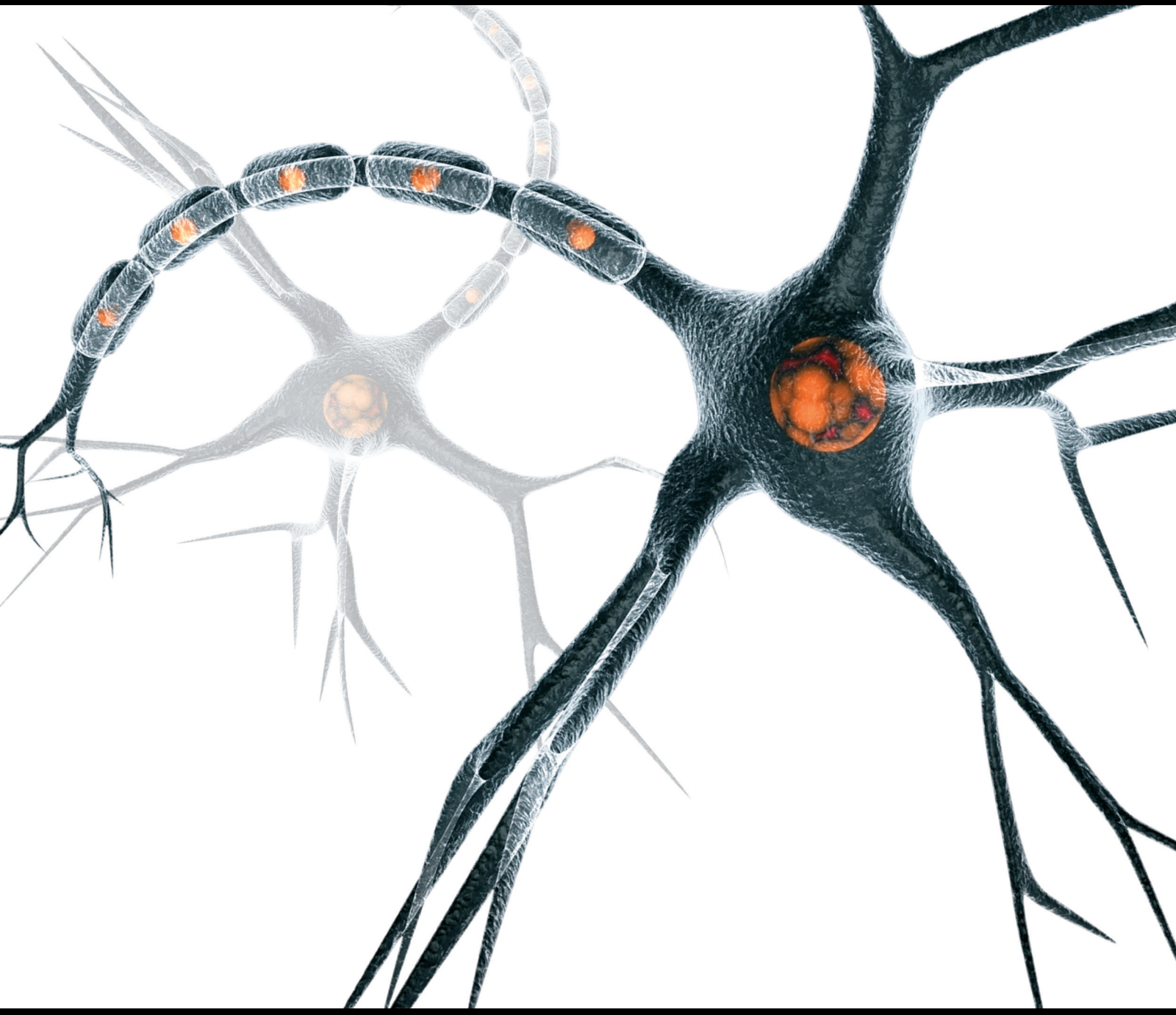
Neural Plasticity

Neural Plasticity in Mood Disorders 2020

Lead Guest Editor: Bingjin Li
Guest Editors: F. Scott Hall and Aijun Li



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Research Article

Brain Networks Connectivity in Mild to Moderate Depression: Resting State fMRI Study with Implications to Nonpharmacological Treatment

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Network mechanisms of depression development and especially of improvement from nonpharmacological treatment remain understudied. The current study is aimed at examining brain networks functional connectivity in depressed patients and its dynamics in nonpharmacological treatment. Resting state fMRI data of 21 healthy adults and 51 patients with mild or moderate depression were analyzed with spatial independent component analysis; then, correlations between time series of the components were calculated and compared between-group (study 1). Baseline and repeated-measure data of 14 treated (psychotherapy or fMRI neurofeedback) and 15 untreated depressed participants were similarly analyzed and correlated with changes in depression scores (study 2). Aside from diverse findings, studies 1 and 2 both revealed changes in within-default mode network (DMN) and DMN to executive control network (ECN) connections. Connectivity in one pair, initially lower in depression, decreased in no treatment group and was inversely correlated with Montgomery-Asberg depression score change in treatment group. Weak baseline connectivity in this pair also predicted improvement on Montgomery-Asberg scale in both treatment and no treatment groups. Coupling of another pair, initially stronger in depression, increased in therapy though was unrelated to improvement. The results demonstrate possible role of within-DMN and DMN-ECN functional connectivity in depression treatment and suggest that neural mechanisms of nonpharmacological treatment action may be unrelated to normalization of initially disrupted connectivity.

1. Introduction

Depression is a widespread psychiatric disorder associated with a number of different symptoms. The diversity of symptoms implies existence of multiple disruptions of neural circuits in depression, and this may be the reason for diverse findings in studies of brain networks in depression.

A body of research considers default mode network (DMN) as a central one for depression development. Depression is mostly associated with increased functional connectivity (FC) within DMN [1–9] with a few contradicting findings [1, 10–13]. External FC of the DMN is increased to anterior cingulate [1, 14–15], thalamus [14], and pars triangularis [3] and decreased to fusiform gyrus, motor cortices [16], cerebellum, insula [17], thalamus, putamen, and calcarine sulcus [18] with mixed findings for hippocampus [1, 18–19]. On internetwork level, depression is associated with less coupling of DMN and anterior salience network (ASN) [2]

and DMN and executive control network (ECN) [1] or more ventral DMN and ECN FC [19].

Within-DMN FC is positively correlated with the number of previous depressive episodes [2] with mixed results for current severity [2, 16]. DMN external connectivity to subgenual anterior cingulate is positively correlated with the duration of current depressive episode [14], while posterior cingulate FC is negatively correlated to Montgomery-Asberg Depression Rating Scale (MADRS) [13] and Hamilton Depression Rating Scale (HAM-D) [18] scores. DMN-ASN [4] and DMN-ECN [8] connectivity is inversely correlated with HAM-D score. However, DMN-ECN links are related to depression severity [20] and rumination levels [19].

Task-positive network disruptions are also frequent in depression. Within-network FC of executive control network (ECN) may be excessive [8, 21–23] or deficient [15, 24] in depression. These findings may be partly explained by increased global ECN intraconnectivity and less FC between its prefrontal and parietal nodes [21]. Network's external connectivity is diminished in depression [25] to cerebellar and primary visual network [26] and to various brain regions [17].

Within-ECN coupling in depressed women is correlated with negative self-directed thoughts [27], and ECN-DMN FC is related to rumination [19]. However, within-ECN, ECN-DMN, and some other external ECN FC are negatively associated with HAM-D score [8, 17].

Anterior salience network (ASN) comprising key cortical emotional areas may be over- [21], under- [2], or normally [1] connected in depression. Increased FC of ASN to left precentral and left angular gyri [28] and to lateral prefrontal areas [22] and effective connectivity of both to and from precuneus [3] is related to depression. Major depression is characterized by weakened ASN FC to medial frontal gyrus and of anterior cingulate to posterior insula, middle temporal gyrus, and cerebellum [28–29].

Within-ASN and ASN-DMN FC are inversely related to number of previous depressive episodes [2] and to HAM-D score [4, 28]. However, ASN FC with prefrontal cortex is associated with subjective depression [22].

Depression may be related to impaired FC of some other networks, e.g., sensorimotor [30–33], ventral and dorsal attention [32–33], language [25], affective [11, 17, 31], visual [23, 33], and audial [23, 33]. Some researchers also proposed spatial brain patterns that they view as networks of depression [34–36] or its certain features like rumination [37] or social emotion disruption [5].

Results of above mentioned studies look rather inconsistent, with many networks demonstrating impairment in few studies only. Evidence for increased or decreased FC of three major networks sounds mostly equivocal. The only solid result is increased within-DMN FC, although even this one is actually a generalization of data from certain brain regions which are different from study to study. The relationships between FC measures and depression severity are unclear for all global networks, including DMN. In some studies, FC findings were unrelated to clinical or behavioral measures [11, 23, 38].

Little is known about modification of network FC in depression following nonpharmacological treatments. Psychotherapy-related results comprise reduced dorsal DMN FC to dorsal anterior cingulate after short course of behavioral activation in subclinical depression [39] and ventral attention network intra- and interconnectivity decrease correlated with improvement on MADRS following the cognitive-behavioral treatment for depression or posttraumatic stress disorder [40]. Brakowski et al. [41] in their review claim that psychotherapy influences predominantly fronto-limbic circuit.

FMRI neurofeedback targets fronto-limbic circuit via either amygdala or prefrontal cortex activity or effective connectivity between these regions. Training of left amygdala upregulation with positive autobiographical memories leads to increase of amygdala FC to number of areas including frontal cortices [42, 43], which is consistent with fronto-limbic FC restoration hypothesis. Right amygdala deactivation training in healthy volunteers also triggered increase in amygdala—lateral prefrontal cortex FC [44]. Last, a proof-of-concept was reported for effective connectivity training aimed at increasing prefrontal influences on amygdala and decreasing of reverse ones in bottom-up direction [45].

Thus, existing data on network FC changes related to psychotherapy and fMRI neurofeedback do not look conclusive. Preliminary data show some fMRI neurofeedback protocols influence FC in fronto-limbic system; however, more research is needed to establish solid brain network correlates of treatment process.

The aim of the current study was to examine network FC differences between healthy volunteers and patients with mild to moderate depression and test their correlations with depression estimates. In parallel, dynamics of network FC were studied in patients who received either no treatment or some nonpharmacological support such as cognitive-behavioral therapy or neurofeedback. Besides, the role of baseline connectivity scores as treatment response predictors, and correlations of neural and clinical changes were estimated. Last, between-group differences were matched to dynamic differences in order to identify networks that differentiate depressed participants from healthy and change along with treatment or spontaneous symptom reduction.

2. Materials and Methods

2.1. Participants. This study continues our research on network correlates of depression published in [26] with substantially increased sample. The intergroup study involved 21 healthy volunteers received a compensation for a participation and 51 participants featuring mild depression (F32.0), moderate depression (F32.1), or dysthymia (F34.1, single patient) (see Table 1). The dynamic study involved 15 patients with mild or moderate depression scanned twice with 2-3-month interval between the recordings without any treatment received. Eight patients featuring similar conditions received a brief cognitive-behavioral therapy course and 6 patients underwent real-time fMRI neurofeedback course. These groups were also scanned pre- and posttreatment. Subsamples were derived from the major sample of 51 patients.

Table 1: Demographic and clinical characteristics of the groups involved in the study.

Group	Sex	Age, Mean ± SD	IQ, Mean ± SD	MADRS, Mean ± SD	BDI, Mean ± SD	ZSRDS, Mean ± SD
Healthy controls, $N = 21$ (HC)	6 M, 15 F	33.8 ± 8.5	106.0 ± 16.1	—	4.6 ± 4.5	32.1 ± 5.9
Total depressed, $N = 51$ (DEP-51)	13 M, 38 F	33.1 ± 9.5	103.7 ± 14.6	26.7 ± 4.4	20.7 ± 10.0	46.4 ± 7.0
No treatment, $N = 15$ (DEP-NT)	5 M, 10 F	35.2 ± 9.4	100.7 ± 15.2	—	18.4 ± 11.2	44.6 ± 8.3
Treatment, $N = 14$ (DEP-TR)	3 M, 11 F	29.8 ± 8.7	104.7 ± 12.7	28.4 ± 2.4	25.9 ± 10.0	50.9 ± 5.1
Psychotherapy, $N = 8$ (DEP-CBT)	3 M, 5 F	29.1 ± 8.2	109.8 ± 11.1	28.4 ± 2.9	24.1 ± 8.9	48.3 ± 4.6
Neurofeedback, $N = 6$ (DEP-NFB)	6 F	30.7 ± 10.2	96.6 ± 11.5	28.4 ± 1.9	28.3 ± 11.7	55.2 ± 2.3

N: sample size; M: males; F: females; SD: standard deviation; MADRS: Montgomery-Asberg depression rating scale; BDI: Beck depression inventory; ZSRDS: Zung self-rating depression scale. DEP-NT, DEP-TR, DEP-CBT, and DEP-NFB groups are parts of DEP-51 sample.

The sample size for the intergroup study is a tradeoff between preventing false positives and collecting groups of realistic size taking into account MR scanning expenses. Sample size estimation based on expected significance of $p < 0.05$ with any Bonferroni-derived correction ($p < 0.0009$ uncorrected) was not practical from this point of view, so sampling was terminated at the point of expected significance of $p < 0.01$ uncorrected assuming statistical power of 0.8, standard deviation of 0.3 and effect size of 0.8 considered as large so we targeted the most notable effects. Thus, sample size was estimated as $n = (2.56 + 0.84)^2 \times 2 \times 0.3^2 / (0.8 \times 0.3)^2 = 36.125$ for one group, which is 72 for two groups that matches our sample: 21 + 51 = 72. Results significant at $p < 0.05$ were initially marked with further elimination of those results that were absent in the dynamics study to partly counter the false positives problem.

The sample of the dynamics study is even more dependent on practical reasons because each patient of the real-time fMRI neurofeedback group received 11 MR scanning sessions (8 training and 3 diagnostic ones). Thus, with more sessions devoted to each patient in our study, our sample size was comparable to or slightly less than ones of the majority similar studies in depression [46–49] excluding few recent large sample ones [42, 50].

All participants were screened to exclude neurological or psychotic level mental disorders, psychotropic medication or drugs severely influencing blood flow, and contraindications to MRI. Depression condition had not to be bipolar, seasonal, or secondary to other disease. IQ > 70 was proven with Raven Progressive Matrices test for all participants, and self-regulation ability was established in treatment groups with 3 sessions of frontal alpha-asymmetry-based electroencephalographic neurofeedback. All the participants signed informed consent prior to inclusion in study. The study protocol was in accordance with Helsinki Declaration and was approved by local ethic board of Institute of Molecular Biology and Biophysics.

2.2. fMRI Acquisition. The fMRI study was carried out in the International Tomography Center, Novosibirsk, using a 3 T Ingenia scanner (Philips). Functional T2∗-weighted Ssh echo planar imaging scans were acquired using the following parameters: voxel size $2 \times 2 \times 5$ mm, repetition time/echo time = 2500/35 ms, and fat suppression mode. The reference anatomical image was obtained by the T1W 3D turbo field echo method with a voxel size of $1 \times 1 \times 1$ mm. The instruction for participants was to lie still with eyes closed for 6 minutes.

2.3. fMRI Analysis. The first five volumes of each series were discarded to ensure the steady state. The preprocessing of fMRI images was performed with the Matlab (Mathworks, Inc.) and SPM12 (Wellcome Trust Center for Neuroimaging University College London) software. The batch included motion correction, slice timing, normalization of the images to MNI space (resampled at 2 mm3), and smoothing with Gaussian kernel of 8 mm. The default settings were used. Shift to 2 mm or rotation to 2 degrees were considered as excessive head movements. One patient's data were excluded because of head movement and another's due to prominent MR artifacts.

