients exhibited positive connectivity between the left LB and the right default mode LP and left dorsal attention IPS, which were not observed in control subjects. In terms of negative connectivity, both groups demonstrated links between the left LB and the default mode PCC. However, control subjects showed negative connections with the cerebellar posterior, right fronto-parietal PPC and LPFC, and bilateral salience RPFC, which were absent in bipolar patients. Conversely, bipolar patients had a negative connection between the left LB and the visual medial network, a connection that was not found in the control subjects.

Positive similarities were found between control subjects and bipolar patients in the connections of the right and left CM with the cerebellar anterior and bilateral lateral sensorimotor areas. However, differences emerged in the positive connectivity of the right CM. Control subjects showed links to the right language IFG, while bipolar patients connected to the right language pSTG. Additionally, control subjects exhibited positive connections between the right CM and bilateral salience insula, salience SMG, and salience ACC, but these were absent in bipolar patients. Conversely, bipolar individuals had a positive connection between the right CM and the right default mode lateral parietal region, which was not observed in controls. Negative similarities were found in the negative connectivity between the bilateral CM and the default mode posterior cingulate cortex in both groups. Negative differences were also apparent, as control subjects demonstrated negative connections between the right CM and bilateral fronto-parietal regions, whereas bipolar patients showed negative connection to visual networks. For the left CM, controls had negative connections with bilateral fronto-parietal and right dorsal attention areas, which were lost in the bipolar group. Conversely, bipolar patients exhibited negative connectivity between the left CM and visual medial, visual occipital, and bilateral lateral visual regions, which were absent in control subjects.

Positive similarities were found between control subjects and bipolar patients in the connections of the right and left MF with the default mode MPFC and bilateral LP. However, differences emerged in the positive connectivity of the right MF. Bipolar patients exhibited connections with the cerebellar anterior, right salience insula, and bilateral lateral and superior sensorimotor regions, which were absent in control subjects. Additionally, the language network connections of the right MF differed, as control subjects had connection to the right language IFG and right pSTG, while bipolar patients connected to the left language IFG and bilateral pSTG. The negative connections in control subjects showed connection between the right MF and the default mode PCC, right fronto-parietal LPFC, bilateral PPC, and bilateral salience RPFC, all of which were lost in bipolar patients. Conversely, bipolar patients did not exhibit any negative connections with the right MF. For the left MF positive similarities were found with the default mod MPFC and bilateral LP. Differences emerged in the language network, as control subjects had connections with the right and left language IFG and right language pSTG, while bipolar patients connected with the left language IFG and left language pSTG. Bipolar patients also exhibited a positive connection between the left MF and the superior sensorimotor region, which was absent in control subjects. Negative similarities were observed between controls and bipolar patients in the connections between the left MF and the default mode PCC as well as the right dorsal attention IPS. Differences were found in the salience network, as control subjects had negative connections with the bilateral salience RPFC while bipolar patients connected to the right salience insula and right salience SMG. Finally, bipolar patients showed negative connectivity between the left MF and the visual medial region, which was not present in control subjects.

5. Discussion

This study focuses on exploring the differences in functional connectivity between six amygdala sub-regions and eight regional networks in patients with bipolar disorder (BD) compared to control subjects, using resting-state functional MRI (rsfMRI). This approach provides valuable insights into the complex neural dynamics underlying BD, a condition characterized by dramatic shifts in mood, energy, and activity levels.

The results of our study suggest that altered connectivity patterns within sub-regions of the amygdala play a crucial role in the pathophysiology of bipolar disorder. The findings indicate there are fundamental differences in the sub-regions connectivity of the amygdala between BP and control subjects. The VTM of the amygdala is primarily involved in emotional processing, while the CM plays a role in emotional regulation. A significant distinction was noted in the connectivity between the bilateral CM and bilateral VTM amygdala sub-regions. In control subjects, the right VTM exhibited stronger connection with the right CM but this connectivity was lost in BP. Additionally, the left VTM showed weaker connection with the right CM in the BP compared to control subjects. According to some studies which are matching our result indicates that the dysregulation of connectivity within the amygdala sub-regions characterized by an increase in the coupling between the VTM and CM sub-regions [26]. As result that may disrupt the delicate balance between emotional reactivity and cognitive control [26]. This imbalance between emotional and cognitive processes, stemming from the aberrant sub-regions of amygdala connectivity may be a critical factor underlying the mood dysregulation and affective instability characteristic of BD [26].

