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Hippocampal functional connectivity-based discrimination between bipolar and major depressive disorders

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ABSTRACT

Despite the impressive advancements in the neuropathology of mood disorders, patients with bipolar disorder (BD) are often misdiagnosed on the initial presentation with major depressive disorder (MDD). With supporting evidence from neuroimaging studies, the abnormal functional connectivity (FC) of the hippocampus has been associated with various mood disorders, including BD and MDD. However, the features of the hippocampal FC underlying MDD and BD have not been directly compared. This study aims to investigate the hippocampal resting-state FC (rsFC) analyses to distinguish these two clinical conditions. Resting-state functional magnetic resonance imaging (fMRI) data was collected from a sample group of 30 patients with BD, 29 patients with MDD and 30 healthy controls (HCs).

One-way ANOVA was employed to assess the potential differences of the hippocampus FC across all subjects. BD patients exhibited increased FC of the bilateral anterior/posterior hippocampus with lingual gyrus and inferior frontal gyrus (IFG) relative to patients MDD patients. In comparison with HCs, patients with BD and MDD had an increased FC between the right anterior hippocampus and lingual gyrus and a decreased FC between the right posterior hippocampus and right IFG.

The results revealed a distinct hippocampal FC in MDD patients compared with that observed in BD patients. These findings may assist investigators in attempting to distinguish mood disorders by using fMRI data.

1. Introduction

Bipolar disorder (BD) and major depressive disorder (MDD) are two psychiatric conditions associated with high suicide rates and impose considerable social and economic effects. In the United States and Canada, the expenses associated with major depressions are equivalent to those related to heart disease, diabetes, and back problems and are higher than the costs of hypertension (Wade and Häring, 2010). BD and MDD patients usually show similar severe clinical symptoms during depressive episodes. Patients with BD who present a major depressive episode are likely to be misdiagnosed with MDD, and thus commonly treated with antidepressants only (Baldessarini et al., 2007; Ventimiglia et al., 2009). However, although standard antidepressant medications are effective in treating major depression, evidence on their use in treating bipolar depression is less and remains insufficient to guide clinical practice (Sachs et al., 2007). Most patients with BD (depending on their mood states, the severity of symptoms or illness trajectories) often respond to a combination of therapy rather than a monotherapy (Khoo, 2012; McInerney and Kennedy, 2014). A proper treatment for the depressive episodes in BD remains a subject for debate, but a consensus exists among researchers that developing distinguishing biomarkers (biologically) between the two disorders before launching treatment is essential. This matter entails an understanding of the pathophysiology related to BD and MDD (NIH/National Institute of Mental Health, 2007; Shim et al., 2017).

Due to misdiagnosis, no appropriate treatment is provided for

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unrecognized BD during the early onset stage. Notably, timely and effective treatment is of great importance in preventing the risk of recurrence and chronicity of the depressive episodes (Singh and Rajput, 2006; Farb et al., 2015).

In clinical practice, distinguishing between BD and MDD at an early stage is a critical task for clinicians to avoid risks of misdiagnosis and hence inappropriate medication treatments. Thus, considerable interest has been devoted to the neurobiological basis underpinning emotion processing and mood regulation. Yet, the number of structural and functional research has exponentially incremented supporting brain abnormalities that might help in distinguishing these disorders. Neuroimaging techniques, such as magnetic resonance imaging (MRI), represent non-invasive, widely available, and relatively low-cost tools for investigating these affective disorders (He et al., 2019; Kempton et al., 2011; Pang et al., 2018). However, studies are limited on the role of the hippocampus in discriminating BD and MDD. Accumulating evidence has indicated the importance of the hippocampus in the pathogenesis of MDD (MacQueen and Frodl, 2011). Patients with MDD have consistently shown hippocampal volume reduction (Campbell and Macqueen, 2004) and hippocampal functioning impairments in memory- encoding (Bremner et al., 2004; Campbell and Macqueen, 2004) and emotion regulation and motivation (Rive et al., 2013). Implicit negative memory biases are associated with regions that are critical for the consolidation of emotional memories such as the hippocampus. Thus, these regions are implicitly relevant to MDD (Mathews and MacLeod, 1994; Hamilton and Gotlib, 2008) and play a role in the maintenance of depression (Mathews and MacLeod, 1994).