GIFT 3.0.a software was used to perform spatial independent components analysis (ICA). The optimal number of components according to the minimal description length criterion was 20 for volunteers/patients design and 17 for pretreatment/-posttreatment design. ICA was performed using Infomax algorithm with the option to reduce the stochasticity namely ICASSO and intensity normalization. The individual dynamics were reconstructed from the group data with the GICA, procedure of reverse reconstruction, for each participant. The extracted components in spatial domain were described by z-scores of weight coefficients, which indicated the degree of presence of the component time course in a particular voxel.

The average group activation maps for each component and the coefficients of their spatial correlation with gray, white matter and cerebrospinal fluid masks were constructed. Components correlating with mask of either white matter or cerebrospinal fluid more than with one of grey matter were considered as artifacts and excluded from analysis. After that, the correlations with masks of classical resting state networks were calculated for the remaining components. The primary set of components' maps we used was FMRIB/RIC one https://www.fmrib.ox.ac.uk/datasets/brainmap+rsns/, in cases whereNo comma, no strong match to FMRIB/RIC set was found Stanford maps were also tried http://findlab.stanford.edu/functional_ROIs.html. The composition of the components was determined at the threshold $t = 2$. FNC toolbox (http://mialab.mrn.org/software/fnc) was used to calculate temporal correlations between the dynamics of the selected components.

With the Lag-Shift algorithm, the coefficients and the lag times for each pair of networks were computed. The time shift was selected to maximize an absolute value of correlation coefficient. Intergroup differences were estimated with the Student's t test for independent samples, the dynamics of the networks intercorrelations from the first to the second recording—with the t test for paired samples.

For study 1, in each participant, the Pearson correlation coefficient between time series of the components and 6 rigid body head motion parameters were calculated. Additional tests were performed excluding all pairs involving components with correlation coefficient with any motion parameter above margin in certain participant. $R > 0.5$, $r > 0.4$, and all $p < 0.05$ were tested, and $r > 0.4$ was empirically chosen as a tradeoff between reducing maximal allowed correlation and preserving the majority of data units (85.8%). Thus, t test was repeated with exclusion of components correlating with motions to degree of 0.4 or higher, so results significant at first test with all data included and nonsignificant at second test with some data excluded were considered as motion-related false positives. For dynamic comparisons, no such additions were implemented for small samples. Interactions between functional connectivity and depression scales were measured with Spearman correlation implemented in IBM SPSS 21.0 software.

2.4. Clinical and Psychological Measures. Russian versions of Beck Depression Inventory (BDI) and Zung Self Rating

Table 2: Independent component analysis results for depressed vs. controls comparison.

IC no.	GM	WM	CSF	Accepted	Best match
1	0.07	-0.05	0.00	Yes	Default mode network ($r = 0.69$)
2	0.11	-0.09	-0.03	Yes	Right frontoparietal network ($r = 0.69$)
3	0.15	-0.19	0.17	No	
4	0.06	-0.16	0.29	No	
5	0.11	-0.07	-0.03	Yes	Medial visual network ($r = 0.82$)
6	0.02	-0.02	0.01	No	
7	0.00	-0.05	0.12	No	
8	0.20	-0.19	0.02	Yes	Audial network ($r = 0.62$)
9	0.08	-0.07	-0.02	Yes	Left frontoparietal network ($r = 0.76$)
10	0.23	-0.20	-0.03	Yes	Lateral visual network ($r = 0.46$), occipital pole ($r = 0.40$)
11	0.11	-0.11	0.05	Yes	–/Stanford ventral DMN ($r = 0.48$)
12	0.14	-0.17	0.12	No	
13	0.01	0.01	-0.02	Yes	Executive control network ($r = 0.62$)/Stanford dorsal DMN ($r = 0.43$)
14	0.26	-0.25	0.11	No*	
15	-0.44	0.36	0.05	No	
16	0.21	-0.21	0.06	Yes	Default mode network ($r = 0.57$)
17	0.15	-0.19	0.07	Yes	–/Stanford language network ($r = 0.43$)
18	-0.06	0.10	-0.08	No	
19	0.09	-0.12	0.06	No	
20	0.17	-0.17	0.09	Yes	Cerebellum network ($r = 0.37$)

IC: independent component; GM: gray matter; WM: white matter; CSF: cerebro-spinal fluid; r: correlation coefficient; *excluded for an artifact localization based on visual examination.

Depression Scale (ZSRDS) were introduced to participants. Ones who were observed in dynamics filled the forms twice, at the start and finish point. Treatment groups also were assessed with Montgomery-Asberg depression rating scale (MADRS) by an experienced psychiatrist during the interview in the beginning and end of treatment course. Some participants did not show up for the post-course assessment which led to some missing data points.

2.5. Treatments. Cognitive behavioral therapy sessions took place in a special room in the Institution of Molecular Biology and Biophysics. A psychiatrist and a clinical psychologist together led treatment groups of five patients at a time. Course covered such topics as ABC and ABCDE models, automatic thoughts detection, links between automatic thoughts and emotions, cognitive distortions, thoughts modification techniques, positive reappraisal, and assertiveness. So, course involved some training and educational aspects. Individual treatment led by one of the specialists comprised more personalized and symptom-focused intervention, problems detection, work with priorities, belief-emotion links, automatic thoughts, and cognitive distortions detection and modification, practicing in ABC model. It also dealt with behavioral and motivational difficulties and included home assignments after each session. In total, each participant of this group received 8 individual and 8 group sessions.

Neurofeedback was performed at the International Tomographic Center with the facility discussed in 2.2.1 and aimed at improving the participants' ability to regulate left medial prefrontal cortex which is supposed to be involved in positive emotions regulation through connections to amygdala. The total scanning time was approximately 30 minutes for each session. Five minutes were spent on the placement of participant into scanner and acquisition of reference images, and 25 minutes were devoted to neurofeedback per se. On even sessions, participants spent 10 minutes of neurofeedback time for a transfer run in which they received no feedback and had to rely on their established strategies of signal regulation. In total, each participant of this group received 8 individual sessions.

3. Results

In study 1, 11 of 20 components suited criterion of grey matter prevalence (see Table 2), which led to 55 pairs. Seven pairs demonstrated intergroup differences significant at $p < 0.05$ (see Table 3). After exclusion of motion-correlated data, five of them still featured significant differences (see Table 3), assuming these results were unrelated to motion (Figure 1).

FC in two pairs was demonstrated to be slightly positively correlated with ZSRDS scores in combined group of healthy and depressed participants (see Table 4). No significant results were found in separate groups.

In study 2, 13 of 17 components were considered as grey matter ones (see Table 5), so 78 pairs were tested. Differences in a few pairs were found in patients who did not receive the treatment (see Table 6, Figure 2). FC in some pairs changed after the psychotherapy course or after neurofeedback course (see Table 6, Figure 3). FC in a few pairs changed while

Table 3: Results of depressed vs. controls comparison in all cases (left part) and in cases correlated with 6 solid body motion parameters less than $r = 0.4$ on individual level (right part).

Pair	All cases				$r < 0.4$ with motion parameters			
	HC, Mean ± SD	DEP-51, Mean ± SD	t	p	HC, Mean ± SD	DEP-51, Mean ± SD	t	p
1-9 (DMN-LFr)	−0.09 ± 0.27	0.14 ± 0.32	−2.93	0.005	−0.11 ± 0.27	0.13 ± 0.33	−2.88	0.005
1-16 (DMN-DMN)	0.52 ± 0.19	0.35 ± 0.38	2.59	0.012	0.54 ± 0.19	0.38 ± 0.34	2.34	0.023
2-20 (RFr-Cer)	0.04 ± 0.32	0.21 ± 0.30	−2.13	0.037	0.02 ± 0.33	0.19 ± 0.31	−1.99	0.051 (n/s)
5-8 (mVis-AN)	0.15 ± 0.36	0.37 ± 0.38	−2.32	0.023	0.15 ± 0.36	0.39 ± 0.36	−2.50	0.015
5-17 (mVis-LN)	0.13 ± 0.29	−0.02 ± 0.35	1.89	0.066 (n/s)	0.15 ± 0.28	−0.10 ± 0.32	2.96	0.005
9-16 (LFr-DMN)	−0.12 ± 0.21	0.07 ± 0.29	−2.97	0.004	−0.13 ± 0.21	0.08 ± 0.29	−3.31	0.002
11-13 (DMN-ECN)	0.03 ± 0.37	0.23 ± 0.30	−2.34	0.022	0.02 ± 0.38	0.23 ± 0.31	−2.27	0.027
11-17 (DMN-LN)	0.04 ± 0.30	0.18 ± 0.34	−2.13	0.037	−0.16 ± 0.30	0.01 ± 0.32	−1.97	0.055 (n/s)

SD: standard deviation; DMN: default mode network; LFr: left fronto-parietal network; RFr: right fronto-parietal network; Cer: cerebellar network; mVis: medial visual network; AN: audial network; LN: language network; ECN: executive control network; t: t test value; p: 2-tailed significance level; n/s: nonsignificant.

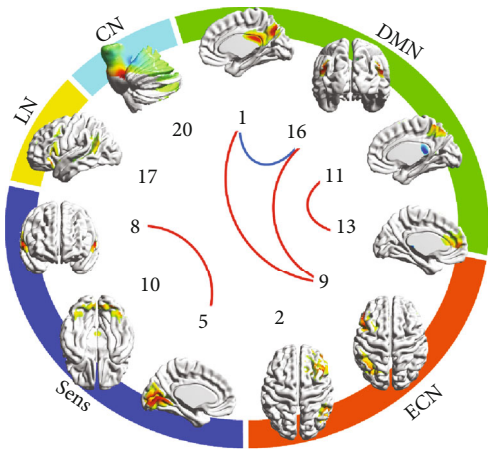

Figure 1: Results of depressed vs. controls comparison. IC numbers match ones of Tables 2 and 3. IC spatial distribution on the most representative cerebral (cerebellar for #20) surface is given. These surface maps were prepared using BrainNet Viewer software. ICs are grouped by relation to functional specialization to DMN, ECN, sensor, language, and cerebellar. Blue lines show pairs with more connectivity in controls, red lines show pairs with more connectivity in depressed patients ($p < 0.05$ uncorrected).

Table 4: Correlations of connectivity in IC pairs and depression scores.

Pair	Both groups—ZSRDS	
	r	p
1-9 (DMN-LFr)	0.273	0.026
1-16 (DMN-DMN)	−0.129	n/s
5-8 (mVis-AN)	0.116	n/s
9-16 (LFr-DMN)	0.296	0.016
11-13 (DMN-ECN)	0.196	n/s

DEP-51 and HC groups taken together; analysis on separate groups led to no correlations significant at $p < 0.05$. DMN: default mode network; LFr: left fronto-parietal network; mVis: medial visual network; AN: audial network; ECN: executive control network; r: correlation coefficient; p: 2-tailed significance level; n/s: nonsignificant.

considering both treatment groups as one sample (see Table 6, Figure 3).

Among pairs mentioned in dynamic comparisons, 1-3 and 5-11 changes were correlated with ZSRDS scores' dynamics in no treatment group positively and negatively, respectively (see Table 7). Psychotherapy group featured no such correlations, while in neurofeedback group, 1-3 and 5-13 FC changes were positively related to ZSRDS score dynamics, and 3-17 and 7-17 were negatively correlated with MADRS score changes (see Tables 8 and 9). 1-3 changes were associated positively with BDI and ZSRDS score dynamics, while 5-11 to ZSRDS only; 10-12 changes were related inversely to MADRS scores changes in combined treatment groups (see Table 10).

When depression scores' changes were correlated with baseline connectivity scores of the pairs that featured a significant dynamic changes in FC (which means identifying network predictors of clinical improvement), the following results were demonstrated (Tables 7–10). In no treatment group, ZSRDS score change was positively correlated with 5-11 and 10-12 pairs baseline FC, while BDI score increase was negatively related to initial FC in 3-17, 7-11, and 14-16 pairs. In combined treatment group, 7-17 coupling was inversely related to MADRS score change and 10-12 was positively correlated to estimates of MADRS and ZSRDS. In psychotherapy group, 3-17 initial FC was negatively linked to ZSRDS score change. In neurofeedback group, 1-3 start FC was negatively associated with ZSRDS score dynamics, while MADRS change was inversely correlated with 5-11 baseline FC and positively with 10-12 FC.

Correlations of component masks of bigger and smaller samples were computed (see Table 11). Only two pairs of components were identified both in first and second parts of study: 1-16 (10-12 in dynamics test) and 11-13 (11-16 in dynamics test) (Figure 4).

4. Discussion

4.1. Study 1: Intergroup Results. The first result is decreased within-DMN FC in depressed group, with one component

Table 5: Independent component analysis results for dynamics study.

IC no.	GM	WM	CSF	Accepted	Best match
1	0.20	0.09	0.08	Yes	Medial visual network ($r = 0.78$)
2	0.14	0.03	0.15	No	
3	0.21	0.05	0.17	Yes	Occipital pole ($r = 0.36$)
4	0.19	0.01	0.25	No	
5	0.27	0.08	0.13	Yes	Audial network ($r = 0.69$)
6	0.24	0.17	0.21	No	
7	0.21	0.12	0.08	Yes	Right frontoparietal network ($r = 0.71$)
8	0.16	0.03	0.31	No	
9	0.28	0.13	0.07	Yes	Lateral visual network ($r = 0.59$)
10	0.18	0.10	0.08	Yes	Default mode network ($r = 0.75$)
11	0.23	0.17	0.11	Yes	Executive control network ($r = 0.64$)
12	0.22	0.11	0.11	Yes	Default mode network ($r = 0.31$), left frontoparietal network ($r = 0.29$)
13	0.22	0.20	0.14	Yes	Sensorimotor network ($r = 0.66$)
14	0.26	0.17	0.22	Yes	—
15	0.22	0.17	0.10	Yes	Left frontoparietal network ($r = 0.75$)
16	0.24	0.15	0.17	Yes	Default mode network ($r = 0.39$)
17	0.25	0.17	0.11	Yes	—

IC: independent component; GM: gray matter; WM: white matter; CSF: cerebro-spinal fluid; r: correlation coefficient.

of the pair suiting classical DMN topography including portions of precuneus, posterior cingulate, bilateral temporo-parietal junction, and medial prefrontal cortex, and another is located mostly in posterior cingulate and precuneus. As mentioned in the introduction section, most studies in the field highlighted within-DMN overconnectivity among features of depression. This is the most reliable functional connectivity marker of depression across studies. Moreover, depression-related DMN nodes FC show reliability of 0.5-0.76 [19]. Note that increased FC of components 11 and 13 in our study aside from DMN–ECN connectivity represents coupling of precuneus and portion of medial prefrontal cortex. However, some studies indicating underconnectivity of posterior cingulate within the DMN also exist. According to [10, 13], patients with major depression lack connection of posterior cingulate with prefrontal cortex and temporo-parietal area. Sad mood induction in depression leads to posterior cingulate uncoupling from the prefrontal cortex and precuneus [51]. Some antidepressant medications increase FC of posterior cingulate to medial prefrontal area [52], and psychotherapy increases it to precuneus [38], which may suggest that low strength of these connections is related to depression.

So decreased FC of these DMN subsystems is not in line with majority of the studies, yet has some limited support from the previous research. DMN is known for its role in processing of internal states including both psychological and physical, self- and close others-related information, and for some kinds of social cognition like theory of mind [53]. Disruption of connections between the nodes of the system may reflect difficulties in some social skills requiring applying other's perspectives (empathy, emotional intelligence, theory of mind) or in relationships with close others which are frequent in depression.