Recent neuroimaging research has highlighted the importance of examining specific subregions of the amygdala when investigating the neural correlates of mood disorders. For example, Gong et al. (2022) found altered functional connectivity (FC) of the basolateral and centromedial amygdalar nuclei in individuals with bipolar disorder compared to healthy controls. This study specifically reported significant disruptions in the connectivity patterns within these amygdala subregions, emphasizing the need to

consider these subregions separately rather than as a single unit [5].

Similarly, volumetric and functional MRI studies have reported structural and activation abnormalities in these same amygdala subregions in patients with major depressive disorder. Benson et al. (2014) identified volumetric reductions in the basolateral amygdala in individuals with major depressive disorder, while Cullen et al. (2014) demonstrated abnormal activation patterns in the centromedial amygdala during emotional processing tasks. These findings are consistent with the notion that different subregions of the amygdala may be differentially affected in mood disorders, thereby contributing to the heterogeneity observed in these conditions [35,36].

The findings from these studies indicate that there are significant alterations in the functional connectivity (FC) patterns within amygdala subregions in individuals with bipolar disorder (BD) and other mood disorders. These disruptions in connectivity suggest a potential role of amygdala subregions in the pathophysiology and manifestation of these disorders. Specifically, the basolateral amygdala has been implicated in the processing of sensory information and the formation of emotional memories, while the centromedial amygdala is more involved in the regulation of emotional responses and autonomic functions. The differential involvement of these subregions may explain some of the varied symptoms observed in mood disorders.

Collectively, these studies contribute to our understanding of the neural mechanisms underlying mood disorders and have implications for the development of more targeted diagnostic and treatment approaches. By focusing on the distinct functional roles and connectivity patterns of the amygdala subregions, researchers can gain a more nuanced understanding of how these brain structures contribute to the onset and progression of mood disorders. This could ultimately lead to the identification of specific biomarkers for bipolar disorder and major depressive disorder, facilitating early diagnosis and personalized treatment strategies.

In our study, we further explore these insights by using resting-state functional MRI (rsfMRI) to examine the functional connectivity between six amygdala subregions and eight regional networks in bipolar disorder patients compared with control subjects. By investigating these specific subregions, we aim to build on the existing literature and provide a more detailed characterization of the neural disruptions associated with bipolar disorder. Our findings will contribute to the growing body of evidence supporting the critical role of amygdala subregions in mood disorders and may help inform the development of targeted therapeutic interventions.

Default mode network (DMN) one of the most networks has been investigated in bipolar disorder [37]. In this study, there are some changes were seen in DMN network among BP and control subjects this suggests a pivotal role in the disorder's pathophysiology [38]. Even though the knowledge of BD increased recently, less is known about resting-state regional brain activity within the DMN in depression episode BD compared to control subjects [38]. In our result, positive connection was seen between left IF, left CM and mPFC in BP but not in control subjects, this alteration in connectivity could lead to reflect an excessive focus on emotional content and regulation during euthymic episode [39,40]. There are some changes in connectivity were seen between left VTM with bilateral LP in BP, but this connection was not seen in control subjects. Moreover, positive connection has been seen in left LB with right LP and this connection not seen in control subjects. These changes in connectivity perhaps lead to findings may be indicative of the decreased emotional control and cognitive flexibility seen in depression episode [27]. The visual network (VN) is known to be involved in higher-order visual processing but in BP visual processing usually impaired even during euthymic episode [2]. There are a lot of connections have been seen in BP not in control subjects such as the connection in left IF, left SF, bilateral VTM, bilateral LB with visual medial and visual occipital. Even though the exact clinical implications are still under discover, Some authors suggest that disruptions of the visual system might be an indicator of all psychotic diseases, exhibiting reduced performance on visual discriminating tests and a generalized attentional deficit [2]. These impairments in VN could be a key area of investigation in future research on BD. The individuals with BD exhibit alternations in connectivity compared to control subjects in cerebral networks. The findings in this study show positive connection in right IF and right MF with cerebral anterior in BP but this not seen in control subjects. Also, the findings show negative connection in right LB in control subjects with cerebral posterior, this connection was not seen in BP. Furthermore, connection was seen in left LB with cerebral posterior in control subjects but in BP was seen with cerebral anterior. This alternations abnormality in functional connectivity within the cerebral network in BD may help explain the clinical manifestation of cognitive impairment associated with the condition [29]. The dysfunctional of cerebral network suggests that might be associated with functional abnormalities in BD during depression episodes in neural networks supporting cognitive processing [29]. The sensorimotor network (SMN) also exhibits altered connectivity in BD compared to control subjects. There is positive connection in right VTM with bilateral sensorimotor and superior sensorimotor, this connection was not seen in BP. Also, there is positive connection was seen in control subjects in right LB with superior sensorimotor but was not seen in BP. These findings suggest a potential link between SMN activity and self-consciousness in BD [29]. These results highlight the need for further investigation into the role of the SMN in BD. The most highlighted findings in this result were seen in the frontoparital regions (FPN). There is complete loss of connectivity in sub-regions of amygdala with frontoparital regions in BP compared to control subjects. Some research matches our result which has implicated a dysconnectivity within the dorsolateral prefrontal cortex (dlPFC) [41]. Therefore, this alternation could lead to the alternation between (hypo)mania and depression episodes, potentially reflected as abnormal brain network connectivity in patients with the disorder [41]. The results revealed distinct patterns of both positive and negative connectivity within the salience network (SN) and the most significant changes in the sub-regions of amygdala based on the findings. It has been noted that there are positive connections between the left SF, right CM, and salience ACC, as well as between the left CM, salience ACC, and salience RPFC. These positive connections were absent in the BP. Furthermore, the control subjects demonstrated negative connectivity between left SF, bilateral LB, bilateral MF, and salience RPFC, in addition to the right VTM between salience RPFC and salience ACC. However, these negative connectivity patterns were not observed in the BP. These findings may suggest that the loss of connectivity within the SN in BP compared to control subjects has been linked to difficulties in cognitive control and the ability to appropriately allocate attention and resources in BP [30]. Also, emotional instability and mood swings characteristic [42]. As well Disruptions in this network may contribute to the decision-making deficits and reward processing abnormalities [43]. It was also observed, based on the results, that