Studies on hippocampal volumes in patients with BD have been contradictory, showing no alterations (Bertolino et al., 2003; Brambilla et al., 2003), smaller volumes (Bearden et al., 2008; Blumberg et al., 2003; Cao et al., 2016a) and even an enlarged volume in subjects with BD compared with healthy controls (HCs) (Javadapour et al., 2010; van Erp et al., 2012). The inconsistency of the results could be due to the exposure to the neuroprotective effects of lithium or the methodological factors in these studies (Hajek et al., 2012; Kempton et al., 2011). A recent study, however, reported that patients with late-stage BD have reductions in the hippocampus (Cao et al., 2016b). Furthermore, hippocampal formation is heterogeneous; it consists of different subregions that are functionally and structurally connected to diverse brain areas comprising prefrontal cortex, anterior thalamic nuclei, amygdala, basal ganglia and hypothalamus, which form the neuroanatomical network of mood regulation (Drevets, 2000). These factors make this core structure an obscure prime target for further investigations (Eichenbaum et al., 2007; Nestler et al., 2002; Phillips et al., 2003; Seminowicz et al., 2004).

Resting-state approaches define the brain state conditions observed through the changes in blood flow when no explicit task is being performed. Therefore, the brain creates a low level of blood-oxygen-level-dependent signal fluctuations (typically ranging from 0.01–0.08 Hz) that can be measured using functional MRI (fMRI). Generally, studies based on psychiatric and neurological disorders are often conducted under resting-state condition due to several motivating factors. Resting-state fMRI is a powerful tool that can effectively allow investigating the human connectome without the need to learn complex task paradigms and can be easily collected and aggregated into large-scale databases. It is also very appropriate for studying various patient populations, including those who cannot perform tasks very accurately because of physical impairment, cognitive dysfunction or even during vegetative states (Woodward and Cascio, 2015; Cui et al., 2017; Liao et al., 2018). Numerous studies have investigated the role of altered resting-state FC (rsFC) between patients with different psychiatric disorders such as MDD (Greicius et al., 2007), BD (during euthymic, manic or even depressive episodes) (Syan et al., 2018, 2017; Wang et al., 2016), schizophrenia (Li et al., 2018; Wang et al., 2017), autism spectrum disorder (Chen et al., 2019, 2017; Guo et al., 2018)...etc. Das et al. (2014) found an impaired rsFC between patients with BD and those with borderline personality disorder compared with HCs among the networks involved in determining social salience, self-referential processing, and emotion regulation. In addition, Du et al. (2015) conducted a discriminative study between BD, schizophrenia, and schizoaffective disorder by investigating rsFC to explore different biomarkers through GIG-ICA. They revealed that the regions reflecting different FCs were mainly located in the frontal, parietal, precuneus, cingulate, supplementary motor, insula, and supramarginal cortices. Consistent with these findings, Anand et al. (2009) indicated the decreased resting-state corticolimbic connectivity in unmedicated patients with BD (in manic and depressive phases) and MDD compared with HCs.

This study observed the variations in the hippocampal rsFC among diagnosis groups (i.e. patients with BD and MDD) and HCs to examine the intergroup differences. These differences signify that the newly examined neural mechanisms underpinning the overlapping symptoms might noticeably differ between diagnosis groups. Although MDD is related to abnormal FC of the hippocampus to the cortical regions, results are still inconsistent whether these abnormalities in the hippocampal FC emerge in patients with BD compared with those with MDD (Drysdale et al., 2017; Geng et al., 2018).

1.1. Objective

This present study is amongst the pioneering works that investigated the role of an altered hippocampus rsFC in bipolar and unipolar depression. Thus, we compared rsFC of the hippocampus with the lingual gyrus, temporal pole, and inferior frontal gyrus (IFG) in similarly depressed patients diagnosed with BD and MDD compared with one another and with HCs. We hypothesized that BD individuals would display alterations in regions involved in the cognitive control of emotions (left IFG, left temporal pole) while MDD would display changes of rsFC with brain regions implicated to emotional processing (lingual gyrus, right IFG).

2. Materials and methods

2.1. Participants

A total of 29 participants with MDD, 30 participants with BD, and 30 HCs were recruited from the mental health center of Chengdu, Sichuan, China. By using the Structured Clinical Interview for DSM-IV (SCID-IV patient edition), all patients were screened by two experienced psychiatrists. Patients with MDD and BD were diagnosed based on the DSM-IV criteria. Exclusion criteria included having a personality disorder or mental retardation, any history of loss of consciousness, substance abuse and neurological illness. A 24-item Hamilton Depression Scale (HAMD) scores were estimated for each participant. Patients with BD and MDD were treated with antidepressants, antipsychotics, and mood stabilizers. HCs with corresponding age and gender were recruited by advertisements and screened with the SCID (non-patient version) to ensure the lifetime absence of psychiatric illnesses. The clinical and demographic data are shown in Table 1.

