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ORIGINAL RESEARCH

Exploring the Effects of Temperament on Gray Matter Volume of Frontal Cortex in Patients with Mood Disorders

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Background: Patients with bipolar disorder (BD) and patients with major depressive disorder (MDD) have relatively specific temperament and structural abnormalities of brain regions related to emotion and cognition. However, the effects of temperament factors on the structure of frontal and temporal cortex is still unclear. The aims of this study were to explore the differences and relationships between temperament characteristics and the gray matter volume of frontal and temporal cortex in patients with BD or MDD.

Methods: T1-weighted magnetic resonance imaging (MRI) data, demographic and clinical information were obtained from 279 depressed patients (90 patients with BD, 189 patients with MDD) and 162 healthy controls (HC). Temperament was assessed with the Chinese short version of Temperament Evaluation of Memphis, Pisa and San Diego – Auto questionnaire (TEMPS-A). The Desikan-Killiany atlas was used for yielding gray matter volume by FreeSurfer 6.0 software suite. A total of 22 frontal and temporal regions were chosen as regions of interest (ROIs).

Results: Compared with patients with MDD, patients with BD had higher TEMPS-A total scores and scores on cyclothymic, irritable and hyperthymic subscales. The gray matter volume in bilateral rostral middle frontal gyrus (RMFG), left temporal pole and right superior frontal gyrus were reduced in patients with BD. Patients with MDD only had lower gray matter volume in bilateral temporal pole. In the pooled patients, there were negative associations between hyperthymia and gray matter volume in right RMFG.

Conclusion: Patients with BD and MDD had different temperament characteristics. The prominent temperament subscales in patients with BD were cyclothymia, irritable and hyperthymia. Patients with greater hyperthymia had lower gray matter volume in right frontal gyrus. Temperament may reflect an endophenotype in patients with mood disorders, especially in BD.

Keywords: bipolar disorder, major depressive disorder, temperament, gray matter volume

Background

Bipolar disorder (BD) and major depressive disorder (MDD), as the primary mood disorders, are two of the most common mental disorders with an ever-increasing prevalence and global burden of disease in the past two decades.[1] Despite the increased awareness of mental health, and updating of diagnostic criteria and treatment guidelines, it remains difficult to achieve early detection and prevention of BD and MDD. One of the main reasons lies in the ambiguity of etiology.

There are several etiological hypotheses for mood disorders based on the Bio-Psycho-Social disease model. Temperament is one of the proposed disease factors.

Temperament is comprised of stable psychological traits in terms of intensity, speed, flexibility and directivity of psychological activities, which shows individual variation in the populations.[2] Previous studies implied that temperament could be an endophenotype for mood disorders.[3,4] Yuan and colleagues' study[5] suggested patients with BD were more likely to be cyclothymic, depressive, hyperthymic, irritable and anxious in temperament when compared with healthy individuals. Interestingly, patients with MDD also had high cyclothymic and irritability scores.[6] Patients with both BD and MDD had higher level of harm avoidance and lower level of persistence.[7] However, patients with BD and patients with MDD had relatively specific temperament characteristics.[7,8] Temperament could be used for differentiation between BD and MDD and between the subtypes of BD.[9] The effects of temperament on clinical symptoms have also been studied extensively. Harm avoidance was positively related to the lifetime burden of depressive episodes in mood disorders.[8] Patients with cyclothymic, anxious, and irritable temperaments had more complicated presentations.[10] The temperament characteristics in mood disorders such as low self-directedness and high self-transcendence were associated with suicide attempts.[11] Impulsivity and poor controllability could increase the risk of suicidal acts in patients with BD who had suicidal ideation.[12] In addition, patients with different temperament characteristics tended to have distinguishing treatment outcomes.[13,14] The above pieces of evidence indicate that temperament might be a potential indicator for early detection and outcome prediction.