Three results suggest that DMN subnetworks are linked to task-positive networks to a larger degree in depression, namely, posterior cingulate/precuneus and multinode DMN component are overconnected with left fronto-parietal areas, while superior precuneus is hypersynchronized with bilateral frontal component related mostly to ECN. This implicates disruption of normal relationships between three key networks of triple network model [54], namely, DMN, ECN, and ASN assuming DMN is anticorrelated with two others. Global increase of DMN–ECN FC is not a typical finding in depression (see results directly contradicting ours in [8] and indirectly in [38, 52]); however, it is possibly related to some depression-specific cognitive processes [19]. So the difference between ours and previous results may be caused by relatively mild and supposedly more "psychogenic" conditions in our case lacking some neural markers typical for more serious conditions while sharing cognitive features of depression such as rumination and cognitive control deficits.

Note that DMN–left frontoparietal network is the pair discriminating between healthy and depressed people to the highest degree and the only one showing significant correlation with depression assessment score when groups are combined. This may show the importance of laterality and be related to frontal asymmetry described in models by Davidson and Heller. According to these models, left prefrontal activity is related to positive emotions and to approach motivation, while right corresponds to negative emotions and withdrawal motivation (see [55] for a review). Relatively active right prefrontal area and idling left prefrontal cortex together may be a neurophysiological signature of depression. From this point, increased coupling of the network containing left dorsolateral prefrontal area with DMN may

Table 6: Results of baseline vs. repeated measure comparison in no-treatment group ($N = 15$), combined treatment group ($N = 14$), CBT group ($N = 8$), and NFB group ($N = 6$).

Pair	Pre, Mean ± SD	Post, Mean ± SD	t	p
No treatment group				
3–17 (OccP–?)	0.16 ± 0.30	−0.01 ± 0.36	2.21	0.044
7–11 (RFr–ECN)	0.31 ± 0.12	−0.02 ± 0.33	3.75	0.002
7–17 (RFR–?)	0.31 ± 0.16	0.09 ± 0.26	2.58	0.022
10–12 (DMN–DMN/LFr)	0.45 ± 0.15	0.31 ± 0.18	2.21	0.044
10–14 (DMN–?)	−0.49 ± 0.17	−0.34 ± 0.22	−2.34	0.035
Combined treatment group				
1–3 (mVis–OccP)	0.17 ± 0.40	0.50 ± 0.22	−3.71	0.003
5–13 (AN–SMN)	0.43 ± 0.33	0.55 ± 0.27	−2.61	0.022
11–16 (ECN–DMN)	0.14 ± 0.36	0.37 ± 0.22	−2.44	0.030
14–16 (?–DMN)	−0.01 ± 0.34	0.19 ± 0.25	−2.48	0.028
15–17 (LFr–?)	0.25 ± 0.3	−0.01 ± 0.35	2.21	0.046
Cognitive behavioral therapy group				
1–3* (mVis–OccP)	0.30 ± 0.38	0.53 ± 0.28	−2.35	0.051 (n/s)
5–11 (AN–ECN)	0.36 ± 0.32	0.54 ± 0.24	−3.53	0.010
5–13 (AN–SMN)	0.45 ± 0.30	0.61 ± 0.15	−2.39	0.049
14–16 (?–DMN)	−0.07 ± 0.39	0.22 ± 0.26	−2.85	0.026
15–17 (LFr–?)	0.28 ± 0.35	−0.13 ± 0.38	2.50	0.040
fMRI neurofeedback group				
1–3 (mVis–OccP)	0.01 ± 0.39	0.47 ± 0.14	−3.00	0.030
11–16 (ECN–DMN)	−0.10 ± 0.17	0.28 ± 0.26	−3.35	0.020
13–14 (SMN–?)	0.30 ± 0.26	−0.04 ± 0.42	3.26	0.022

SD: standard deviation; DMN: default mode network; LFr: left fronto-parietal network; RFr: right fronto-parietal network; mVis: medial visual network; AN: audial network; ECN: executive control network; SMN: sensorimotor network; OccP: occipital pole network; ?: IC does not match any classical network; t: t test value; p: 2-tailed significance level; n/s: nonsignificant. *marginally significant result is given for it corresponds to significant results in NFB group and in combined treatment group.

indicate its passivity resulting in less approach motivation and less positive mood which is one of the most important depression-related signs.

The last result is an overconnectivity of medial visual cortex with audial cortex in depression. Sensor systems are mentioned in few depression studies to date. FC between visual and audial networks is disrupted in depression and may be used as a marker of a disorder [33]. Depressed patients are known to spend less time in a state of strong connectivity between auditory and visual networks [8], which is in contrast with our results. More research on the role of sensor networks in depression should be conducted to interpret it accurately.

4.2. Study 2: Treatment-Related Results. Functional connectivity of fronto-parietal networks and key task-positive systems, are of great interest. Right fronto-parietal network diminishes its coupling with other ECN areas and also with superior parietal region in no treatment group. Left fronto-parietal network also decreases FC with superior parietal component. Common tendency that corresponds to normal global connectivity pattern may be an isolation of both fronto-parietal networks from some task-negative regions. Moreover, right fronto-parietal areas become less connected with ECN frontal areas, including prefrontal cortex and anterior cingulate. This may be interpreted in terms of functional frontal asymmetry mentioned in a previous subsection. Isolation of right frontal cortex especially from task positive networks may contribute to mood improvement for reduction of negative emotions. No strong prevalence of data on under- or overconnectivity within-ECN in depression or on increasing or decreasing of ECN areas FC with task-negative networks exist in literature (see Introduction); thus, diminished coupling revealed in our study is partly supported by previous research.

In treatment groups, DMN FC increases to supplementary motor area and to frontal ECN, with coupling to SMN driven by CBT and to ECN by NFB. Baseline DMN–SMN synchronicity is positively related to subsequent improvement in no treatment group. Some data suggest that low DMN FC with motor areas is typical for depression [16, 32], so its increase may be treated as probably associated with an improvement. Indirect data indicate positive association between DMN–ECN coupling and some features of depression [19–20], though direct evidence [1, 8] along with our intergroup comparison

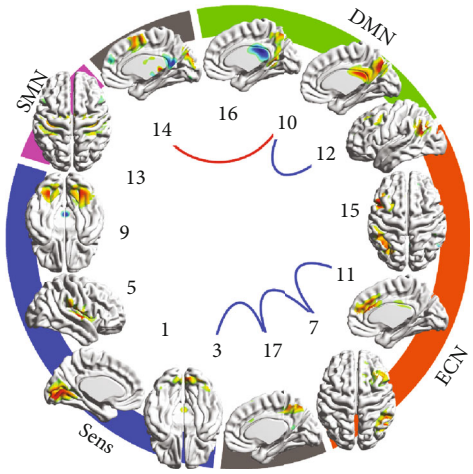

Figure 2: Results of baseline vs. repeated scanning comparison in no treatment group. IC numbers match ones of Tables 5 and 6. IC spatial distribution on the most representative cerebral surface is given. These surface maps were prepared using BrainNet Viewer software. ICs are grouped by relation to functional specialization to DMN, ECN, sensor, sensorimotor, and not matching classical networks. Blue lines show pairs with more connectivity at baseline—decline in time, red lines show pairs with more connectivity at the second measurement—growth in time ($p < 0.05$ uncorrected).

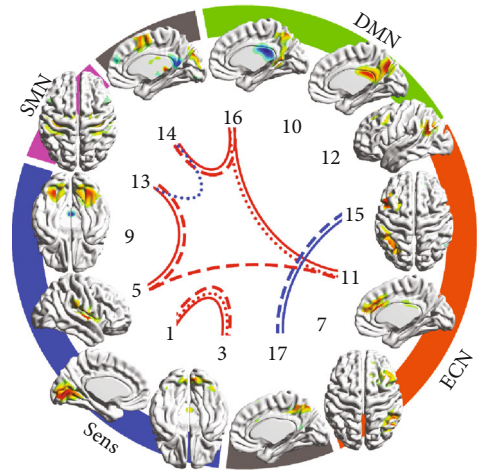

Figure 3: Results of baseline vs. posttreatment comparison in treatment groups. IC numbers match ones of Tables 5 and 6. IC spatial distribution on the most representative cerebral surface is given. These surface maps were prepared using BrainNet Viewer software. ICs are grouped by relation to functional specialization to DMN, ECN, sensor, sensorimotor, and not matching classical networks. Blue lines show pairs with more connectivity at baseline—decline in time, red lines show pairs with more connectivity posttreatment—growth in time ($p < 0.05$ uncorrected). Solid lines indicate both groups together, dashed lines—CBT, dotted lines—NFB.

results demonstrates decreased DMN–ECN FC in depression. Increase of this connection of naturally un- or anticorrelated networks may be even more dysfunctional in terms of global networks interrelations, yet no link to clinical measures is present in our study.

FC within visual system (between occipital pole and medial visual cortex) grows during any treatment course (marginally significantly in CBT group). However, this FC change is positively related to depression scores change which means inverse links to improvement both in treatment and in no treatment conditions. In neurofeedback group, baseline coupling of this pair is negatively correlated to change on Zung scale during treatment, so strength of connectivity in this pair is a predictor of success. These results may be interpreted as a presence of a neural mechanism involving visual systems of occipital cortex which is frequently activated during the treatment of depression yet decreases its effectiveness. The role of FC in this pair as a predictor may be that initial high coupling does not leave enough room for increase in this connectivity score. Depressed patients have less FC [23] and spend less time in a state of increased connectivity of networks within visual system [8, 9], so increase in this connection may be related to improvement. Note also that in no treatment group, FC of occipital pole with a superior parietal component increased which may indicate disruption of the dorsal stream of visual processing or isolation of visual system from the DMN. However, medial visual network does not share this pattern, so interpretation in terms of whole visual system would sound premature. Occipital pole–superior parietal FC at baseline is related to treatment success of CBT and to degree of spontaneous improvement, and its dynamics is also correlated with improvement due to NFB. Thus, in contrast to previously discussed connections increasing in time yet inversely related to improvement, coupling in this pair decreases over time yet directly related to improvement.

Strength of a few connections of auditory system, namely, to SMN and ECN, increases in CBT. This result is supported by data on weak ECN coupling with temporal regions in clinical [8, 17] and subclinical [56] depression, yet some contradicting results also exist [3]. SMN–auditory networks FC also may be in deficit in depression [8]. Despite of not being directly associated with emotions, SMN–auditory network connections may be valuable features of depression [33]. From the dynamic point of view, changes in auditory system FC to ECN are associated with more improvement in no treatment group and less improvement in a combined treatment group. Baseline score of this pair is a negative predictor for no treatment group and positive in neurofeedback group. Auditory–SMN FC is also negatively related to outcome in NFB group.

Last, a decrease of FC within sensorimotor system is detected after neurofeedback course, namely, between components representing paracentral lobule and supplementary motor cortex, and not correlated with clinical estimates. Previous research mentioned within-SMN connectivity among other markers of depression [30, 33] mostly indicating its deficit [8]. Thus, while neurophysiological mechanism of this link is uncertain, integration of different sensor, sensorimotor, and, possibly, other task-positive systems may correspond to some clinical change in depression depending on kind of intervention.

While observing FC changes in a no treatment group and in treatment groups as a whole, one can see that

Table 7: Correlations of baseline scores and pre-post changes in connectivity with pre-post changes in clinical/psychological variables in no-treatment group ($N = 14$).

IC pair	BDI		ZSRDS	
	Baseline	Change	Baseline	Change
1–3 (mVis–OccP)	0.056	0.112	−0.354	0.625*
3–17[a] (OccP–?)	−0.637*	−0.105	−0.38	−0.323
5–11 (AN–ECN)	0.363	−0.32	0.701**	−0.674**
7–11[a] (RFr–ECN)	−0.677**	0.479	−0.372	0.347
10–12[a] (DMN–DMN/LFr)	0.456	−0.02	0.63*	−0.343
14–16 (?–DMN)	−0.598*	0.327	−0.223	0.298

DMN: default mode network; LFr: left fronto-parietal network; RFr: right fronto-parietal network; mVis: medial visual network; AN: audial network; ECN: executive control network; OccP: occipital pole network; ?: IC does not match any classical network; BDI: Beck depression inventory; ZSRDS: Zung self-rating depression scale; $^{*}p < 0.05$; $^{**}p < 0.01$; [a]pre-post difference in connectivity of this pair is significant for this condition.

Table 8: Correlation of baseline scores and pre-post changes in connectivity with pre-post changes in clinical/psychological variables in CBT group ($N = 5$).

IC pair	ZSRDS	
	Baseline	Change
3–17 (OccP–?)	−0.949*	−0.158

OccP: occipital pole network; ?: IC does not match any classical network; ZSRDS: Zung self-rating depression scale; $^{*}p < 0.05$.

Table 9: Correlation of baseline scores and pre-post changes in connectivity with pre-post changes in clinical/psychological variables in NFB group ($N = 4 - 6$).

IC pair	MADRS		ZSRDS	
	Baseline	Change	Baseline	Change
1–3[a] (mVis– OccP)	0	0	−0.9*	1**
3–17 (OccP–?)	0.8	−1**	0.7	−0.4
5–11 (AN–ECN)	−1**	0.8	−0.3	0.5
5–13 (AN–SMN)	−0.4	0.8	−0.5	0.9*
7–17 (RFr–?)	0.2	−1**	−0.2	−0.7
10–12 (DMN–DMN/LFr)	1**	−0.8	0.8	−0.6

DMN: default mode network; LFr: left fronto-parietal network; RFr: right fronto-parietal network; mVis: medial visual network; AN: audial network; ECN: executive control network; SMN: sensorimotor network; OccP: occipital pole network; ?: IC does not match any classical network; MADRS: Montgomery-Asberg depression rating scale; ZSRDS: Zung self-rating depression scale; $^{*}p < 0.05$; $^{**}p < 0.01$; [a]pre-post difference in connectivity of this pair is significant for this condition.

dynamics in a no treatment group are mostly decreasing of FC, and in treatment groups, they are related primarily to the increasing of FC. Certain IC pairs are not crossing over between these conditions. So distinct neurophysiological mechanisms may be suggested in spontaneous depression improvement and in treatment-related one, involving different brain networks and antagonistic mechanisms in terms of FC. Yet this idea requires a thorough investigation with larger samples, to our knowledge, it is the first conceptual neuroscientific approach to specificity of spontaneous improvement in depression.

4.3. Integration of the Data from Two Studies. According to the correlation matrix, most of the ICs in study 1 are strongly correlated with sole component in the study 2. Only few ICs show ambiguous correlations or do not show them at all. Our aim was to identify network connections disrupted in depression (study 1) and changed in the treatment course (study 2), so we performed a search through our results (see Table 11, Figure 4).

First, 1-16 pair representing within-DMN connectivity of posterior cingulate/precuneus region with initially decreased coupling in depression corresponds mostly to 10-12 pair of the dynamic study. It shows links between posterior cingulate/precuneus node and hybrid network including left frontal cortex like fronto-parietal network and left temporo-parietal area with a portion of posterior cingulate like DMN. Visual inspection shows high equivalence of posterior cingulate/-precuneus components in both studies, while the whole-DMN component of study 1 matches IC with no bilateral temporo-parietal pattern and less prominent midline parietal activation. Nevertheless, these pairs may be considered as relatively equivalent. We should remind that connectivity in the 10-12 pair even more decreases in no treatment condition, and its baseline estimate is negatively correlated with treatment success in no treatment group, combined treatment group, and NFB group. Moreover, its change is positively related to treatment effectiveness in a combined treatment group. Thus, this result, if not treated as a false positive, reveals complicated dynamics of brain functional changes in depression and in recovery from depression (most people from no treatment group spontaneously improved on their depression estimates). Thus, FC of DMN may be treated not as a pathological sign, but as a kind of protective or compensatory mechanism activated in some cases (multiple articles showing overconnectivity of DMN in depression) and not activated in others (other studies including ours). Interestingly, it generally fades away with time, while patients preserving this connection relatively strong seem to benefit more from nonpharmacological treatment.