All participants submitted written informed consent before conducting the experiment. The research ethical committee of University of Electronic Science and Technology of China (UESTC) approved the study in compliance with the latest revision of the Declaration of Helsinki.

2.2. Data acquisition

All fMRI data were gathered using the 3T GE DISCOVERY MR750 scanner (General Electric, Fairfield Connecticut, USA) with an eight-channel phased prototype quadrature birdcage head coil in the UESTC. Functional images were acquired using an echo-planar imaging sequence with the following parameters: repetition time (TR), echo time TE = 2000/30 ms, matrix size = 64 × 64, slices = 43,

Table 1
Characteristics of demographic and clinical variables of HC and patients with BD.

Variables	HC (n = 30)	MDD (n = 29)	BD (n = 30)	p-value
Age (years)	31.57 ± 10.33	36.82 ± 10.18	34.26 ± 9.79	0.15[a]
Gender (male / female)	14/16	11/18	15/15	0.63[b]
Handedness (left / right)	1/29	0/29	1/29	0.61[b]
Education (years)	14.43 ± 4.48	13.34 ± 3.73	13.83 ± 3.34	0.57[a]
Mean FD	0.07 ± 0.02	0.07 ± 0.03	0.09 ± 0.06	0.20[a]
Duration of illness (months)	–	69.17 ± 68.61	86.67 ± 73.4	0.36[c]
Age of first onset (years)	–	31.14 ± 9.16	28.07 ± 9.12	0.21[c]
No. of depression episodes	–	2.03 ± 0.85	2.80 ± 1.45	0.02[c]
Duration of single depressive episode	–	4.34 ± 2.89	4.03 ± 3.03	0.69[c]
HAMD score	–	25.76 ± 5.70	21.40 ± 8.07	0.02[c]
Medical				
Medication load index	3.13 ± 1.26		2.28 ± 0.98	0.01[c]
Antidepressants, no. of patients				
Fluoxetine	1		1	
Sertraline	6		11	
Paroxetine	11		4	
Escitalopram	5		3	
Fluvoxamine	0		0	
Venlafaxine	2		1	
Duloxetine	2		1	
Mirtazapine	1		0	
Mood stabilizer				
Valproate	2		17	
Lamotrigine	0		2	
Lithium	0		6	
Antipsychotics				
Olanzapine	2		8	
Quetiapine	8		16	
Risperidone	0		0	
Aripiprazole	1		0	

Abbreviations: HC, Healthy control; MDD, Major depressive disorder; BD, Bipolar disorder; HAMD, Hamilton depression scale.
Values are mean ± standard deviation.
[a] One-way analysis of covariance.
[b] Chi-square t-test.
[c] Two-tailed two-sample t-test.

thickness = 3.2 mm, no gap, field of view = 240×240 mm^2, voxel size = $3.75 \times 3.75 \times 3.2$ mm^3, and flip angle = 90°. For each participant, 255 volumes were obtained.

2.3. Functional imaging data processing

The preprocessing of r-fMRI data was conducted using the SPM12 software to 1-box[1]. After discarding the first five volumes, the images were corrected for the time-delay between slices and the motion movement between volumes. Patients with head motion parameters exceeding 3 mm in the x, y, or z directions or 3° rotation of each axis were not included for further analysis. No participant was excluded based on the criterion. Normalization was then performed on the resulting images by using a unified segmentation of anatomical images, which were resampled into a $3 \times 3 \times 3$ mm^3 voxel size. Multiple regression models were employed to remove the effect of covariance of no interests, including 24 motion parameters, cerebrospinal fluid signals, and white matter signals. The obtained images were smoothened with 6 mm full-width-at-half-maximum Gaussian kernel, linearly detrended, and filtered at the range of 0.01 Hz–0.08 Hz.

2.4. Head motion and artifact detection

To examine the confounding influence of head motion on connectivity, the framewise displacement (FD) across time points (Power et al., 2012; Pang et al., 2016) was calculated for each participant. The measures are described above in Table 1.