Brain structural abnormality, as an aspect of neuropathology, is also associated with mood disorders. Of all the brain regions, the frontal and temporal lobes are the critical structures of affective and cognitive circuits that are implicated in the underlying pathophysiology of mood disorders.[15,16] A series of large-scale magnetic resonance imaging (MRI) studies conducted by the ENIGMA consortium demonstrated that patients with BD and MDD had reduced cortical thickness in frontal and temporal areas and smaller volume of subcortical structures.[17–20] The volume of prefrontal and temporal cortex was found to be decreased.[21,22] Moreover, compared with patients with MDD, patients with BD had smaller gray matter volume and thinner cortical thickness in these regions.[23,24] Remarkably, brain structural abnormalities were not correlated with the severity of symptoms, but were influenced by genetic factors, age, living habits, age of onset, duration of disease, number of mood episodes, psychiatric medications and even body mass index.[17,18,25,26] These might imply that the change of brain structure is a long-term process that started well before the onset of disease. Therefore, the effects of temperament on the brain development should not be ignored.

Numerous neuroimaging studies in healthy populations have revealed associations between temperament and brain structure and function. Schilling and colleagues' study[27] suggested that impulsiveness was related to the gray matter volume in the left orbitofrontal cortex among adolescence. Cyclothymic, hyperthymic and anxious temperaments were correlated with white matter properties in a wide brain area, including bilateral frontal and temporal regions.[28] Healthy individuals with significant cyclothymic temperament had higher glucose metabolism in the right superior parietal gyrus.[29] The ascending scores in self-directedness predicted higher brain serotonin transporter binding potential in the raphe nucleus.[30] In the aspect of integrative brain function, cyclothymic and depressive temperaments had opposite relationships with the variability of intrinsic neuro-networks, especially the sensorimotor network.[31] These studies consistently show that temperament affects brain structure and function.

The associations between structural and functional brain changes and temperament were detected in relatives of patients with BD.[32,33] Previous studies have also suggested that temperament could affect the brain function of patients with MDD.[34,35] However, the effects of temperament on the morphology of frontal and temporal cortex have not yet been understood fully. For this reason, we conducted this study to examine both temperament and brain structure in patients with mood disorders. We hypothesized that the brain volumes of frontal and temporal gyrus and the temperament characteristics in patients with BD are different from those in patients with MDD and healthy control subjects (HCs). Moreover, we hypothesized that temperament characteristics are associated with gray matter volume in these different regions.

Methods

Participants

The participants included in our study were from two clinical trials (http://www.clinicaltrials.gov; Clinical Trial Registry ID: NCT01938859 and NCT01764867), which were conducted in the Division of Mood Disorders, Shanghai Mental Health Center (SMHC), Shanghai Jiao Tong University from July 2013 to June 2017. The studies

were approved by the Institutional Review Board of the SMHC. All participants signed a written informed consent at enrolment to comply with the Declaration of Helsinki.

In this study, enrolled patients with BD or MDD were right-handed Han Chinese with education levels of junior high school or above, and between 18–45 years old. They were screened by well-trained psychiatric residents using the Chinese version of the MINI-International Neuropsychiatric Interview (M.I.N.I.) in the out-patient clinic of SMHC. The diagnosis was made by two senior doctors based on the Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition-Text Revision (DSM-IV-TR). All participants were required to be in a current depressive episode with Hamilton Depression Rating Scale-17 items (HAMD) total score ≥ 17, score of HAMD item-1 ≥ 2 and total score of Young Mania Rating Scale (YMRS) ≥ 10. However, patients with rapid cycling, current mixed affective episode, other psychiatric comorbidity, substance and alcohol abuse, history of neuromodulation treatment (e.g. electroconvulsive therapy) within 6 months or a history of brain trauma or severe physical condition were excluded. The exclusion criteria also included any contraindication for MRI (e.g. metal implant or claustrophobia), pregnancy or planning for pregnancy or lactating.

Healthy control participants matched with patients in age, sex, ethnicity and education were recruited from local community and college through posted advertisements. All eligible HCs had no history of mental illness, with HAMD total score < 7 and YMRS total score < 5, no history of substance use, head trauma or other significant medical conditions, no family history of major psychiatric disorders, and no contraindication for MRI.