Second, FC in 11-13 pair in study 1 (precuneus with prefrontal cortex suiting partly within-DMN and partly DMN–ECN synchronicity) augmented in depression group matches 11-16 pair of study 2. This pair defines coupling between an

Table 10: Correlation of baseline scores and pre-post changes in connectivity with pre-post changes in clinical/psychological variables in a combined treatment group ($N = 10 - 11$).

IC pair	MADRS		BDI		ZSRDS	
	Baseline	Change	Baseline	Change	Baseline	Change
1–3[a] (mVis– OccP)	−0.156	0.361	−0.489	0.615*	−0.627	0.774**
5–11 (AN–ECN)	0.009	0.202	−0.265	0.469	−0.492	0.64*
7–17[a] (RFr–?)	−0.672*	0.41	0.043	−0.123	0.064	−0.299
10–12 (DMN–DMN/LFr)	0.716*	−0.734*	0.51	−0.369	0.646*	−0.433

DMN: default mode network; LFr: left fronto-parietal network; RFr: right fronto-parietal network; mVis: medial visual network; AN: audial network; ECN: executive control network; OccP: occipital pole network; ?: IC does not match any classical network; MADRS: Montgomery-Asberg depression rating scale; BDI: Beck depression inventory; ZSRDS: Zung self-rating depression scale; *$p < 0.05$; **$p < 0.01$; [a]pre-post difference in connectivity of this pair is significant for this condition.

Table 11: Correlation of IC maps from the patients vs. controls study (left column) and from dynamics study (right column).

IC no.	Best match
1 (DMN)	10, DMN ($r = 0.85$)
2 (RFr)	7, RFr ($r = 0.78$)
3	2 ($r = 0.69$), n/a
4	8 ($r = 0.81$), n/a
5 (mVis)	1, mVis ($r = 0.85$)
6	3, OccP ($r = 0.39$); 9, lVis ($r = -0.55$)
7	13, SMN ($r = 0.75$)
8 (AN)	5, AN ($r = 0.72$)
9 (LFr)	15, LFr ($r = 0.74$)
10 (lVis, OccP)	3, OccP ($r = 0.58$); 9, lVis ($r = 0.46$)
11 (vDMN)	16, DMN ($r = 0.57$); 17 ($r = 0.56$)
12	5, AN ($r = 0.19$)
13 (ECN, dDMN)	11, ECN ($r = 0.63$)
14	4 ($r = 0.69$), n/a
15	6 ($r = -0.64$), n/a
16 (DMN)	12, DMN, LFR ($r = 0.41$); 16, DMN ($r = 0.41$)
17 (LN)	12, DMN, LFR ($r = 0.55$)
18	14 ($r = 0.57$); 11, ECN ($r = 0.41$)
19	17 ($r = -0.22$)
20 (Cer)	2 ($r = 0.39$), n/a

(v)DMN: (ventral) default mode network; LFr: left fronto-parietal network; RFr: right fronto-parietal network; Cer: cerebellar network; mVis: medial visual network; AN: audial network; LN: language network; ECN: executive control network; SMN: sensorimotor network; OccP: occipital pole network; n/a: artifact or does not correspond to any classical network; r: correlation coefficient.

IC of precuneus and temporo-parietal junction (DMN) with another one covering a large portion of prefrontal cortex, mostly medial, with anterior cingulate and associated primarily with ECN. Frontal systems in studies 1 and 2 are topographically similar, while DMN components feature some differences not discarding their relation to DMN. FC in this pair grows posttreatment in combined group and in NFB group; however, neither its baseline score, nor its changes predict clinical outcomes. So in contrast to previous pair coupling initially lower in depression and decreasing over time, this pair FC is higher in depression and even increases after treatment.

These data show that common approach of searching for fMRI biomarkers of depression and considering their changes to normal values as a success indicator may be inappropriate in some cases, for in our study network connectivity patterns changed in "more pathological" direction yet symptoms improved over time, so both no treatment and treatment condition were not deleterious. Abnormal values of FC may be associated, aside from disorder symptoms, with some compensation processes or condition- and symptom-unrelated changes. They also may be either state- or trait-related, and modification of trait-related functional brain changes seems questionable.

Collected data support crucial role of within-DMN and DMN-ECN FC in depression and demonstrate need for a further study of the relationships between these networks coupling and development and treatment of depression for using a relatively big sample of depressed patients we found decrease of within-DMN FC that contradicts typical findings in the field. Interrelations between depression severity, recurrence and aetiology, and network organization should be examined thoroughly for these data were collected in a sample of participants with relatively mild and predominantly psychogenic depression. In treatment effects on brain connectivity, more research of nonpharmacological treatments is needed.

4.4. Clinical Implications. The largest portion of the discussion above was devoted to network neuroscience features of depression and more to fundamental than to applied science. So we summarize practical implications of the article in a separate subsection.

First, FC biomarkers of depression do not look solid and universal because our study revealed some results contrary to the mainstream of the existing body of research. Inconsistencies may be related to sample differences (depression severity, presence or absence of some certain symptoms, racial/ethnic sample composition, and other demographics) or details in acquisition and analysis of fMRI data. Thus, resting state FC biomarkers of depression are premature for usage in diagnostics and evaluation of treatment success in depression.

Second, across potential FC features of depression itself and of improvement from depression, our results suggest

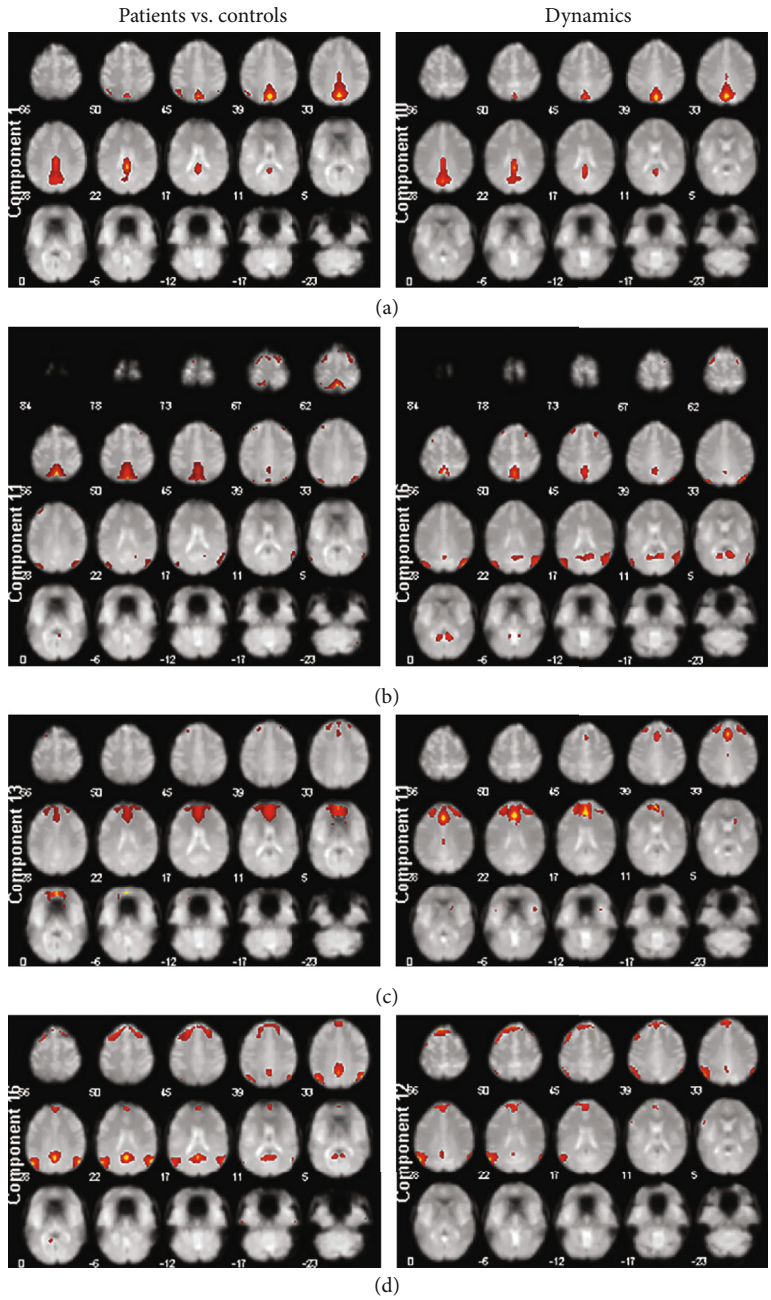

Figure 4: Slice-based maps of matched components demonstrating significant differences in both studies. In each panel, left map suits to depressed vs. controls study (IC number from the Table 2), and right one suits to baseline vs. repeated measure study (IC number from the Table 5). Slice rows with no or negligible activity are omitted. (a) IC1 from study 1 and IC10 from study 2; (b) IC11 from study 1 and IC16 from study 2; (c) IC13 from study 1 and IC11 from study 2; (d) IC16 from study 1 and IC12 from study 2.

that left frontoparietal network coupling to DMN and right frontoparietal network coupling to ECN are of use. These findings support usage of approaches targeting prefrontal cortices in mild depression with respect to activity lateralization, such as EEG and fMRI neurofeedback, transcranial direct current stimulation, and transcranial magnetic stimulation of prefrontal cortex.

Third, according to our data, DMN hyperconnectivity revealed in the majority of studies of depression should be treated as a target of neuromodulation with great caution for our study shows its presence in depression is ц optional, and correlational analysis shows it may be related to spontaneous compensatory processes, not to disorder itself.

5. Limitations

The key limitation of the study is an approach to results extraction. Corrections for multiple comparisons were not implemented, and none of the results mentioned would reach corrected significance level. Instead, we considered

valuable effects present both in study 1 and study 2 that addresses possibility of false positives from logical point of view and not from statistical one. The second limitation is a small size of dynamic groups which could be a source of false positives for absence of multiple comparison corrections. Third limitation is an incomplete match of components of study 1 and study 2 that may rise the question of equivalence of the corresponding ICs.

6. Conclusions

Though no intergroup results reached a corrected significance level, the most prominent differences were increased functional connectivity between left frontoparietal network and subsystems of the DMN. Intergroup differences reflected also in dynamic comparisons were (1) decreased within-DMN FC even more diminished over time and negatively related to treatment outcome and (2) increased DMN–ECN FC augmented after neurofeedback treatment. These results contribute to model of frontal emotional asymmetry in depression, demonstrate deficient DMN connectivity in depression in contrast to majority of the studies published to date, and show need of further investigation of interrelations of three global networks in depression.

Data Availability

The MRI and fMRI datasets generated for this study can be downloaded from http://openneuro.org/ repository without any access restriction, study 1 https://openneuro.org/datasets/ds002748, study 2 https://openneuro.org/datasets/ds003007.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Research Article

Altered Functional Integration in the Salience and Default Mode Networks in Euthymic Pediatric Bipolar Disorder

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Accumulating studies demonstrate emotional and cognitive dysregulation in the euthymic period of pediatric bipolar disorder (PBD). However, the relative contribution of functional integration in human brain to disturbed emotion and cognitive function in the euthymic PBD patients remains unclear. In this study, 16 euthymic PBD patients and 16 healthy controls underwent resting-state functional magnetic resonance imaging. A data-driven functional connectivity analysis was used to investigate functional connectivity changes of the euthymic PBD. Compared with healthy controls, the euthymic PBD exhibited greater global functional connectivity density in the left anterior insula and lower global functional connectivity density in the right temporoparietal junction, the left angular gyrus, and the bilateral occipital lobule. A distant functional connectivity analysis demonstrated altered integration within the salience and default mode networks in euthymic PBD. Correlation analysis found that altered functional connectivity of the salience network was related to the reduced performance in the backward digit span test, and altered functional connectivity of the default mode network was related to the Young Mania Rating Scale in euthymic PBD patients. Our findings indicated that disturbed functional integration in salience and default mode networks might shed light on the physiopathology associated with emotional and cognitive dysregulation in PBD.

1. Introduction

Bipolar disorder (BD) is a chronic and debilitating mental illness and has been increasingly diagnosed in pediatric age children (G. Z. [1]). In addition, retrospective studies indicated that symptoms in 55-60% of adults with BD begin in childhood or adolescence [2]. Therefore, it is important to understand the developmental pathophysiology of BD by investigating pediatric bipolar disorder (PBD). Substantial evidence indicates that cognitive impairment and emotional lability are present not only in periods of acute mood symptoms but also in periods of euthymia in PBD ([3]; G. Z. [1, 4]). However, little is known about the neurocognitive mechanisms of the euthymic phase of PBD.

Functional magnetic resonance imaging (fMRI) has been broadly used to investigate euthymic PBD [5, 6]. Many studies have provided evidence for changes of brain function in BD, such as changes in the corticolimbic pathways during mood episode [7, 8]. Recently, intrinsic functional connectivity (FC) based on resting-state fMRI has been employed to reveal stable and reliable functional brain networks, such as the default mode network (DMN), and the salience network (SN), which are associated with cognition and emotion [9, 10]. Moreover, altered functional connectivity has been considered a potential

biomarker for psychiatric disorders [11, 12]. Many imaging studies have demonstrated inconsistent functional changes in brain networks in different neural phenotypes in BD patients due to heterogeneity in the analysis methods used [5, 13]. However, intrinsic functional connectivity analysis provides a useful approach to investigate the neural architecture of euthymic PBD patients.

In the current study, we firstly evaluated the global functional connectivity feature by using an unbiased data-driven method. These features are obtained from global functional connectivity density (FCD), which may be more sensitive in detection of functional alterations of the distribution of brain hubs [14, 15]. Then, we assessed the distant functional connectivity of those brain regions in which we observed a significantly different global FCD in euthymic PBD patients. We predicted that the euthymic PBD patients would exhibit altered functional connectivity, and these changes may contribute to the neural physiopathology of PBD.

2. Methods

2.1. Participants. This study recruited 16 PBD patients during clinical remission from the child and adolescent psychiatric clinic of the Second Xiangya Hospital of Central South University (Changsha, P. R. China) from January to July, 2012. All patients were required to meet the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV) criteria for BD with a current remission episode. The exclusion criteria included the diagnosis of bipolar disorder subtype or current mixed episode. Sixteen age- and sex-matched healthy control (HC) subjects were recruited through advertisements in local public schools. All participants were 10-17 years old, right-handed and of Han ethnicity. They could follow the instructions to keep still during MRI scanning. The additional exclusion criteria for all participants included the presence of major sensorimotor handicaps, history of neurological disorder, history of electroconvulsive therapy, lower score of full-scale intelligence quotient (IQ < 80), and standard fMRI contraindications (e.g., metallic implants, retractors or braces, and claustrophobia). The study was approved by the ethics committee of the Second Xiangya Hospital of Central South University. Written informed consent was obtained from the parents of all participants.