2.5. Hippocampus seed definition

Similar to a previous work presented by Qin et al. (2016), we exploited the same seed definition in which the coordinates of the seeds were as follows: anterior (aHIP), middle (mHIP), and posterior (pHIP) hippocampus as shown in Table 2.

2.6. Hippocampus FC analysis

For each hippocampus seed, a correlation analysis was conducted between the seed ROI and the remaining voxels in the rest of the brain. The resulting r values were converted using Fisher's r-to-z transformation to improve the Gaussianity of their distribution. A one-way ANOVA was employed to compare the difference of FC maps among the three groups. Age, gender and education were modeled as covariates of no interests. The multiple comparison correction was conducted at cluster level of $p < 0.05/6$ (for correcting six hippocampus FC comparisons) by employing AlphaSim programmed in REST toolbox with a height threshold of $p < 0.005$ and extent thresholds of 40 voxels for left aHIP, 44 voxels for right aHIP, 72 voxels for left mHIP, 56 voxels for right mHIP, 65 voxels for left pHIP, and 73 voxels for right pHIP.

Post-hoc analysis of two-tailed, two-sample t-test was conducted on brain areas that survived multiple comparison corrections to determine the direction of FC changes among the three groups. Statistical significance was considered at $p < 0.05/3$ (Bonferroni corrected). Brain region data are summarized in Table 3.

[1] http://www.fil.ion.ucl.ac.uk/spm/software/spm12/.

Table 2
Coordinates for seeds in the left and right hemisphere were defined in the MNI stereotaxic (Qin et al., 2016), aHipp, anterior hippocampus; mHipp, middle hippocampus; pHipp, posterior hippocampus.

	X	*Y*	*Z*
aHIP	± 24	−14	−20
mHIP	± 26	−26	−12
pHIP	± 26	−24	−4

Table 3
Brain clusters showing a significant effect in the FC with the hippocampus. aHIP, anterior hippocampus; pHIP, posterior hippocampus; IFG, inferior frontal gyrus; BD, bipolar disorder; MDD, major depressive disorder.

Seed regions	Brain regions	Cluster size Voxels	*Z* score	MNI *X*	*Y*	*Z*
Right aHIP	Lingual Gyrus	92	10.8433	3	−72	−12
Left aHIP	Left temporal Pole	11	8.8322	−24	12	−33
Left pHIP	Left IFG	69	10.8786	−51	3	30
Right pHIP	Right IFG	74	9.6028	60	18	12

3. Results

3.1. Abnormal hippocampus FC among BD, MDD, and HCs

ANOVA results revealed that some regions exhibited significant differences for the FC of hippocampus among MDD, BD, and HC. Post-hoc analysis showed that compared with HCs, patients with BD had increased FC between the right aHIP and lingual gyrus, between left aHIP and left temporal Pole, between right pHIP and right IFG, and between left pHIP and left IFG. While MDD patients had increased FC between right aHIP and lingual gyrus, and decreased FC between left pHIP and left IFG (Figs. 1, 2).

Compared to MDD patients, patients with BD had increased FC between left aHIP and left temporal Pole (Fig. 1), between left pHIP and left IFG, and between right pHIP and right IFG (Fig. 2).

4. Discussion

This study investigated the functional relationships and neural circuitry between the hippocampus and other brain areas in patients with phenotypically similar major depressive episodes due to BD or MDD. Consistent with our hypothesis, BD was associated with an increased rsFC between left aHIP and left temporal Pole, between pHIP and IFG compared to HCs and MDD. Unexpectedly, MDD was associated with an increased FC between right aHIP and lingual gyrus compared with BD and HCs. This increase is possibly due to antidepressant responsiveness showed by the recruited patients with MDD with a relatively short period of illness (Jung et al., 2014). In summary, these findings draw distinct functional underlying neuroanatomies for major depressive episodes due to BD against MDD. If these results stand robust when replicated to a single level (Gordon et al., 2017), then they might help in developing new imaging-based approaches that facilitate distinguishing BD from MDD at a group level. Considering the relative dearth of antecedent seed-based rsFC studies separating bipolar and unipolar depression on the regions of default mode network and other functionally connected networks, we drew upon cautious evidence from different prior studies in the literature. In line with our results, group comparisons between different hippocampal functional connections conducted by Cao et al. (2012) revealed a decreased FC between left hippocampal and bilateral middle frontal gyrus in MDD patients.