Clinical Evaluation Instruments and Assessment

Demographic information and clinical characteristics of all participants were collected. The severity of current symptoms was assessed using HAMD, Hamilton Anxiety Rating Scale (HAMA) and YMRS. The Chinese short version of Temperament Evaluation of Memphis, Pisa and San Diego - Auto questionnaire (TEMPS-A) was used to evaluate the temperament characteristics. The short version of TEMPS-A is a self-reported, yes-or-no type of questionnaire with 39 items that generate 5 temperament subscales including cyclothymic, depressive, irritable, hyperthymic and anxious.[36] The Chinese version has excellent reliability (Cronbach α = 0.92, test-retest correlation coefficient = 0.90) and validity.[5]

Neuroimaging Acquisition and Data Processing

All participants were scanned on the same Siemens Magnetom Verio 3T scanner (Erlangen, Germany) at the Radiological Department of SMHC after the clinical assessment. The T1-weighted magnetic resonance imaging (MRI) data were obtained using a 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the repetition time (TR) = 2530 ms, time to echo (TE) = 3.65 ms, inversion time (TI) = 1100 ms, field of view (FOV) = 256×256 mm, matrix = 256×256, 1 mm isotropic voxels, flip angle (FA) = 7º, bandwidth = 180 Hz/pixel, echo spacing = 8.5 ms, and in-plane acceleration factor = 2. In total, 105 patients with BD, 225 patients with MDD and 196 HCs were scanned successfully.

The FreeSurfer 6.0 software suite (http://surfer.nmr.mgh.harvard.edu/) was used to process the T1-weighted MRI data. The procedure included removing non-brain tissue, Talairach transformation, automatic segmentations of cortical and subcortical regions, intensity normalization, and automated topology correction. The Desikan-Killiany atlas was used to yield 68 gray matter volume measures and the total intracranial volume (TIV). In this study, we included the following 22 regions in frontal and temporal cortex as the regions of interest (ROIs): bilateral caudal middle frontal gyrus, inferior temporal gyrus, lateral orbitofrontal gyrus, medial orbitofrontal gyrus, middle temporal gyrus, inferior frontal gyrus (consisting of pars opercularis, pars orbitalis and pars triangularis), rostral middle frontal gyrus (RMFG), superior frontal gyrus, superior temporal gyrus, frontal pole and temporal pole.

The quality control protocol for the T1-weighted MRI dataset consisted of two steps: a visual inspection done by a trained neuroradiologist and then the ENIGMA protocol (http://enigma.ini.usc.edu/) and Qoala-T[37] were used for double checking. As a result, 90 patients with BD, 189 patients with MDD and 162 HCs were enrolled.

Statistical Analysis

The statistical analyses were performed with IBM SPSS Statistics 23 for Windows (Chicago Inc., USA). The Kolmogorov–Smirnov test was used to evaluate the normality of measurement data. The Kruskal–Wallis test or Mann–Whitney *U*-test were performed for abnormally distributed variables. The chi-square test was used for categorical

variable. The post hoc multiple comparisons of demographic, clinical information and TEMPS-A scores were corrected by Bonferroni.

Regarding the gray matter volume, analysis of covariance (ANCOVA) with age, sex, education years and TIV as covariates was conducted. The multiple comparisons of all ROIs were corrected by false discovery rates (FDR).[38] In addition, the effect size was evaluated by Cohen's *d*.

To explore the relationships between the demographic, clinical characteristics and temperament and the gray matter volume in ROIs in pooled patients, multiple forward stepwise linear regression analyses were performed with FDR for multiple comparison correction. The gray matter volume in ROIs with significant differences between groups were chosen to be the dependent variables. The independent variables included TIV, sex, education year, age of onset, number of mood episodes, illness duration, HAMA total score, HAMD total score, YMRS total score, the scores of TEMPS-A subscales and medication history.

All the statistical analyses were two-tailed with significance threshold set at P<0.05 (Bonferroni or FDR correction).