2.2. Clinical and Psychological Assessment. All patients were diagnosed independently by two experienced psychiatrists for Affective Disorders and Schizophrenia for School aged Children Present and Lifetime Versions (K-SADS-PL). Current mental states were assessed using the Young Mania Rating Scale (YMRS) and Mood and Feelings Questionnaire (MFQ). To evaluate the effects of PBD on cognitive function, psychological measurements for all participants included the Digit Span Test (DST), the Trail Marking Test (TMT), and the Stroop Color-Word Test (SCWT). The DST includes the forward digit span test (DST-F) and backward digit span test (DST-B) to evaluate attention and executive processes. The SCWT is used to assess the ability to inhibit cognitive interference and is composed of three parts. The participant is asked to name the color of a series of dots in SCWT-A, to name the color-ink words in SCWT-B, and to name the color of words whose meanings are different from ink colors in SCWT-C. The TMT is frequently used neuropsychological tests in clinical practice and is comprised of part A (TMT-A) and part B (TMT-B). The TMT-A includes numbered circles only, whereas the TMT-B contains more numbered circles and squares. The participant is asked to connect these numbers in order.

2.3. Image Acquisition and Preprocessing Analysis. All image data were acquired using a Siemens 3T Siemens Trio scanner (Siemens, Munich, Germany). To minimize head motion, we fixed the subjects' heads using foam pads. The axial T1-weighted anatomical images were acquired using a spoiled gradient recall sequence, generating 176 slices (repetition time (TR) = 2300 ms, echo time (TE) = 2.03 ms, flip angle (FA) = 9°, slice thickness = 1 mm, matrix size = 256 × 256, and field of view (FOV) = 256 mm × 256 mm). Resting-state functional images were collected using echo planar imaging (EPI) [TR = 2000 ms, TE = 30 ms, FA = 90°, FOV = 240 mm × 240 mm, matrix = 64 × 64, and slice thickness = 4 mm], generating 30 slices. The functional scanning lasted for 510 s, yielding a total of 255 volumes. During the resting-state scanning, the subjects were asked to lie with their eyes closed, not to fall asleep, and not to think of anything in particular. To ensure magnetic field stabilization, the first five volumes were discarded.

All image data were preprocessed using the Neuroscience Information Toolbox (NIT) [16]. The preprocessing procedure included slice time correction, realignment, and spatial normalization ($3 \times 3 \times 3\ \text{mm}^3$). We excluded subjects with exceeded head motion (more than 2 mm translation or 2° rotational movements). The linear regression analysis was utilized to remove several nuisance covariates from the time course of all brain voxels of the functional data. These covariates included 12 head motion parameters (six head parameters and its derivative), white matter signal, cerebrospinal fluid signal, and global signal. Then, the temporal passband filtering (0.01-0.08 Hz) was conducted on the time courses of functional data to remove low-frequency drift and to minimize high-frequency physiological noise.

2.4. Global Functional Connectivity Density Analysis. For each subject, the global FCD map was obtained using Pearson's linear correlation from individual preprocessed time course. The threshold of the correlation coefficient, Tc, was used to determine significant connection between two voxels. The global FCD value at a given voxel was defined as the number of voxels with significant connections in the whole brain with the given voxel. The global FCD map reflected the total number of functional connections per voxel.

We chose a dynamic threshold range from 0.4 to 0.8 in 0.05 steps, to obtain more reliable and robust findings. The total nine Tc thresholds were used in our study. To address variability in all global FCD across subjects, each individual global FCD map was normalized by dividing by the mean value across voxels in a given subject. For all FCD maps, we created nine normalized maps for the nine Tc thresholds for each subject. Spatial smooth with 6 mm Gaussian kernel

Table 1: Comparison of clinical and neuropsychological measurement between the euthymic PBD patients and healthy controls.

	Euthymic PBD	HC	*P* value
Gender (male/female)	7/9	5/11	0.716[a]
Age (mean ± SD, years)	15.12 ± 1.71	14.06 ± 1.48	0.070[b]
Education (mean ± SD, years)	8.19 ± 1.80	7.19 ± 2.04	0.152[b]
Age of onset (mean ± SD, years)	13.13 ± 2.09		
BD type (I/II)	10/6		
Familial history (yes/no)	5/11		
Medications			
Lithium	6 (38%)		
Valproate	11 (69%)		
Atypical antipsychotics	13 (81%)		
K-SADS-PL comorbidity diagnoses			
ADHD	4 (25%)		
OCD	1 (6%)		
Anxiety	3 (19%)		
Tic	1 (6%)		
MFQ score (mean ± SD)	7.50 ± 4.37	5.56 ± 3.18	0.385[c]
IQ (mean ± SD)	106.69 ± 10.54	105.00 ± 7.00	0.609[c]
YMRS score (mean ± SD)	5.38 ± 1.69	3.59 ± 1.90	0.009[c]
SCWT-A (mean ± SD)	55.94 ± 11.34	64.81 ± 11.34	0.003[c]
SCWT-B (mean ± SD)	73.88 ± 13.41	86.56 ± 8.71	0.001[c]
SCWT-C (mean ± SD)	33.63 ± 7.54	39.50 ± 7.84	0.006[c]
TMT-A (mean ± SD)	37.83 ± 13.48	30.50 ± 9.29	0.004[c]
TMT-B (mean ± SD)	98.44 ± 49.70	82.17 ± 29.51	0.237[c]
DST-F (mean ± SD)	8.75 ± 1.81	9.00 ± 1.10	0.758[c]
DST-B (mean ± SD)	4.50 ± 1.41	5.87 ± 1.63	0.019[c]

[a]Chi-square test; [b]two-sample *t*-test; [c] two-sample *t*-test controlled by age, gender, and education years. ADHD: attention-deficit/hyperactivity disorder; DST-B: backward digit span test; DST-F: forward digit span test; HC: healthy controls; IQ: intelligence quotient; K-SASADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; MFQ: Child Mood and Feelings Questionnaire; OCD: obsessive-compulsive disorder; PBD: pediatric bipolar disorder; SCWT: Stroop Color-Word Test; TMT-A: part A of trail making test; TMT-B: part B of trail making test; YMRS: Young Mania Rating Scale.

of full-width half maximum (FWHM) was used to minimize the differences in the functional anatomy of the brain across subjects.

Group analyses of all global FCD maps were conducted using one-sample *t* -tests ($P < 0.05$, FDR corrected). For each global FCD map for each threshold, Tc, we conducted a two-sample *t*-test comparing the euthymic PBD and HC groups, controlling for the age, gender, and education years.

To identify robust differences of global FCD between the euthymic PBD and HC groups, we only included the clusters exhibiting a significant difference in at least 4 consecutive Tc values of FCD comparisons. Then, these clusters were used as regions of interest (ROIs) for the subsequent functional connectivity analyses.

2.5. Functional Connectivity Analysis. For the FC analysis, the normalized functional images were further processed using spatial smoothing using a 6 mm Gaussian kernel of FWHM. Then, the general regression analysis was performed to minimize the reflection of nuisance signals, as mentioned above. After filtering (0.01-0.08 Hz), FC analysis was performed by calculating the Pearson's correlation coefficients between the average time course of each ROI and that of each voxel in the whole brain. A Fisher *z*-transformation for correlation coefficients was applied. Therefore, individual *Z*-score FC maps were defined for each ROI and subject. One-sample *t*-tests were conducted within the euthymic PBD and HC groups. Then, we performed two-sample *t* -tests to detect the differences in the FC maps between the euthymic PBD and HC groups within the masks from the union set of the one-sample tests results of the FC maps ($P < 0.05$, FDR corrected) of the two groups, controlling for age, education years, and gender effects.

2.6. Correlation Analyses between Functional Connectivity and Clinical and Psychological Measurements. We used a partial correlation analysis to explore the relationship between clinical and psychological measurements and FC features including the global FCD of each ROI and the FC map of ROIs, controlling for the effects of age, education years, and gender.

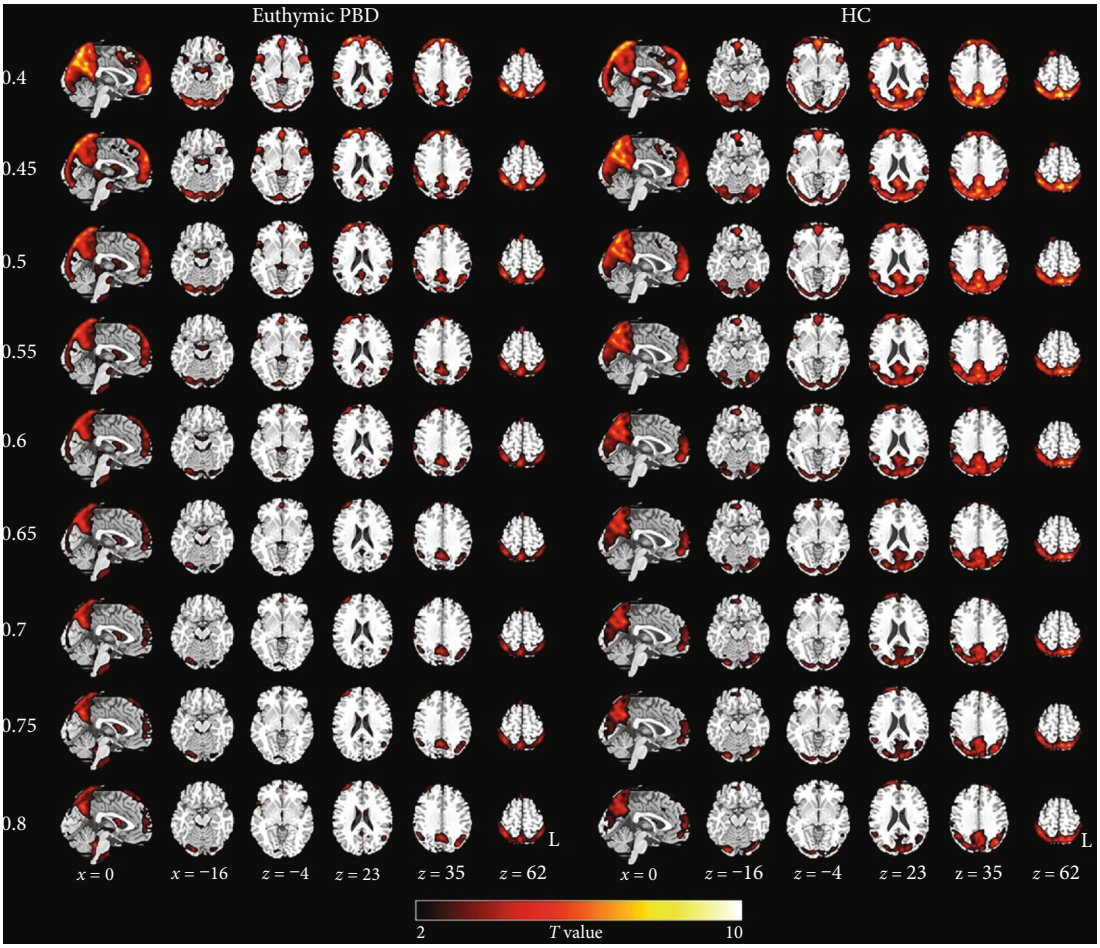

Figure 1: The global FCD maps for the nine Tc thresholds in the euthymic pediatric bipolar disorder (PBD) and healthy controls (HC) groups (one-sample t-test, $P < 0.05$, FDR corrected, cluster size > 621 mm^3). L: left; R: right.

3. Results

There was no significant difference in gender, age, education years, IQ, MFQ, TMT, and DST-F scores between the euthymic PBD and HC groups ($P > 0.05$). The YMRS, SCWT, and DST-B scores showed significant difference between the two groups ($P < 0.05$). Table 1 shows these clinical data and neuropsychological measurement in detail.

3.1. Global Functional Connectivity Density Analysis. We illustrated the distribution of the global FCD for the nine Tc in the euthymic PBD and HC groups (Figure 1). For almost all Tc thresholds, we found the highest global FCD in the precuneus, angular gyrus, inferior parietal lobule, occipital cortex, superior temporal cortex, superior frontal gyrus, and the cerebellum, while the cluster size of the regions grew smaller as the Tc threshold increased. The pattern of regions exhibiting highest global FCD was similar as that of previous studies.

We conducted a two-sample t-test to compare data from the euthymic PBD group and HC group for each threshold ($P < 0.005$, cluster size > 270 mm^3). We summarized all differences of global FCD resulting from the nine Tc thresholds to obtain stable differences between groups (Figure 2).

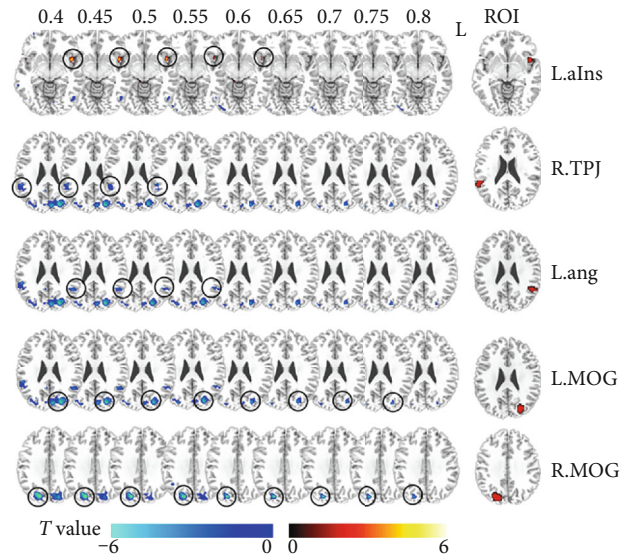

Figure 2: The differences of global FCD maps between the euthymic PBD and HC groups in 9 Tc thresholds separately ($P < 0.005$, cluster size > 270 mm^3). The left part shows 5 ROIs' position and designation; L: left. ROIs' abbreviations are consistent with those shown in Table 2.

Table 2: Five ROIs determined in global FCD analysis.

Brain regions	Abbreviation	Peak MNI coordinate			Brodmann	Size of ROIs (mm^3)
		x	y	z		
Left anterior insula	L.aIns	-45	9	-9	48	459
Right temporoparietal junction	R.TPJ	51	-39	24	42	405
Left angular	L.Ang	-45	-51	21	39	918
Left middle occipital gyrus	L.MOG	-24	-84	21	18, 19	3051
Right middle occipital gyrus	R.MOG	21	-81	33	18, 19	324

FCD: functional connectivity density; MNI: Montreal Neurological Institute; ROI: regions of interest.

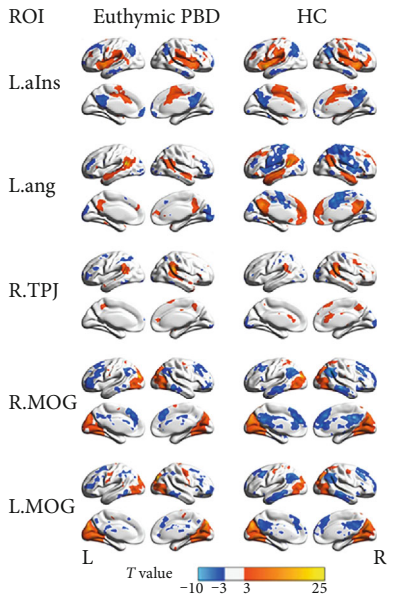

Figure 3: The group-level functional connectivity maps seeded at 5 ROIs in the euthymic pediatric bipolar disorder (PBD) and healthy control (HC) groups (one-sample t-test, $P < 0.05$, FDR corrected, cluster size > 621 mm^3). L: left; R: right. ROIs' abbreviations are consistent with those shown in Table 2.