Considering the observed disrupted rsFC associated with BD, our findings extended prior research that suggests higher functional connectivity within limbic and frontal brain regions compared with HCs (Das et al., 2014; Syan et al., 2017; Torrisi et al., 2013). Inconsistent with our findings, Oertel-Knöchel et al. (2015) suggested a reduced FC between the left hippocampus and the medial temporal lobe in BD patients compared with HCs. Their findings complement those of other resting-state BD studies manifesting hypoconnectivity and hyperconnectivity between the limbic and frontal brain regions (Anand et al., 2009; Chepenik et al., 2010; Öngür et al., 2010). A potential explanation for the contradicting results of these studies might be the different mood states of patients. Oertel-Knöchel et al. (2015) conducted their study among remitted BD patients, whereas our sample comprised bipolar depressed patients. Hence, the hippocampal rsFC in remitted BD patients was associated with cognitive impairments but

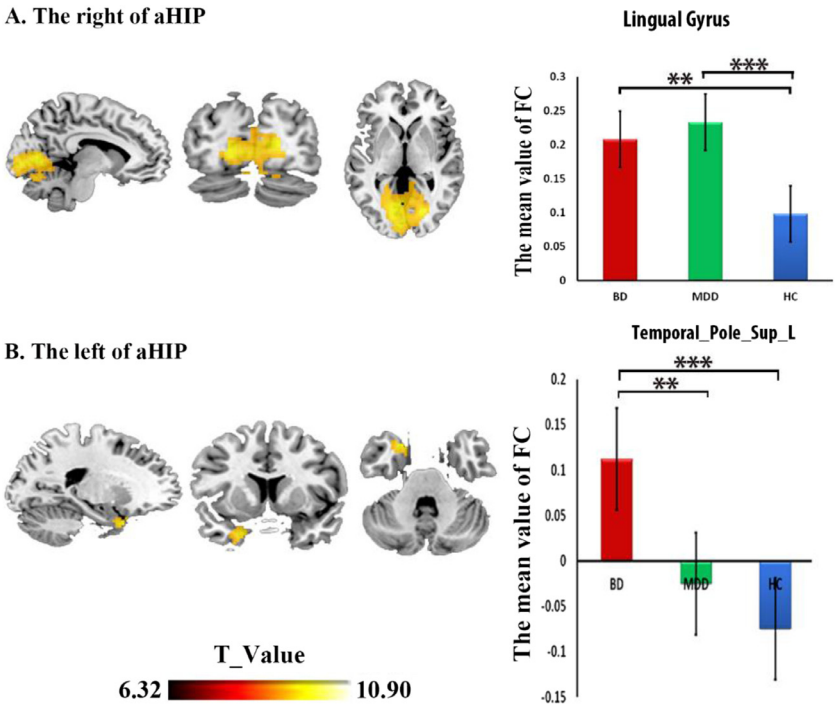

Fig. 1. Significant differences in FC among MDD, BD, and HC in the right aHIP (A) and left aHIP (B). The results of the post-hoc *t*-test were shown in the box-plot. Lines designate pairwise comparisons reaching statistical thresholds: $*p < 0.005$; $**p < 0.0005$; $***p < 0.00005$. MDD, major depressive disorder; BD, bipolar disorder; HC, health control; aHIP, anterior hippocampus; Temporal_pole_sup, superior temporal pole.