Results

Demographic and Clinical Characteristics

There were no differences in age and sex between groups. HCs had more years of education than patients with BD. Of the patients with BD, 31 were BD type I (BD-I), 59 were BD type II (BD-II). Compared with patients with MDD, patients with BD had earlier ages of onset, higher numbers of mood episodes and longer illness duration. Although YMRS scores were low in all groups, the BD group had higher scores than both MDD and HC groups. There were no differences between BD and MDD groups in HAMD and HAMA total score, percentage of positive family history of psychiatric disorders and percentage of never-medicated patients (Table 1). Of all the patients, only 72 (30.38%) had a history of psychiatric medication treatment. In the BD group, only 5 (6.49%) patients were on mood stabilizers, 4 (5.19%) patients were on antipsychotics, and 10 (12.99%) patients were on antidepressants. In the MDD group, 31 (19.38%) patients were on antidepressants, 7 (4.38%) patients were on antipsychotics, and 2 (1.25%) patients were on mood stabilizers.

Temperament Characteristics

As shown in Tables 2 and S2, regardless of diagnosis and history of treatment with psychotropics, the TEMPS-A total scores and all subscale scores except the hyperthymic subscale were significantly higher in patients than those in HCs. No difference was found in the hyperthymic subscale score between patients with MDD and HCs. Compared with patients with MDD, patients with BD had higher TEMPS-A total scores and cyclothymic, irritable and hyperthymic subscale scores.

Patients with BD-I had the same temperament characteristics. The TEMPS-A total score and the scores of all subscales in patients with BD-I were higher than those in HCs, while the TEMPS-A total score, the score of

Table 1 The Demographic Information and Clinical Characteristics of Participants

Variables	BD (N=90)	MDD (N=189)	HC (N=162)	Values	P
Age (years)	26.44 (5.87)	27.84 (6.19)	27.77 (5.21)	4.042	0.133
Sex (Male/Female)	36/54	71/118	67/95	0.539	0.764
Education (years)	14.78 (2.43)	14.98 (2.83)	15.51 (2.75)	8.424	0.015[a,c]
BD subtypes (I/II)	31/59	n/a	n/a		
HAMD total score	21.82 (4.48)	21.20 (4.11)	1.58 (1.76)	301.31	<0.001[a,c,d]
YMRS total score	2.46 (3.17)	1.11 (1.51)	1.00 (1.92)	26.855	<0.001[a,c,d,e]
HAMA total score	17.70 (7.04)	17.05 (6.44)	n/a	6598.000	0.713
Age of onset (years)	20.16 (5.52)	25.13 (7.17)	n/a	3714.500	<0.001[b]
Number of episodes	5.37 (6.31)	1.65 (1.08)	n/a	1033.500	<0.001[b]
Illness duration (months)	73.48 (57.31)	45.00 (55.30)	n/a	3401.500	<0.001[b]
Positive family history of psychiatric disorders (n, %)	16 (21.05)	26 (15.95)	n/a	0.931	0.335
Never medicated (n, %)	52 (67.53)	114 (70.80)	n/a	0.265	0.607

Notes: Continuous variables are shown as mean (standard deviation); Medication status and family history are shown as number (percentage). P values were assessed using chi-square, Kruskal–Wallis test or Mann–Whitney test. [a]Differences between three groups (P < 0.05); [b]Differences between patients with BD and patients with MDD (P < 0.05); [c]Post-hoc tests between patients with BD and healthy controls survived Bonferroni correction (P < 0.017); [d]Post-hoc tests between the patients with MDD and healthy controls survived Bonferroni correction (P < 0.017); [e]Post-hoc tests between diagnostic groups survived Bonferroni correction (P<0.017).

Abbreviations: BD, bipolar disorder; MDD, major depressive disorder; HC, healthy control; HAMD, Hamilton Depression Scale; YMRS, Young Mania Rating Scale; HAMA, Hamilton Anxiety Scale; n/a, not available or not applicable.