Compared with the HC group, the euthymic PBD group showed increased global FCD in the left anterior insula at five consecutive Tc thresholds comparisons (from 0.4 to 0.6). We also found significantly decreased global FCD for more than half of thresholds at four clusters in the euthymic PBD group compared with the HC group. These clusters included the right angular gyrus, the left temporoparietal junction (TPJ), and the bilateral middle occipital cortex (MOG). In total, we identified five clusters of significantly altered global FCD in the euthymic PBD group. These regions were defined as regions of interest (ROIs) in the subsequent FC analysis (Table 2).

3.2. Functional Connectivity Analysis. For each ROI, we assessed a whole brain FC map for each group using one-sample t-test ($P < 0.05$, FDR-corrected, cluster size > 621 mm^3). Figure 3 shows these connectivity patterns of the FC map in the euthymic PBD and HC groups. In both groups, the regions that showed a positive correlation with the left anterior insula included the bilateral insula, dorsal anterior cingulate cortex, bilateral TPJ, supplementary motor area, and bilateral middle prefrontal cortex, which had been identified as the salience network in previous studies. The right supramarginal gyrus showed positive correlation with bilateral supramarginal cortex, the right middle prefrontal cortex, the anterior cingulate cortex, and precuneus. The left angular, which was identified as a node of the default mode network, positively correlated with the precuneus, posterior cingulate cortex, bilateral ventromedial prefrontal and inferior parietal cortex, and bilateral superior temporal gyrus and crus II of the cerebellum. In two groups, the seeds of bilateral MOG positively correlated with the occipital cortex, cuneus lobe, calcarine gyrus, and lingual gyrus.

The results of the two-sample t-test showed that four of the five ROIs exhibited significant differences between the euthymic PBD and HC groups ($P < 0.005$, cluster size > 621 mm^3) (Figure 4). Compared with the HC, the euthymic PBD exhibited decreased FC between the left anterior insula and right anterior insula and increased FC between the left anterior insula and the right TPJ. In the FC map of the left angular as seed, the euthymic PBD exhibited increased FC in the temporal gyrus and decreased FC in the bilateral angular and precuneus. The decreased FC between the bilateral MOG and the middle-inferior occipital cortex and cuneus were also identified in the euthymic PBD group (Table 3).

3.3. Results of Correlation Analyses. The correlation analysis showed a negative relationship in the FC between the left anterior insula and the left TPJ and the DST-B ($r = -0.559$, $P = 0.024$) in the euthymic PBD group. The functional connectivity between the left angular and the right angular was negatively correlated to the YMRS score ($r = -0.57$, $P = 0.022$) in the euthymic PBD group (Figure 5).

4. Discussion

In this study, we demonstrated altered intrinsic FC in the brain of euthymic PBD using resting-state fMRI. We observed increased global FCD in the left anterior insula and decreased global FCD in the right TPJ, the left angular and bilateral occipital lobule in the euthymic PBD patients. Functional connectivity analyses based on ROI showed a distinct altered integration within the salience and default mode networks in euthymic PBD. Our findings indicate that resting-state FC based on a data-driven approach could be useful for evaluating altered pathophysiology in euthymic PBD patients.

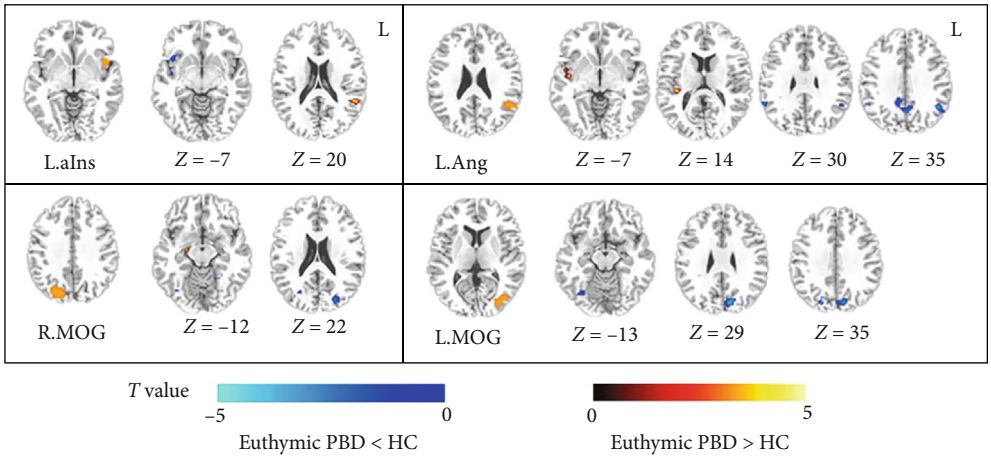

Figure 4: The difference of functional connectivity maps seeded at 4 ROIs between the euthymic pediatric bipolar disorder (PBD) and healthy control (HC) groups ($P < 0.005$, cluster size > 621 mm^3). The left column for each subgraph shows the seed. The hot color represents higher correlation coefficients, and the cold color represents lower correlation coefficients in the euthymic pediatric bipolar disorder (PBD). ROIs' abbreviations are consistent with those shown in Table 2.

Table 3: The significantly altered functional connectivity between the euthymic PBD and HC groups in 4 seed maps.

ROI	Regions	MNI coordinate			T value	Cluster size (mm^3)
		x	y	z		
L.aIns	Right insula	42	15	-12	-3.51	648
	Left temporoparietal junction	-48	-45	1	4.61	1080
	Right superior temporal cortex	37	-30	14	5.62	1674
L.Ang	Left angular	-51	-54	33	-4.37	1215
	Right angular	56	-51	26	-4.15	702
	Precuneus	3	-59	33	-4.17	1566
L.MOG	Left cuneus	-9	-84	24	-4.78	3078
	Right inferior occipital cortex	39	-75	-9	-3.99	1971
R.MOG	Right hippocampus	24	-12	-15	5.57	648
	Left cuneus	-24	-84	21	-4.78	3024

ROIs' abbreviations are consistent with those shown in Table 2. HC: healthy controls; MNI: Montreal Neurological Institute; PBD: pediatric bipolar disorder; ROI: regions of interest.

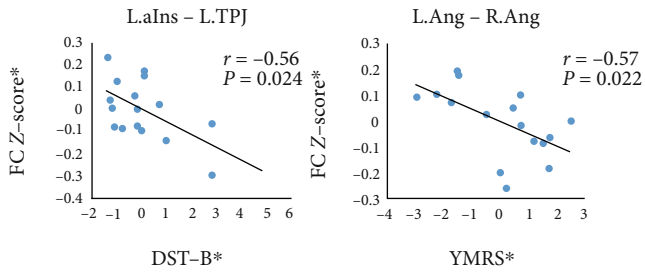

Figure 5: The relationship between the functional connectivity and psychological and clinical variables. ∗ represents the adjusted values controlling for the influence of the age, gender, and education years by the linear regression model.

Using global FCD analysis, we observed significantly increased global functional connectivity in the left insula and decreased global functional connectivity in the right TPJ in the euthymic PBD patients compared to controls. The anterior insula and TPJ have been identified as key regions involved in the salience network, which is implicated in monitoring, detecting, and regulating salient stimuli from the internal and external environment [17]. This integration of the salience network may play a role for fundamental cognitive and behavioral function, and its alteration was

found to associate with alteration of psychiatric symptoms in psychosis [18, 19]. Consistent with previous researches, abnormal emotional processing, as well as cognitive impairment, such as attention, processing speed, and working memory, characterized euthymic PBD [4, 20]. In the study, we observed impaired neuropsychological functioning, including decreased scores of the CWSW and DST-B and more completion time of TMT-A in euthymic PBD patients compared to controls. These measurements are commonly employed to examine cognitive function, and successful completion of these tests requires reasonable allocation of attention, flexibility, and working memory [21, 22]. The insula is considered a critical hub in mediating dynamic interactions in oriented attention and internally self-related cognition [23]. The TPJ, which is located at the ventral-anterior section of the inferior parietal lobule and the posterior end of the superior temporal sulcus, is thought to either shift attention to goal-directed cognitive processing or understand others' mental state [24–26]. A recent task fMRI study had suggested that BD patients showed less activation and altered FC in regions within the salience network during an emotion-cognition integration task [7]. Our further voxel-based whole FC analysis showed enhanced FC between the left insula and the TPJ and decreased FC between the bilateral insula in the euthymic PBD patients. We found a negative correlation between the DST-B and FC between the left insula and the left TPJ in the euthymic PBD. Considering the critical role of the insula and TPJ in cognitive and emotional processes, our finding suggested that the altered functional integration within the salience network in euthymic PBD might contribute to the underlying mechanisms of impaired higher-level cognitive processes in patients.

Growing evidence has suggested that the DMN is compromised in many neuropsychiatric disorders [6, 27, 28]. The DMN, which contains the ventral-middle prefrontal cortex, bilateral angular gyrus, the precuneus (poster cingulate cortex), and bilateral temporal gyrus, is associated with self-referential and introspective states [29]. The left angular gyrus has been repeatedly implicated in episodic and semantic cognition, and the connection of the angular gyri with other DMN regions may act as a connector hub for global integration of information [30]. We observed the increased global FCD in the left angular gyrus in euthymic PBD patients. Further FC analysis revealed that the left angular gyrus showed increased FC with the right superior temporal cortex and decreased FC with the precuneus and right angular gyrus. Here, we observed a negative correlation between the FC of bilateral angular gyrus and the YMRS in the euthymic PBD. In other words, the lower FC between the bilateral angular gyrus was associated with the worse mental state. The precuneus involvement in introspective processes such as self-referential and emotional processing was associated with attenuated activity toward external events [29]. Therefore, we suggested that the altered interaction of regions of the DMN might serve to impair mental processing in the euthymic PBD patients.

The euthymic PBD patients exhibited decreased global FCD in the bilateral MOG, which may serve as the potential functional basis for the deficits in visual processing [31]. A few task fMRI studies found abnormalities in MOG during emotion face processing task in PBD patients [32, 33]. Our previous study also found decreased functional activity in MOG, which was associated with the performance of cognition in PBD patients (W. [34]). Therefore, we speculated that the reduced FC in the MOG might impair the perception during self-referential processing in the euthymic PBD patients.

Several limitations of our study must be noted. First, the sample size of participants was relatively small, and the larger samples would help to confirm results presented here. Second, our sample included the euthymic PBD patients with type I and type II. Although we agree that there might be differences in FC in subtypes of PBD, it would have been very difficult to exclude an entire subtype of BD according to our study design. Finally, the majority of PBD patients were taking psychotropic medication when scanning. Few studies have suggested that drug treatment may affect functional neuroimaging measures [35]. Future studies will use the prospective design to clarify the contribution of medicine and subtypes of PBD to altered neuroimaging features of PBD patients.

5. Conclusions

In summary, we demonstrated that the euthymic PBD exhibited increased global FCD in the left anterior insula and decreased global FCD in the left angular and bilateral occipital lobule. Functional connectivity analyses showed a distinct altered integration within the salience and default mode networks in euthymic PBD. The altered functional integration was associated with altered emotional and cognitive processing in the euthymic PBD. These findings indicate that disturbed functional integration in salience and default mode networks might have potential implications for the physiopathology of the PBD.

Data Availability

The fMRI data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflict of interests.

Authors' Contributions

Author contributions included conception and study design (Weifang Cao, Qing Jiao, and Guangming Lu), data collection or acquisition (Weijia Gao, Yan Yin, and Linyan Su), statistical analysis (Dong Cui, Xiaojuan Wang, and Haoran Chen), interpretation of results (Weifang Cao, Yongxin Guo, and Jianfeng Qiu), drafting the manuscript work or revising it critically for important intellectual content (Weifang Cao, Qing Jiao, and Haoran Chen), and approval of the final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (all authors).

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Research Article

The Mediating Effects of Coping Style on the Effects of Breath Count Mindfulness Training on Depressive Symptoms among International Students in China

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Mindfulness training has gained popularity in the scientific field and has been proposed as an efficient way for emotional regulation. Mindfulness-based cognitive therapy (MBCT) is designed especially for depressive people in reducing risk of depression relapse and is recommended in national guidelines as a treatment choice for relapse prevention in recurrent depression. The aim of the current study was to investigate the effects of mindfulness training on depressive symptoms of international students and probe into the mediating role of mindfulness in stressful events and depression. In addition, we introduced a new kind of mindfulness training, the breathing exercise-based mindfulness training, which is based on the integration of Buddhism and Daoism. Self-report questionnaires assessing the coping style, abnormal depressive behavior, and stressful live events were completed in 260 international students in China (mean age = 21.4 years). The results showed that (1) many international students showed depression symptoms, (2) stressful life events play a completely mediating role in the initiation of depression and anxiety, and (3) mindfulness training for 8 weeks significantly reduced the depressive symptoms, and it was also related to a positive coping style. This study has certain theoretical significance in exploring the mechanism of the occurrence and development of depression among international students and provides useful tools for this special group of international students. In addition, the international students can also learn Chinese culture through the training. These findings indicate that mindfulness training and positive coping style are interrelated with treating depressive symptoms for international students.

1. Introduction

With the growing influence of Chinese education, the number of students studying in China continues to increase. In 2017, China was already the destination for the largest population of overseas students in Asia [1]. Mental health problems of these international students caused by cultural shocks have gradually become the focus of education management. Studies have shown that there are many emotional problems among these students, such as loneliness, anxiety, and depression [2]. Depression is a worldwide emotional disorder that affects an individual's adjustment to school [3, 4] and sometimes leads to self-harm or suicide. Depression also increases the risk of cardiovascular disease, raising the death rate for depressed people to 80% [5]. Therefore, it is an important task to deal with the mental health of overseas students in China, to understand their depressive mood states, especially to explore the causes of their depression.

Even though depression is the leading cause of disability worldwide [6], there is no efficient treatment for this disease, for the underlying neural mechanism of emotion is unclear [7]. The most widely accepted theory about affective disorders is the monoamine theory, which suggests that monoamines, including norepinephrine, dopamine, and serotonin (5-HT), are the major reasons for emotion disorders [8], and the first line of treatment for depression also targets these monoamines [9]. However, psychological therapy has also been used for depressive disorders, such as mindfulness-based cognitive

therapy (MBCT) [10]. Mindfulness is a kind of meditation originating from an Eastern Buddhist document and was introduced to the Western culture by Kabat-Zinn [11]. Later practices have given rise to many different mindfulness training programs, including mindfulness-based cognitive therapy (MBCT) [12], which is specially developed to psychologically treat individuals at risk of depressive relapse [13].

MBCT was described as a "program that focuses on learning how to mindfully attend to body sensations through the use of body scans, gentle stretching, and yoga mindfulness exercises, along with discussion and practices geared toward applying mindfulness" [14, 15]. MBCT trains an individual's awareness and acceptance of both negative and positive emotions [16], being awarene to daily life experiences, including coping with stress [17]. MBCT was designed originally as a relapse prevention for people with a history of recurrent depression [18,19]; it is not clear if MBCT can be used to people with current diagnosis of depressive disorders. Mindfulness invites participants to bring their full awareness to current experiences, but people with a current stressful life are likely to experience negative emotional feelings [20]. In addition, previously, we have shown that a negative coping style is related to stress-induced mood disorders such as anxiety and depression [21]; there are few studies about mindfulness with coping style in people under stress during their depressive episodes.

Even though some studies have suggested to use MBCT to people who are experiencing a current episode of depressive disorders [22], majority of research has focused on clinical intervention studies to evaluate the efficacy of mindfulness therapy on normal populations [23]. Here, we try to use mindfulness training in the international students. International students represent a special group of people, who just moved from their homeland and need to adapt the new environment. And their major problem is getting accustomed to the new environment, just like what mindfulness proposed to bring their full awareness to current experiences. The current study is aimed at exploring the effect of mindfulness training on depression and the mediating role of coping style between stressful event and depression. It also sought to identify the mediating role of coping style between mindfulness training and depression. It was hypothesized that mindfulness training can help the depressive international students adapt to school life, and coping style played a partial mediating role between depression and mindfulness training.