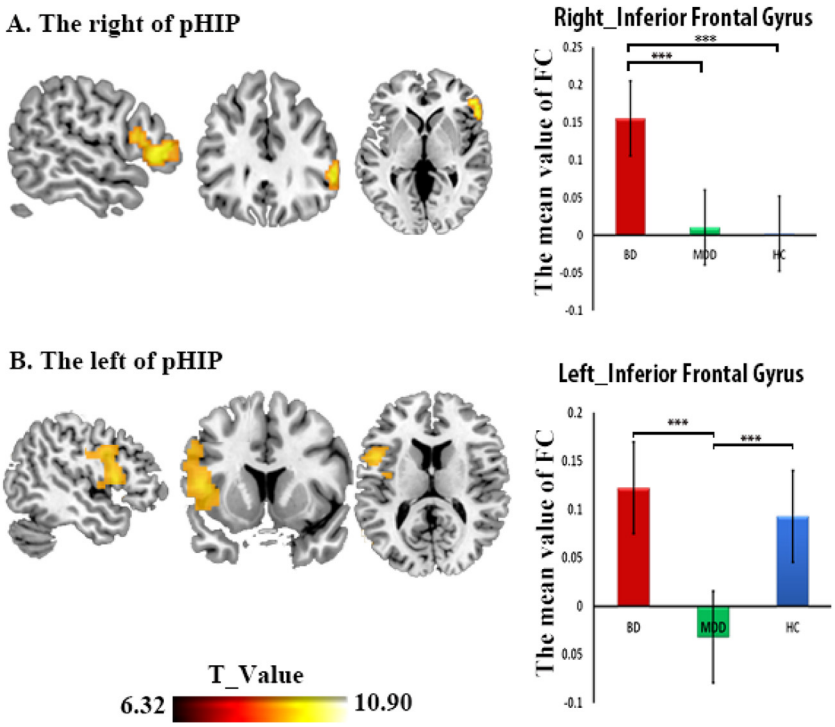

Fig. 2. Significant differences in FC among MDD, BD, and HC in the right pHIP (A) and left pHIP (B). The results of the post-hoc *t*-test were shown in the box-plot. Lines designate pairwise comparisons reaching statistical thresholds: $*p < 0.005$; $**p < 0.0005$; $***p < 0.00005$. MDD, major depressive disorder; BD, bipolar disorder; HC, healthy control; pHIP, posterior hippocampus.

was separate from acute clinical symptomatology (Hasselbalch et al., 2011; Senturk et al., 2007).

The hippocampus, a core region within the limbic system, is involved in learning and consolidating memory, such as forming new memories, and connecting emotions to those memories; thus, it has been implicated in the etiology of MDD and BD (Campbell and Macqueen, 2004; Frey et al., 2007). At the cellular and molecular level, evidence from neuroimaging and post-mortem studies reported several alterations in the morphology and the cellular architecture associated with the hippocampus as depression progresses. Individuals with BD and MDD showed hippocampal volumetric abnormalities (Javadapour et al., 2010; Neumeister et al., 2005; Sheline et al., 2003, 1996), and decreased neuropil and hippocampal atrophy (Stockmeier et al., 2004). Consequently, the hippocampus has been potentially assumed to mediate the relationship between pain, depression and cognitive deficits by regulating gene expression (Zhu et al., 2017). Therefore, core symptoms such as cognitive dysfunction and the impairments in concentration in depressed patients due to BD or MDD are related to the hippocampus and other alterations within brain regions that are functionally connected to it. Attention has been devoted to the paralimbic regions implicated in neurobiological research on BD.

The dominant dichotomic view of the characterization of differential patterns of FC along the longitudinal axis of the hippocampus is that the posterior (or dorsal) hippocampus is ascribed to learning, memory, and cognitive functions while the anterior (or ventral) hippocampus mediates anxiety, emotion, and affect related behaviors (Fanselow and Dong, 2010; Strange et al., 2014). Therefore, neuropsychological and functional studies on humans benefitted from works in experimental animals in dissociating the roles ascribed to the hippocampal subfields. Tract-tracing studies on animals is an example in which the aHIP is involved in the retrieval of emotional memories through its connectivity with some temporal lobe regions such as the amygdala (Kishi et al., 2006; Pitkänen et al., 2006). Moreover, the aHIP and the amygdala are abundantly connected with other extended limbic system areas including the temporal pole, implicating its contribution to emotional and social processes (Qin et al., 2016; Zeidman et al., 2015) However, cognitive deficits were reported due to altered connectivity with the prefrontal cortex and temporal gyrus along with other impacting factors such as aging (Blum et al., 2014). The pHIP is also connected to other brain regions that directly affect BD and MDD, such as the parahippocampal gyrus, insula, and the temporal pole (Blum et al., 2014).