Table 2 The Differences of Temperament Between Groups (TEMPS-A)

Variables	BD	MDD	HC	Values	P
TEMPS-A total score	20.59 (6.17)	15.29 (6.37)	6.44 (5.11)	173.739	<0.001[a,b,c,d]
TEMPS-A Cyclothymic	8.85 (2.65)	6.49 (3.16)	1.92 (2.37)	174.835	<0.001[a,b,c,d]
TEMPS-A Depressive	4.68 (2.10)	4.06 (2.29)	0.78 (1.23)	173.296	<0.001[a,b,c]
TEMPS-A Irritable	2.44 (1.88)	1.55 (1.58)	0.73 (1.12)	57.024	<0.001[a,b,c,d]
TEMPS-A Hyperthymic	3.36 (2.31)	2.02 (1.89)	2.30 (1.95)	17.409	<0.001[a,b,d]
TEMPS-A Anxious	1.27 (1.18)	1.18 (1.06)	0.70 (0.82)	17.199	<0.001[a,b,c]

Notes: Variables are shown as mean (standard deviation); P values were assessed using Kruskal–Wallis test or Mann–Whitney test. [a]Differences between three groups ($P < 0.05$); [b]Post-hoc tests between patients with BD and healthy controls survived Bonferroni correction ($P < 0.017$); [c]Post-hoc tests between the patients with MDD and healthy controls survived Bonferroni correction ($P < 0.017$); [d]Post-hoc tests between diagnostic groups survived Bonferroni correction ($P < 0.017$).
Abbreviations: BD, bipolar disorder; MDD, major depressive disorder; HC, healthy control; TEMPS-A, the Chinese short version of Temperament Evaluation of Memphis, Pisa and San Diego – Auto questionnaire.

cyclothymic, irritability and hyperthymic subscales were higher than those in patients with MDD (Table S1).

In patients with BD-II, the total score of TEMPS-A, the score of cyclothymic, depressive and irritable subscales were higher than those in HCs, while TEMPS-A total score, score of cyclothymic and hyperthymic subscales were higher than those in patients with MDD (Table S1).

There were no differences in scores of TEMPS-A between patients with BD-I and patients with BD-II (Table S1).

Gray Matter Volume of Frontal and Temporal Cortex

Figure 1 illustrates the effect size of patient–control differences in gray matter volume of 22 ROIs. Compared with HCs, patients with BD had significantly lower gray matter volume in the bilateral RMFG, left temporal pole and right superior temporal gyrus (Cohen's d range: −0.47~−0.10, FDR correction) (Figure 1A and Table S3). The gray matter volume in the left superior frontal gyrus in patients with BD tended to be lower than that in HCs (Cohen's $d = -0.13$, $P_{FDR} = 0.05$). The gray matter volumes in the left inferior temporal gyrus, left temporal pole and bilateral RMFG in patients with BD-I were smaller than those in HCs (Cohen's d range: −0.48~−0.29, FDR correction); patients with BD-II only had decreased gray matter volume in the left temporal pole (Cohen's $d = -0.46$, $P_{FDR} < 0.001$) (Table S5). There were no differences between patients with BD-I and patients with BD-II (Cohen's d range: −0.62~0.22). In never medicated patients, only the gray matter volume in the left temporal pole was decreased when compared with HCs (Cohen's $d = -0.50$, $P_{FDR} = 0.007$) (Table S6). No frontal and temporal regions with increased gray matter volume survived FDR correction.

Compared with HCs, patients with MDD only had significantly lower gray matter volume in the bilateral temporal pole (Cohen's $d = -0.37$ and −0.27, $P_{FDR} < 0.01$) (Figure 1B and Table S4). Patients with MDD also had