2. Methods

2.1. Participants. 260 foreign students were recruited from Jiangsu University and Nanjing University of Chinese Medicine. The investigators distributed the questionnaires to the students and explained the instructions, which includes the purpose of the test, the principle of voluntariness, and the anonymous way of answering the questions. 24 students' questionnaires had missing answers or wrong answers, and they were removed, with an effective rate of 90.7%. The Lie scale in EPQ-RSC of the Eysenck Personality Questionnaire, was further adopted. The study showed that the reliability and validity of the L subscale were relatively high, which reached the requirements of psychometrics [24]. The total effective students' questionnaires were 213, with an effective rate of 90.7% and a total effective rate of 81.92%. Among them, 112 were boys and 101 were girls.

All the procedures are done according to the ethic assessment sessions taking place in class during school time, supervised by members of the research team. The survey lasted half an hour, and the questionnaires were collected on the spot. The research was approved by the Human Research Ethics Committee of Jiangsu University. Information about the study was provided, and informed consent and assent were obtained from each participant.

2.2. Research Tools

2.2.1. Self-Rating Depression Scale (SDS). The self-rating depression scale (SDS) compiled by Zung (1965) was used to measure the students' depression level [25]. There are 20 items in this scale, and each item is scored on a scale of 4. The higher the score means the higher the degree of depression. This scale is easy to operate, and the score is not affected by age, gender, economic status, and other factors. It is one of the commonly used self-measuring scales for depression. In this study, the confirmatory factor analysis results of the questionnaire showed good structural validity, and the fitting indicators were as follows: $x^2 = 1.903$, df = 1, TLI = 0.950, GFI = 0.994, CFI = 0.992, and RMSEA = 0.077. In this study, Cronbach's α is 0.76.

2.2.2. The Life Event Test. The life event test includes 48 most popular life events, which includes three aspects: family life (28), work and study life (13), and social and friends (7), and 2 empty questions. The score ranges from 1 to 4 depending on its effects on the person's mind and also the effect duration on his mind, for example, from one month to half a year.

2.2.3. The Simple Coping Style Questionnaire. The Simple Coping Style Questionnaire (SCSQ) contains 20 items assessing the coping style, scores 0 (never) to 3 (always). Items 1-12 belong to positive coping and 13-20 belong to negative coping. If the average difference between positive coping and negative coping is greater than 0, it is positive coping and less than 0 is negative coping. The current study total questionnaire internal consistency $\alpha = 0.76$.

2.3. Mindfulness Training and Psychological Therapy. The MBCT training includes one hour of cognitive therapy with the knowledge about depression and mindfulness and also some idea about meditation. Then, they received 20 minutes of audio-guided training in "attention to breath," based on a mindfulness-based stress reduction program. The participants were required to "focus their attention on sensing the air slowly entering and leaving the nose," while listening to the audio file, in which they were instructed to relax the body and concentrate on their breath sensations. For the mindfulness training, it is hard for the subjects to concentrate or focus their attention on "here and present." In order to focus their attention on "here and present," they can do one kind of

breathing exercise: count the numbers from one to ten while breathing in, and then, hold the breath for ten seconds, and then, slowly breathe out. Then, after some training, they can go to an advanced level of breathing exercise: count the numbers 1-10 while breathing in, hold the breath for 10 seconds, then count the numbers 1-10 while breathing in again, and hold the breath for 10 more seconds. They can scan their bodies while holding the breath, thinking the air going to any part of the body they were scanning, such as the foot and leg. Each participant practices at least half an hour a day with the audios.

2.4. The Analysis of Salivary Cortisol Contents. The detailed procedures for analyzing salivary cortisol contents were described previously [26]. Briefly, at 9:00 am, the subjects were asked to wash their mouths with distilled water and, 5 minutes later, to put some sterilized absorbent cotton under the tongue to take saliva. 1 ml saliva was dissolved in 50-microliter methanol for cortisol analysis that was done on a Qtrap 3200 liquid chromatography-tandem mass spectrometer (ABI, USA). Cortisol was ionized with atmospheric pressure chemical ionization and identified in the positive ion mode using the multiple reaction monitoring mode. The assay method had good linearity in the range of 0.8-250.0 pg/mg, showing the square coefficient of correlation at 0.999. It also had good sensitivity, accuracy, and precision, showing limits of detection and quantitation at 0.3 and 0.8 pg/mg, and intraday and interday coefficients of variation less than 15% and recovery ranging between 85 and 115% (Chen et al., 2019), which fit the requirements of hair cortisol measurement.

2.5. Statistical Analysis. All analyses were performed using SPSS 22.0. All statistical tests were two-sided, and the significance level was set at $p < 0.05$. A paired t-test or repeated two-way ANOVA was used to compare differences between groups, and repeated one-way ANOVA was used to test the significant difference among the groups. The general linear regression analysis was used to explore the relations between depression and life events. Asymptotic and resampling strategies were used to examine the mediating role of coping style on the association between depression and stressful life events.

3. Results

3.1. Descriptive Statistics. The demographic characteristics of the international students in categorical variables are shown in Table 1. 97 students have come to China for less than one year, and 116 have come for more than one year.

The degree of depression was measured by the depression index: depression index = score/full score. Depression index < 0.50 means no depression, $0.50 \leq$ depression index ≤ 0.59 was mild depression, $0.60 <$ depression index ≤ 0.69 was moderate depression, and depression index > 0.70 was severe depression. The mean depression index for all participants was 0.46, which suggests a mild depression. Among the students, 82 have no depression, accounting for 38.49%; 72 have mild depression, accounting for 33.80%; 38 students have moderate depression, accounting for 17.84%; and 11 students with severe depression, accounting for 5.16%. The mean depression degree of male students and female students was 49.93 and 42.55, respectively. On the whole, female students encountered fewer depression problems than male students, but the p value was $0.26 > 0.05$, showing no significant statistical significance.

Table 1: Demographic characteristics and depressive behaviors ($N = 213$).

Variables	N	%	Depression (mean ± SD)	p
Majors				
Medicine	89	41.78	47.21 ± 15.28	<0.05*
Science & engineering	52	24.41	48.29 ± 16.44	
Art	29	13.61	44.07 ± 14.80	
Liberal arts	43	20.19	42.66 ± 13.22	
Sex				
Female	101	47.42	48.10 ± 17.94	0.265
Male	112	52.58	43.81 ± 14.60	
Hometowns				
Asian area	124	58.21	49.93 ± 11.58	<0.05*
African area	89	41.78	42.55 ± 12.33	

Note: $^*p < 0.05$.

Table 2: Related studies on depression and life events.

	M	SD	Depression	Life event	Positive coping
Depression	46.29	8.66	1		
Life event	30.54	5.99	0.409*	1	
Positive coping	15.76	4.97	-0.332*	-0.369*	1

Note: the data were analyzed with SPSS, M represents mean, and SD is standard deviation. The right three panels are the Peterson correlation. $^*p < 0.05$.

3.2. Correlation Analysis Life Events and Coping Style and Depression. The correlation analysis results of life event and depression are shown in Table 2. The results showed that depression symptoms were significantly correlated with life events and coping style. The results showed that life events had a significant positive effect on depression and coping style has a significant negative predictive effect on depression. The total score of life events can be regarded as the severity of symptoms. In addition, the subjects can be divided into the no symptom group, suspicious group, and symptom groups according to their scores.

Then, we used depression symptoms as the dependent variable and life events and adaption style as independent variables; the relationships between depression and life events and coping style were calculated. The indirect effect of coping style on the relationship between life events and depression was examined using the SPSS 20.0 PROCESS procedure. The results showed that life events can induce

Table 3: Linear regression of depression and life event and coping style.

Dependent variable	Independent variables	Regression coefficient	Standard regression coefficient	R^2	Adjust R^2	F	t	p
Depression	Life events	0.694	0.409	0.167	0.162	30.353	5.509	0.001
Depression	Positive coping	0.583	0.332	0.110	0.104	18.702	4.325	0.002

Note: $^{**}p < 0.01$.

Table 4: Effects of mindfulness training on depression.

	Before (mean)	SD	After (mean)	SD	p
Narrative	61.71	5.64	43.37	4.87	$<0.01^*$
Mindfulness	63.33	5.27	38.54	4.24	$<0.01^*$
Running	62.26	4.64	56.98	4.79	n.s.$^{\#}$

Note: n.s.: not significant, $^*p < 0.01$ with paired t-test, $^{\#}p < 0.01$, repeated two-way ANOVAs (factor 1: intervention type; factor 2: measurement time).

Table 5: Effects of mindfulness training on blood cortisol (nmol/l).

	Before (mean)	SD	After (mean)	SD	p
Narrative	9.31	0.35	8.32	0.45	$<0.01^*$
Mindfulness	9.35	0.59	8.48	0.44	$<0.01^*$
Running	9.29	0.48	9.18	0.39	n.s.$^{\#}$

Note: n.s.: not significant, $^*p < 0.01$ with paired t-test, $^{\#}p < 0.01$, repeated one-way ANOVA.

depression ($p < 0.01$, Table 3), and positive coping style also affected depression (Table 3, $p < 0.01$). The results showed that life events have a significant positive predictive effect on depression and coping style has a significant negative predictive effect on depression. The total score of life events can be regarded as the severity of symptoms.

3.3. Mindfulness Training on Depression. There are about 110 students who got high depression scores (mild depression and moderate with scores from 0.5 to 0.7) among the total 213 (the 11 students with severely high scores > 0.7 were excluded and suggested to see doctors). The 110 students were randomly divided into three groups, one group of 36 students with normal psychological counseling (narrative therapy by a registered psychological counselor, 2 hours a week, free of charge); 37 students were neglected, telling them they are normal but need more sports, such as half-hour running (once a day); and 37 students were trained with mindfulness training (twice a week, plus self-practice once a day). The results showed that after 8 weeks, both the narrative group and mindfulness training group improved with emotional depression, except the running group. The mindfulness group showed the best result ($p < 0.01$, paired t-test, $n = 36$-37); psychological therapy showed similar therapy results ($p < 0.01$, paired t-test, $n = 36$-37) (Table 4). Further analysis with one-way ANOVA found that the running group shows the least treating results.

Similarly, we measured the salivary cortisol levels before and after the mindfulness training. The present study utilized cortisol content in the saliva as the biomarker of total stress reactivity. Cortisol content was determined with high-performance liquid chromatography-tandem mass spectrometry. The results revealed that salivary cortisol was decreased after mindfulness training (Table 5, $p < 0.01$, repeated one-way ANOVA).

3.4. Effects of Mindfulness Training Are Related to Coping Style. We then analyzed the effects of mindfulness on depression with respect to the coping style. Among the 37 subjects in the mindfulness group, 15 (40.5%) showed positive coping, with the positive coping score averaging 5.43 ± 2.54 ($n = 15$), and 22 showed negative coping, with the negative coping score averaging -6.83 ± 3.82 ($n = 22$). And the mindfulness training showed better results for those with positive coping ($p < 0.01$, one-way ANOVA, $n = 15$-22, Table 6). Consistently, in the narrative therapy group, 19 showed positive coping, with the positive coping score 4.25 ± 3.14 ($n = 19$), and 18 showed negative coping, with the negative coping score averaging -3.14 ± 2.91 ($n = 18$-19, Table 6). These data suggested that the mindfulness training and the coping style are related; mindfulness training affects coping style.

4. Discussion

4.1. Relationship between Depression, Life Events, and Coping Style. There are many adaption problems for international students [27, 28]. Previous studies have reported the relationship between homesickness and depression among international students [29]. As far as we know, there are few studies about the mediating effects of coping style on the mindfulness of depression. Previous studies found that self-esteem partially mediated the association between mindfulness and social anxiety in inland undergraduates [30]. And our previous study found that coping style mediated depression with eating disorders in undergraduates too [21]. In this study, we are the first to use mindfulness training on international students and found that it is a good way to help them accommodate the new environment abroad. In addition, the results of correlation analysis showed that depression was significantly correlated with both life event and coping style. The regression results showed that life events had a significant positive effect on depression, and coping style had a significant negative predictive effect on depression. These findings are consistent with previous studies showing that individuals with negative coping style are more likely to have mood disorders such as anxiety and

Table 6: Effects of mindfulness training affected by the coping style.

Coping style	Before (mindfulness)	After therapy	Before (narrative)	After therapy
Negative coping	64.32 ± 5.18	46.95 ± 6.73	61.28 ± 5.38	44.96 ± 4.68
Positive coping	62.68 ± 4.95	32.91 ± 4.15**	62.37 ± 4.79	42.43 ± 5.74

Note: $^{**}p < 0.01$, repeat one-way ANOVA.

depression [31], highlighting the importance of coping styles established early in life.

4.2. Mindfulness with Buddhism and Daoism. MBCT is derived from mindfulness, which was introduced to the medical field by Kabat-Zinn at the University of Masachusettes for the first time in 1980 [32]. The fundamental component of mindfulness is attention, and it is critically important to pay attention to what is happening "right now and here." Or mindfulness is characterized as paying attention to all stimulations from external senses or internal senses and being purely observing without being involved in the experience [33]. Attention is critical for mindfulness, but it is difficult to sustain. Almost 50% of the time we are awake, our mind is wandering. Here, we used a short breathing exercise to count the numbers while breathing to reduce mind wandering [34].

According to Buddhism, every individual has six "roots" that bother him and make his mind wander. The six roots mean the senses from the "eye, ear, nose, tongue, body, and mind." One good way to remove them is just focusing on one of them, such as a beautiful scenery or a good taste. Focusing on the body sense, such as feeling the breath, has been regarded as a very good way for Buddhism or Daoism. The breath focusing mindfulness is a process of focusing on slow, diaphragmatic breathing and putting oneself in the "moment" [35]. As reported before, breath counting in mindfulness is associated with more meta-awareness, less mind wandering, better mood, and greater nonattachment (i.e., less attention captured by distractors formerly paired with a reward). By breath exercise, counting the numbers while breathing, and holding the breath, the participants can help focus their attention on the present.

For international students to adapt to the Chinese culture, they also need to learn the Chinese culture. Mindfulness is derived from Buddhism; actually, there are many kinds of trainings in the traditional Chinese culture, such as Daoism, meditation, and Chan. The difference lies in the target of the attention: the normal mindfulness usually focuses attention on the body, like scanning the body from foot to head. The breath count mindfulness pays attention to the breath, which is the major topic for Daoism. Daoism is the basis for Chinese philosophy and Chinese medicine, and it has many kinds of psychological training methods, such as meditation, Taichi, or Qigong, or Gongfu. One key point of the Daoism training is "Lian Qi," or "Qi gong," which means to do breathing exercise, to hold the air in the body, like the Gongfu Panda. Actually, everyone is using the Qi every day; for example, when an individual wants to move a heavy object, or tries to hit somebody, or even tries to stretch the body, he would have a deep breath and hold the air inside. In ancient China, the Taoists usually did exercises to keep longevity through external Chinese alchemy, or internal alchemy. External alchemy means using the drugs, while the internal alchemy means doing the breath (Qi) exercise. Breath exercise (Qi Gong) can not only help the individual to direct their attention to the body for signals of "now and here" but also increase the pressure in the belly to exercise the internal organs, such as the stomach and intestine, to increase the blood flow in the organs, or reunite the body and mind and thus the "spirit" [36].