there was hyperconnectivity in the positive connections between right LB and left salience SMG in BP but not seen in control subjects. Increased functional connectivity within the SN in BP, particularly during mood episodes, could suggest dysregulation in the brain's ability to identify and attribute SN to relevant internal and external stimuli [30,31].

Our findings underscore the phenomenon of amygdala hyperconnectivity commonly observed in bipolar mania, contrasting with its lesser prominence in bipolar depression phases. This differential connectivity is critical in understanding the neural mechanisms underlying the distinct mood states in bipolar disorder (BD). Hyperconnectivity of the amygdala during manic episodes has been associated with heightened emotional reactivity and dysregulation, contributing to the characteristic symptoms of mania such as elevated mood, increased energy, and reduced need for sleep. Conversely, during depressive phases, the connectivity patterns often reflect diminished amygdala activity, correlating with symptoms of low mood, anhedonia, and lethargy.

Previous studies have demonstrated that the amygdala plays a pivotal role in emotional processing and regulation, with alterations in its connectivity patterns being implicated in the pathophysiology of BD [5,35,36]. Specifically, the increased connectivity of the amygdala with prefrontal and striatal regions during mania suggests an overactive emotional network, whereas reduced connectivity during depressive episodes indicates a hypoactive state.

These findings align with meta-analytical evidence showing that BD patients exhibit increased resting-state functional activity in regions such as the left middle frontal gyrus and bilateral striatum, alongside decreased activity in regions including the left middle temporal gyrus and left cerebellum [11]. The nuanced understanding of amygdala connectivity across different mood states enhances our knowledge of BD's neural underpinnings and highlights the importance of targeted therapeutic approaches that address these specific neural alterations.

6. Limitations and future directions

Our study has several limitations that should be considered when interpreting the findings. One significant limitation is the reliance on an open-access dataset, which, while providing valuable data, may lack the specificity and control over patient selection that a more targeted dataset could offer. Open-access datasets often include heterogeneous samples that may not perfectly match the specific criteria required for studies focusing on particular subtypes of mental health disorders. This could affect the precision and applicability of our findings to the broader population.

Another limitation is the absence of diffusion tensor imaging (DTI) data, which could provide additional insights into the structural connectivity of the brain. While rs-fMRI provides robust data on functional connectivity, integrating it with DTI could offer a more comprehensive view of the neural underpinnings of bipolar disorder [44,45]. DTI could help correlate functional connectivity findings with structural brain changes, thereby enhancing our understanding of the neural pathways involved in the disorder [44,45].