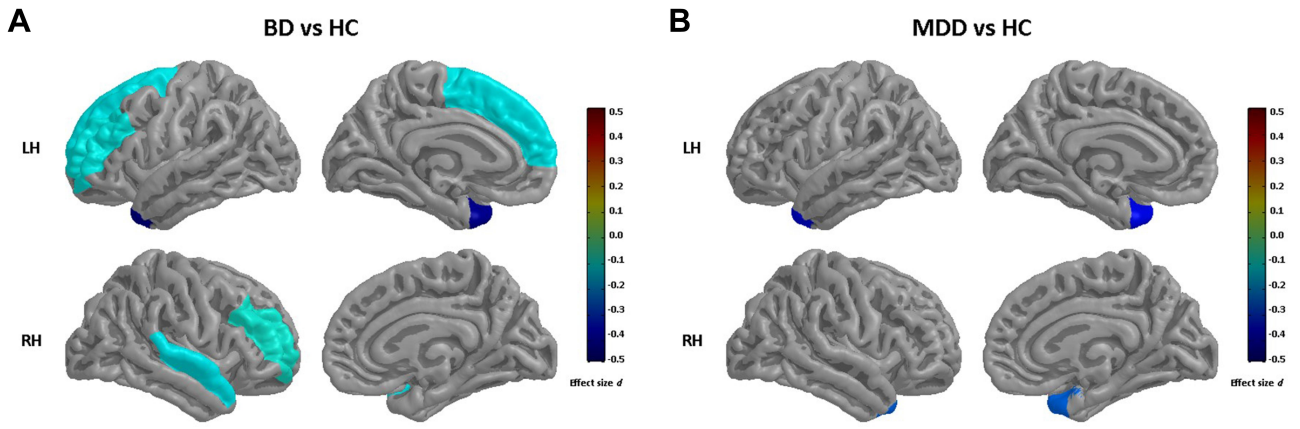

Figure 1 The regions of interest (ROIs) with a significant decrease in gray matter volume in patients with bipolar disorder (BD) and major depressive disorder (MDD). Cohen's d effect sizes are plotted on template image. (**A**) The differential ROIs between patients with BD and healthy controls (HCs); (**B**) The differential ROIs between patients with MDD and HCs.
Abbreviations: LH, left hemisphere; RH, right hemisphere.

slightly reduced gray matter volume in the left inferior temporal gyrus and bilateral RMFG but this did not survive FDR correction (Cohen's *d* range: −0.20~-0.17). There were no frontal and temporal regions showing increased volume. Patients with MDD who were never medicated had the same changes in gray matter volume (Cohen's *d* = −0.49 and −0.44, $P_{FDR} = 0.001$) (Table S6).

There were no significant differences that survived FDR correction between patients with BD and patients with MDD in any gray matter volume (Cohen's *d* range: −0.13~0.23), including the comparisons between BD-I and MDD (Cohen's *d* range: −0.30~0.21), between BD-II and MDD (Cohen's *d* range: −0.09~0.36) and between never-medicated BD and MDD (Cohen's *d* range: −0.09~0.33).

Relationships Between Gray Matter Volume and Clinical Characteristics and Temperament

The relationships between gray matter volume in ROIs with significant differences and all subscale scores of TEMPS-A and clinical variables in pooled patients were explored.

For clinical characteristics, the results indicated that age of onset and illness duration were negatively associated with the gray matter volume in the bilateral RMFG and right superior temporal gyrus ($P_{FDR} < 0.05$). There were no significant relationships that survived FDR correction between number of mood episodes, HAMA total score, HAMD total score, YMRS total score, history of treatment with psychotropics and gray matter volume in any ROIs (Tables S3 and S7).

For temperament, as shown in Table 3, the TEMPS-A hyperthymic subscale score was negatively associated with gray matter volume in right RMFG. The standardized coefficient indicated that after controlling the TIV and the severity of disease (i.e. age of onset and illness duration), when the score of TEMPS-A hyperthymic subscale increased one unit, the gray matter volume in the right RMFG decreased by 16.3% unit. There were no associations between other temperament subscales and gray matter volume of ROIs (Tables S3 and S7).

Discussion

In this study, we reported that patients with BD and patients with MDD had higher scores of cyclothymic, depressive, irritable, and anxious temperaments compared with healthy participants. The scores of hyperthymic temperament in patients with BD were much higher than those in patients with MDD and HCs. In addition, the scores of cyclothymic and irritable temperament were much higher in patients with BD when compared with patients with MDD. Patients with BD had reduced gray matter volume mainly in bilateral RMFG, left temporal pole and right superior temporal gyrus, while the gray matter volume in bilateral temporal pole in patients with MDD was decreased. There were no significant differences in gray matter volume in frontal and temporal cortex between patients with BD and patients with MDD. The gray matter volume of bilateral RMFG and right superior temporal gyrus were negatively associated with age of onset and illness duration. Of all temperament characteristics, hyperthymic temperament was the only one that was negatively related to the gray matter volume, in right RMFG, among all patients.