In addition to the hippocampus, these paralimbic regions consist of temporal lobe structures such as the amygdala together with prefrontal regions within which they share a strong connection, mainly in the orbitofrontal cortex (Chase and Phillips, 2016; Oertel-Knöchel et al., 2015). However, research is limited concerning the temporal pole in BD. This phenomenon implies an influential gap in the literature, not only within the scope of our findings but also in the region's proximity and structural connectivity to other broadly studied regions, such as the amygdala-hippocampal complex (i.e. the hippocampus and parahippocampal gyrus) and the orbital portions of the prefrontal cortex. In this study, BD patients showed an increased FC between hippocampus and left temporal pole and with left IFG which pertain to the prefrontal cortex. At the anatomical level, these alterations are reflected by the limbic-paralimbic and front-limbic pathways. The temporal pole is not only strongly connected with the amygdala, hippocampus, the superior temporal gyrus, and the occipitobasal cortex, but also with the orbitary gyrus and the insula with which it forms the insulo-orbito-polartemporo- complex (Chabardès et al., 2002) that mediates mood regulation and affective processing. Some of the most interesting studies to date on the temporal pole function involved the vacillating mood states between depression and mania (Murai and Fujimoto, 2003). Other studies found that damaged temporal pole can cause acquired BD (Brooks and Hoblyn, 2005; Carran et al., 2003). Moreover, temporal pole has been associated with perception to socioemotional processing including facial recognition (Barbeau et al., 2008), theory of mind (i.e. one's ability to infer the desires, intentions or beliefs of others) (Michel et al., 2013) and emotional reactions to complex auditory stimuli (Lorberbaum et al., 2002; Royet et al., 2000). Moreover, the temporal polar regions are essential for attachment processes, because bilateral temporal pole lesions induce loss of normal emotional attachment in mother monkeys to their infants and to peer monkeys (Kling and Steklis, 1976). Thus, for bipolar disorder, the altered hippocampus-temporal pole, and IFG connectivity may mediate the dysfunction in integrating multiple cognitive and emotional

functions. If replicated, this pattern of connectivity might be a proper biomarker supporting in the diagnosis and distinction of BD from MDD.

Our results presented an altered rsFC between the hippocampus and lingual in MDD patients. The lingual gyrus is a brain structure that is associated with vision-processing, especially relevant to letters and partakes in the analysis of logical conditions (i.e. logical sequence of events) and encoding visual memories. This brain region constitutes part of the occipital lobe that, in front, continues to the tentorial surface of the temporal lobe and connects the parahippocampal gyrus (the region surrounding the hippocampus). Evidence suggests a potential link between the lingual gyrus and hippocampal regions due to the increased signals in the lingual gyrus when the participants were tasked with retrieval of facts while resolving a specific problem. Cho et al. (2012) revealed that the activation was not linked to problem-solving itself but rather with recollection. The lingual gyrus is connected to other neighboring brain areas, which potentially mediates major depressive disorder such as the amygdala. These regions are linked with verbalizing emotion words (Isenberg et al., 1999) and visualizing emotional images (Kehoe et al., 2013). Within the same context, Bogousslavsky et al. (1987) conducted a Stroop test in three aspects: neutral word, color word, and error control. Post-hoc analysis showed that the density of the right lingual gyrus in non-respondent group correlated with better error control (Stroop) and nonverbal memory (Rey–Kim memory test). These results concur with the findings supporting the association of impaired visual memory with a first major depressive episode (Lee et al., 2012) and with MDD adolescents (Baune et al., 2014). Our results were not consistent with other studies coupling a decreased lingual gyrus connectivity in patients with MDD (Jung et al., 2014). These contradicted findings might be referred to the sample itself in terms of medication status, and the response to antidepression treatments or cognitive abilities. This matter urges further research to investigate such rarely addressed core regions in the anatomy of mood disorders.

Potential limitations of this study include the lack of data and subjects used to obtain the statistical analysis. A large sample size yields to accurate results. In addition, this study mainly focused on the hippocampal FC. However, the brain function is shaped and affected by its structure. Hence, the combination of the brain function and structure is highly recommended for further research on MDD and BD. Concerning the fMRI analysis, the seed-based approach followed in this study may restrain the results to cover a limited number of regions of interest. However, potential differences might have existed elsewhere that could have been shown by data-driven approaches. Moreover, the data sample used in this work involved patients who underwent long-term treatment. Thus, the diagnosis results might have been badly influenced.

In summary, the present findings bolster the hypothesis that phenotypically similar major depressive episodes in BD and MDD emerge from different patterns of aberrant functional connectivity. During rest, abnormal hippocampal connectivity with regions from the frontal and occipital lobe and with the temporal lobe may affect emotional regulation and processing dysfunction in both BD and MDD. The observed differences indicated the prospect of differential pathophysiological mechanisms of major depressive episodes in unipolar and bipolar depression. If replicated, such differences may yield future trends towards improving the clinical differentiation between these two types of depression with significant therapeutic and prognostic implications.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.01.004.

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