Additionally, the sample size in our study was relatively small and lacked diversity, which could affect the generalizability of the results. Future studies should aim to include larger and more diverse cohorts to strengthen the validity of the findings. The cross-sectional design of our study also poses a limitation, as it does not allow for the assessment of changes over time. Longitudinal studies are necessary to understand the progression of bipolar disorder and its different phases, such as manic, depressive, and euthymic states. Unipolar depression (MDD) is characterized by persistent feelings of sadness and multiple other symptoms, whereas bipolar disorder involves mood fluctuations between depressive and manic episodes [46]. The differential diagnosis between unipolar and bipolar depression is critical as it directly impacts treatment strategies [46]. Misdiagnosis is common; approximately 60 % of individuals with bipolar disorder are initially misdiagnosed with MDD [47,48]. Promising research using neuroimaging techniques, including resting-state functional MRI (rs-fMRI), suggests that these tools may help in identifying biomarkers to differentiate between bipolar and unipolar depression [47,48]. However, our current study focused on investigating the functional connectivity of the amygdala in bipolar disorder. Including an MDD group would have provided a more comprehensive understanding of the neurobiological distinctions between these disorders.

The influence of medication and treatment history on brain connectivity was not controlled in our study. Psychotropic medications commonly used in bipolar disorder can significantly impact brain structure and function, and understanding these effects is crucial for distinguishing the neural correlates of the disorder from the effects of its treatment [49]. Incorporating detailed neuropsychological assessments could also enrich our understanding of how differences in functional connectivity relate to specific cognitive and emotional processes in bipolar disorder.

Expanding the focus beyond the amygdala to include other critical brain regions implicated in mood regulation, such as the prefrontal cortex and the hippocampus, would offer a more comprehensive picture of the neural networks involved in bipolar disorder [50–52]. Integrating genetic and environmental factors into study designs could also provide insights into the etiology of bipolar disorder, examining how genetic predispositions interact with environmental triggers to affect brain connectivity. This could pave the way for more personalized treatment approaches.

The selection of the ROI approach over seed-based connectivity analysis is another point of consideration. While the ROI method allows for focused and specific analysis of predefined brain areas, the heterogeneity of methods used in the field can undermine the translation of findings towards consensual biological signatures of disease. Acknowledging this issue, future research should strive for methodological standardization to enhance the reproducibility and comparability of results across studies.

Despite these limitations, our findings contribute to the growing body of literature on the neurobiological mechanisms underlying bipolar disorder, emphasizing the importance of the amygdala and its connectivity with other brain networks. Addressing these limitations and exploring future research directions will help improve our understanding and treatment of bipolar disorder.

7. Conclusion

This study primarily focuses on elucidating the functional interplay among the six amygdala subregions and their connections with various key brain networks, shedding light on the intricate neural dynamics underlying emotional and cognitive processes. The amygdala, a multifaceted brain region, is integral to assigning emotional significance to perceptions and cognitive experiences. Notably, our findings underscore the phenomenon of amygdala hyperconnectivity commonly observed in bipolar mania, contrasting with its lesser prominence in bipolar depression phases. The research highlights the amygdala's intricate interactions with several crucial brain networks, including the Default Mode Network (DMN) and the Salience Network (SN). These interactions appear to be pivotal in the pathophysiology and progression of Bipolar Disorder (BD). The study's insights into these dynamic neural relationships contribute significantly to our understanding of BD, offering a nuanced perspective on how various brain networks collaborate and diverge in this complex psychiatric condition. Overall, the study underscores the critical role of the amygdala and its network connections in BD, suggesting that these neural pathways may be influential in the disorder's development and manifestation. This enhanced understanding holds promise for informing future research directions and potentially guiding more targeted therapeutic strategies for managing BD.

Data supporting this study are openly available from (UCLA Consortium for Neuropsychiatric Phenomics LA5c Study) at (https://openfmri.org/dataset/ds000030/).

CRediT authorship contribution statement

Adnan Alahmadi: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ashjan G. Alali:** Formal analysis, Data curation, Conceptualization. **Bayan M. Alzhrani:** Data curation, Conceptualization. **Reema S. Alzhrani:** Investigation, Funding acquisition, Formal analysis. **Walaa Alsharif:** Writing – review & editing, Writing – original draft, Validation. **Shrooq Aldahery:** Writing – review & editing, Writing – original draft, Validation. **Duaa Banaja:** Funding acquisition, Formal analysis, Data curation, Conceptualization. **Njoud Aldusary:** Funding acquisition, Formal analysis, Data curation. **Jamaan Alghamdi:** Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ibrahem H. Kanbayti:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Norah Y. Hakami:** Conceptualization, Data curation, Formal analysis, Methodology.

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.

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