Our findings suggested that in addition to depressive and anxious temperament, both patients with BD and patients with MDD had prominent cyclothymic and irritable temperaments, which is consistent with the results of a meta-analysis.[6] The instability and bipolar switching of mood is one of the typical symptoms of BD.[39] Some patients with MDD also have mood swings, such as those patients who have mixed features.[39] The level of cyclothymic and irritable temperaments might be related with the severity of mood instability.[40] Accordingly, patients with BD (both BD-I and BD-II) had more obvious cyclothymia and irritability than patients with MDD in our study. Of note, unlike the patients with MDD and healthy individuals, we found that patients with BD-I and BD-II had higher hyperthymic temperament. This was contrary to the results of the previous meta-analysis[6] which showed lower scores of hyperthymic subscale in patients with BD and patients with MDD than in healthy individuals. Our findings are more consistent with the clinical impression of BD. Even though all patients with BD in the study were in a major depressive episode, they still presented with hyperthymic temperament, suggesting that this is a stable trait marker[41] for BD that is related to the excitability seen in patients with BD[42] and is not changed by current mood state. Furthermore, the same pattern of temperament characteristics could be found in patients who were never medicated. Hence, hyperthymic temperament might be considered as a candidate endophenotypic difference between BD and MDD.

We included most of the important frontal and temporal regions as ROIs to detect the different brain structures which are related to cognitive and affective regulation. The results showed decreased gray matter

Table 3 Results of Multiple Linear Regression Analysis (Forward Stepwise)

Variables	Left Rostral Middle Frontal Gyrus Adjusted $R^2 = 0.441$			Right Rostral Middle Frontal Gyrus Adjusted $R^2 = 0.451$			Right Superior Temporal Gyrus Adjusted $R^2 = 0.359$		
	Standardized Beta	t	P[a]	Standardized Beta	t	P[a]	Standardized Beta	t	P[a]
TIV	0.617	10.597	<0.001[b,c]	0.646	11.023	<0.001[b,c]	0.544	8.720	<0.001[b,c]
Sex	−0.035	−0.456	0.649	−0.071	−0.944	0.346	−0.052	−0.630	0.529
Education years	0.023	0.391	0.697	−0.069	−1.172	0.243	0.005	0.086	0.931
Age of onset	−0.225	−3.410	0.001[b,c]	−0.268	−4.079	<0.001[b,c]	−0.273	−3.856	<0.001[b,c]
Number of mood episodes	0.022	0.351	0.726	0.069	1.123	0.263	−0.035	−0.528	0.598
Illness duration	−0.266	−4.022	<0.001[b,c]	−0.187	−2.844	0.005[b,c]	−0.194	−2.733	<0.007[b,c]
HAMA total score	−0.032	−0.544	0.587	−0.082	−1.409	0.161	−0.139	−2.234	0.027
HAMD total score	−0.069	−1.186	0.237	−0.059	−1.007	0.315	−0.013	−0.170	0.865
YMRS total score	0.013	0.214	0.831	0.003	0.045	0.964	0.048	0.757	0.450
TEMPS-A Cyclothymic	−0.062	−1.002	0.318	0.014	0.221	0.826	−0.017	−0.241	0.810
TEMPS-A Depressive	0.008	0.134	0.894	−0.056	−0.952	0.343	0.017	0.267	0.790
TEMPS-A Irritable	0.022	0.373	0.710	0.044	0.708	0.480	0.042	0.637	0.525
TEMPS-A Hyperthymic	−0.103	−1.736	0.084	−0.163	−2.761	0.006[b,c]	−0.086	−1.334	0.184
TEMPS-A Anxious	0.000	0.000	1.000	0.028	0.471	0.639	0.015	0.235	0.814
History of treatment with psychotropics	0.055	0.923	0.358	−0.550	−0.927	0.357	0.047	0.719	0.473

Notes: [a]Uncorrected P values; [b]uncorrected $P < 0.05$; [c]survived FDR correction ($P_{FDR} < 0.05$).

Abbreviations: TIV, total intracranial volume; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale-17 items; YMRS, Young Mania Rating Scale; TEMPS-A, The Chinese short version of Temperament Evaluation of Memphis, Pisa and San Diego – Auto questionnaire.

volume in left RMFG and bilateral temporal pole in patients with BD, but only a decrease in bilateral temporal pole in patients with MDD. These changes mainly occurred in patients with BD-I. These abnormalities had been reported in previous studies as well.[17,43] RMFG is one of the hubs for high-order executive functioning such as working memory, executive cognition, emotion regulation and planning.[44–46] The temporal pole has been considered as an association cortex involved in cognitive and socioemotional processes, including semantic memory, empathy, emotion recognition and regulation.[47–49] The cognition and emotion processes in patients with BD and MDD were found to be impaired.[50] The cognitive impairments in patients with BD were worse and involved more domains than those in patients with MDD. Therefore, the brain abnormalities we found were expected. However, the effect sizes of the patient–control differences were small, which might be explained by the impact of demographic characteristics (e.g. age, sex) and clinical variables such as illness duration, number of mood episodes and psychiatric medications on brain structure.[17,18] In our study, patients were generally young and had relatively short illness duration and few mood episodes (as shown in Table 1). Some patients with MDD were in their first mood episode at enrollment. About 70% of the patients were never prescribed psychotropic medications. These factors might reduce the negative effects of diseases on brain structure. For all this, we still captured the negative effects of illness duration on gray matter volume. However, the age of onset also was negatively related to the gray matter volume. This might imply that the age of onset was a nonlinear modulator for the structural brain abnormalities in patients with mood disorders.[51]

According to our results, patients with more prominent hyperthymic temperament had smaller gray matter volume in right RMFG. This was similar with the findings of previous studies that individuals with higher levels of impulsivity and more positive affects had thinner cortical thickness in RMFG.[52,53] One underlying mechanism might be the association between temperament and coping strategy. Individuals with poor coping strategy usually are more sensitive to negative life events which can lead to chronic stress.[54] Higher cortisol in people with chronic stress would then affect the morphological changes of RMFG via an oxidative stress pathway.[55,56] Another potential underlying mechanism is that the temperament as a phenotype can affect the brain structure through genetic factors.[57,58] In addition, serotonin transporter density in the brain was correlated with temperament which might be another mechanism to affect the brain structure.[30] Again, the effect sizes of the associations between temperament and gray matter volume in RMFG in our study were small. We speculated that this is because a variety of factors besides temperament might have effects on the brain structure.[25] However, because of lack of data, we were unable to perform a multivariate analysis to determine the relative contributions of temperament and other clinical factors. Relevant studies are needed in the future.

Limitations

There are some limitations that should be considered. First, the cross-sectional design of this study did not allow exploration of the development of brain structural changes in patients and healthy individuals. Second, patients in this study were in a current depressive episode. The recall bias of medical history and self-rated scores of TEMPS-A might be a potential confounding factor. Third, most of our BD patients were BD-II. This may affect the interpretation of the results in patients with BD-I. Fourth, some patients had a history of psychiatric medication treatment which might affect brain structure and there may be differences in current and past medications between the BD and MDD patients. A strength of our study is that we had a large proportion of patients who were never medicated. Fifth, even though we screened the patients carefully, it is still possible that some patients with MDD may convert to a diagnosis of BD in the future. Sixth, the functional changes related to temperament in patients with mood disorders were not studied, but can be examined in future studies. Finally, because of a lack of data we could not exclude the effects of other potential confounding factors such as childhood maltreatment, lifestyles, or psychosocial adversity.

Conclusion

Our study provided information for understanding the associations between temperament and structure of frontal and temporal cortex in patients with mood disorders. Patients with BD and patients with MDD had different temperament characteristics. The prominent temperament domains in patients with BD were cyclothymia, irritability and hyperthymia. Patients with BD had reduced gray matter volume in frontal and temporal cortex. Patients with more prominent hyperthymia temperament had reduced gray matter volume in bilateral frontal gyrus.

These findings suggest that hyperthymic temperament might be a distinct phenotype for patients with BD. Further cross-sectional and longitudinal studies in non-medicated patients with multivariate analysis are needed to explore the relative effects of temperament and other clinical factors on changes in brain structure and function.

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