4.3. Meditating Role of Copying Style on Mindfulness Training. Massachusetts University Medical Center has adopted more than 10,000 patients in the last 30 years, with each completing the 8-week mindfulness-based stress reduction program. It is reported that every patient who participated in the program liked it and has made a changing point in their lives [37]. And it has reported that various medical syndromes had been markedly decreased after the program, such as depression, anxiety, and sleep disorders [38]. So far, mindfulness training has been used in many medical disorders, such as psoriasis and fibromyalgia, in addition to affective disorders [39].

Mindfulness training may help depressed people gain attention control and reduce the activation of associative networks of negative thoughts, allowing depressive thoughts to enter and leave consciousness without spiraling the individual into depressive rumination [40, 41]. Over time, mindfulness practices may thus reduce the links between depressive thoughts in the associative network [42]. However, mindfulness training is not always effective in depression and anxiety disorders [43]. Previous studies have found inconsistent relationships between trait mindfulness and state mindfulness. The reason might be that the subjects need to have some trait mindfulness and state mindfulness to get good levels of mindfulness experience. Consistently, some studies suggested that self-esteem might mediate this process [44].

Given that depressive patients are characterized by emotional and attention biases as well as negative coping style, this study probed into the role of negative coping style on the effects of mindfulness. And the data in this study found that mindfulness was associated with negative adaptive coping strategies in the face of stress. This is consistent with previous reports that mindfulness-related well-being was mediated by both appraising situations as less stressful and using more adaptive strategies in coping with stress [45]. In all, mindfulness training can help international students get better results for helping them face stressful life events and get greater positive emotions and less negative emotions.

Stress is evolutionarily benefit to all lives, but overwhelming stress is a critical causing factor for many neurological

disorders [46]; for example, oxidative stresses are important factors in neural degenerative disorders, possibly due to increased levels of reactive oxygen species. Stress includes both physiological stress and psychological stress, and recently, it is found that even psychological stress can induce mental disorders or neurological disorders [47]. Sometimes, stress can induce very long-lasting changes in the neural circuits underlying emotional regulations, which facilitate some neurological diseases [48]. Mindfulness is a very useful tool not only to serve as a clinical treatment for patients but also to culture a kind of healthy lifestyle. Mindfulness training can also reduce the stress hormone glucocorticosteroids and serotonin and result in effects on stress and depression. In recent years, an increasing interest in mindfulness-based approaches both in clinical application and in the field of research has proved that MBSR is an established program shown to reduce symptoms of stress, anxiety, and depression. Mindfulness is believed to alter emotional response by modifying cognitive-affective processes [49].

Mindfulness has been proved to be an effective way for emotional regulation, which depends on attention transfer and reappraisal. First, mindfulness training helps individuals to pay attention to what is happening right now and here. This is a good way for attention transfer from worries, which are usually memories of the past or worries for the future. Second, mindfulness can also help cognitive reappraisal, because an individual can treat the worries easily when they are relaxed with deep breathing. Previously, we have hypothesized that the human being has three primary kinds of core affects: reward, punishment, and stress [50], and they exclude from each other [50]. The individuals can have a good mood by focusing on positive emotions (reward) to transfer attention from stressful thoughts. MBCT (mindfulness-based cognitive therapy) was designed to help depressive patients, with cognition. Cognition is associated with depression symptoms. Individuals in a major depressive episode often display impairment in cognitive control [51]. Cognitive models of depression posit that negatively biased self-referent processing and attention have important roles in the disorder [52]. Yoon et al. [53] suggested that patients with depression having mild cognitive impairment (MCI) showed poorer cognitive function than nondepressed patients with MCI in some cognitive domains. Improvement in depression was related to improvement or prevention of the decline in cognitive measures. For instance, depressed patients may have persistent negative thoughts; rumination interacts with negative cognitive styles to predict the duration of depressive symptoms; rumination enhances the effects of depressed mood on thinking, making it more likely that people will use the negative thoughts and memories activated by their depressed mood to understand their current circumstances. Depressed people, particularly depressed ruminators, find it difficult to inhibit negative thoughts and tend to choose the wrong cognitive activities to distract themselves [54]. A dysphoric mood is maintained through attention and memory functions biased toward negative information, and these cognitive biases also expose individuals to recurrent depression; Xu et al. [55] indicate that there is a negative bias in automatic visual deviance detection. Ruohonen et al. [56] investigated age- and depression-related alterations in the ERPs to sound intensity changes; depression-related effects were found for sensory gating when controlling for medication status or when only nonmedicated depressed participants were included in the analysis. In the depression group, general overexcitability in the processing of sounds was only observed in nonmedicated participants, so the results highlight the importance of studying nonmedicated groups when searching for biomarkers for depression. In other words, cognitive involvement may influence depression-related effects.

4.4. Limitations and Prospects of the Study. There are some shortcomings in this study, which need to be improved in future studies. Mindfulness-based cognitive therapy has been proved to be effective for emotional disorders, such as depression and anxiety disorders. Many reports have found that mindfulness training can help appease emotional arousal. Mindfulness training is sure to affect the nervous system [57]. Mindfulness can affect attention, emotion, and self-consciousness; what is the neural mechanism? What is the neural network that is involved? Neurobiological effects of meditation and mindfulness can be detected in the brain, particularly in areas related to attention and memory, in perception and sensory processing, or in self- and autoregulation, including control of stress and emotions [58]. In addition, monoamine has been proved to be the substrate for emotions [59]; what are the effects of mindfulness training on the monoamines?

Data Availability

Original data are available if required.

Conflicts of Interest

There is no interest conflict among the authors.

Authors' Contributions

Zeng Z, Wang F, and Gu S planned the study and wrote the paper; Liang F, Feng R, and Li Y did the investigation; and Wang F and Zeng Z analyzed the data.

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Research Article

The Relationship between Insecure Attachment to Depression: Mediating Role of Sleep and Cognitive Reappraisal

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Previously, we have shown that neuromodulators are important factors in stress-induced emotional disorders, such as depression, for example, serotonin is the major substance for depression. Many psychological studies have proved that depression is due to insecure attachment. In addition, sleep is a major symptom of depression. Furthermore, serotonin is the substrate for both sleep and depression. To explore the role of sleep in the relationships between insecure attachment and depression, we investigated 755 college students with Close Relationship Inventory, Emotion Regulation Questionnaire, Self-rated Depression Scale, and Pittsburgh Sleep Quality Index. The results showed that (1) insecure attachment positively predicted poor sleep quality; (2) sleep quality partially affected depression, possibly due the same stress neuromodulators such as norepinephrine and cortisol; and (3) cognitive reappraisal moderated the mediating path leading from attachment anxiety to poor sleep quality. These findings highlight the moderating role of cognitive reappraisal in the effects of attachment anxiety on sleep quality and finally on depression. In conclusion, sleep quality links attachment anxiety and emotional disorders.

1. Introduction

Emotion disorders, such as depression is the leading cause of disability worldwide [1]. However, there is no efficient treatment for this disease, for the underlying neural mechanism of emotions is unclear [2]. The most widely accepted theory about affective disorders is the monoamine theory, which suggests that monoamines, including norepinephrine, dopamine, and serotonin (5-HT) are the major reasons for emotion disorders [3], and the first line of treatment for depression also targets these monoamines [4]. However, there are still many controversies about monoamine neurotransmitters affecting the emotion processes, for example, it is well known that 5-HT is a major neurotransmitter that is involved in depression; and sleep is also modulated by 5-HT in raphe nuclei, but how sleep affects depression is not clear. Our previous studies suggested that monoamine is related to emotional arousal [5], which might affect sleep, and poor sleep might in turn causes emotional depression [6].

Sleep disorder has become a health problem that affects almost all the people around the world. The 2017 Nobel Prize in biology and medicine has been awarded to three American scientists, Michael, Jeffrey, and Michael, for their work in studying the neural mechanisms by which the body clock works, highlighting the importance of sleep. Many papers are still reporting the mechanisms and functions of sleep, for example, it is found that sleep helps metabolite clearance [7]. In addition, it is found that sleep can also affect the glymphatic system to clear the big molecules in the brain [8], and it is reported that glymphatic system might induce depression in Alzheimer's disease [9]. Our previous studies also reported that sleep is an important time for the recuperation

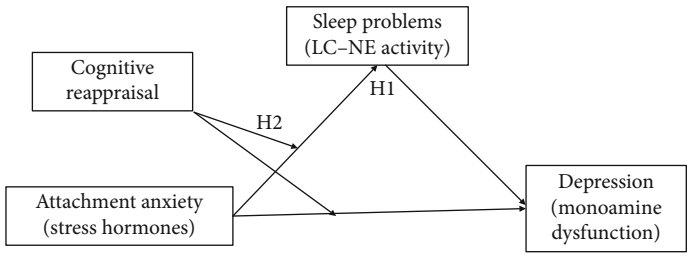

Figure 1: The hypothetical model.

and rejuvenation of the brain [10]. In all, sleep can induce many kinds of neurological and psychological diseases, such as emotion disorders, substance use, low academic performance, and physical dysfunctions [11]. Unfortunately, the underlying neural mechanism of sleep problems is not clear yet, sleep-related psychological factors have got little empirical results yet.

Some studies found that sleep quality may be affected by one dispositional factor: insecure attachment [12]. Attachment theory proposed by Bowlby suggested that an individual's personality development and emotional disorders are associated with maternal and infant attachment, and the destruction of attachment bonds in childhood can lead to a lifelong emotional disorders, manifested as a sudden onset of depression or anxiety [13]. For nearly half a century, many investigations have probed into the mechanisms about attachment theory, including neural changes underlying the attachment [14]. Many studies have found that insecure attachment is related to many kinds of mental disorders, such as depression [15], and many studies also showed that attachment is related to stress responses, for example, maternal deprivation can enhance activity of the hypothalamic-pituitary-adrenal axis [16], thus release of cortisol, which consequently leads to monoamine dysfunction and thus sleep problems and depression [17]. Overall, unsafe mother-infant attachment can lead to sleep problems in infants and young children. Unfortunately, studies on sleep in the relationship from attachment to depression is relatively lacking.

Attachment theory holds that early attachment relationships influence the brain development, and also epigenetics [18]. These changes, in turn, act as explanatory filters to influence and guide the individual's future cognitive and emotional processing (attention, memory, anticipation, attribution, etc.), which further shapes the individual's attachment development and emotional health in adulthood. Thus, we speculate that, similar to the adverse effects of maternal and infant insecure attachment on individual sleep, adult insecure attachment may also have an adverse effect on the sleep quality of adult individuals and thus emotional disorders. Even though some studies have also suggested that adults with insecure attachment reported poorer sleep quality than those with secure attachments [19]. However, the underlying relationship among them is not clear, for example, which dimensions of attachment predict sleep disturbance, avoidance, or anxiety or both? Or what factors can possibly be the pathways? Here, we try to probe in the causal relationship among them.

1.1. Mediating Effect of Sleep. Many reports suggested that insecure attachment is closely related to emotional disorders, such as depression, because they are all influenced by the HPA axis and monoamine systems. In addition, insecure attachment can induce sympathetic nervous system and norepinephrine release, which affect sleep qualities. Sleep problems in turn will affect the physical and mental states, including emotional disorders. Thus, we hypothesize that adulthood insecure attachment positively predicts an individual's sleep quality. Sleep problem has been proved to impair college students' mental and physical health, and sleep disorders can cause depression-like behaviors [20]. Thus, we hypothesize that sleep problem mediates the relationship between adulthood insecure attachment and depression (H1) (Figure 1).

1.2. Mediating Effects of Cognitive Reappraisal. Cognitive reappraisal is an emotional regulation strategy that reduces emotional response by changing the re-recognition of emotional events. Cognitive reappraisal is not only a well-adapted response but also a positive adaptive ability. People who adopt positive strategy can actively change their perception of the personal meaning of emotional events or their own understanding of emotional events [21]. Previous studies show that cognitive reassessment plays an important role in improving psychological adaptability, protecting established interpersonal relationships, and promoting mental health [22]. Our previous studies suggested that reappraisal is important for good sleep and positive emotions [23]. Early cognitive behavioral therapy also aims to alleviate negative emotions and eliminate bad behaviors by adjusting and changing the distorted cognitive model of the interviewee and improving cognitive reappraisal ability.

According to the reverse regulation theory, cognitive reappraisal can help people correctly evaluate the information in the current situation and prevent impulsive behaviors [24]; in addition, it can also reduce HPA axis-releasing cortisol, reduce emotional arousal, and induce good sleep. In other words, cognitive reappraisal can reduce stress hormone release and promote individuals' adaptation to emotional factors, improve response quality, and help individuals maintain emotional balance. Risk buffer model points out that protective factors can buffer or weaken the adverse effects of risk factors [25]. Studies have confirmed that cognitive reappraisal can reduce norepinephrine-induced emotional arousal, and thus reduce the risk effect of negative coping style. Thus, we predict that cognitive reappraisal affects the adult insecure attachment-induced depression. Therefore,

Table 1: Means, standard Deviations, and correlations for all variables ($N = 755$).

	M	*SD*	1	2	3	4	5
(1) Avoidance	2.82	0.84	—				
(2) Anxiety	3.68	1.05	0.29**	—			
(3) Depression	3.83	0.59	0.16**	0.33*	—		
(4) Cognitive reappraisal	5.22	0.99	-0.17**	0.01	0.04	—	
(5) Sleep quality	6.37	2.72	0.16**	0.23**	0.27**	0.02	—

Note: $^{**}p < 0.01$.

we hypothesize that the mediating effects of sleep quality would be weaker in individuals with high cognitive reappraisal than those with low cognitive reappraisal level (H2).

To sum, we intend to investigate the relationships among adulthood insecure attachment and depression as well as its mediating and moderating mechanisms. Based on previous theories and studies, we hypothesize that sleep problem would mediate the effects of insecure attachment on depression, and the mediating effect would be regulated by the level of cognitive reappraisal. The hypothetical model is shown in Figure 1.

2. Methods

2.1. Participants. 867 college students in Jiangsu province participated in our survey. All the procedures are done according to the ethic assessment and were approved by the Human Research Ethics Committee of Jiangsu University. The participants were informed and gave a written consent. 53 surveys were incomplete, and an additional 59 participants reach the excluding criterion (with obvious psychiatric diseases, such as depression). In all, 755 (87.08%) usable surveys were obtained from the students, which included 298 (39.47%) male and 457 (60.53%) female, averaged age is 19.8 ± 2.3 years (SD = 2.41, range = 17-25 years). 262 (34.70%) participants were freshmen, 299 (39.60%) were sophomore, and 193 (25.70%) were juniors or above. No significant difference in grade distribution between the genders of the participants was found ($\chi^2(3) = 1.02$, $p = 0.80$).

2.2. Materials

2.2.1. Attachment. Adulthood insecure attachment was investigated with the Chinese version of the Experience in Close Relationship Inventory (ECR), which includes 36 items and two dimensions: attachment anxiety and attachment avoidance. Each item is scored from 1 to 7 (1 means "not at all consistent" and 7 means "very consistent"). After reversing the score of some items, the score of all the questions was calculated. A higher score indicates less attachment security. The Chinese version of the scale has got good validity and reliability and is wildly used among Chinese mainland students. And we got the Cronbach's alpha to be 0.71 for the avoidance dimension subscale and 0.88 for the anxiety dimension subscale.

2.2.2. Self-Rated Depression Scale (SDS). Self-Rating Depression Scale (SDS), compiled by Zung (1965), was used to measure the students' depression level. There are 20 items in this scale, and a scale 0-4 was scored for each item. A higher score means a higher degree of depression. This scale is easy to operate, and the score is not affected by age, gender, economic status, and other factors. It is one of the commonly used self-measuring scales for depression [26]. In this study, the confirmatory factor analysis results of the questionnaire showed good structural validity, and the fitting indicators were as follows: $x^2 = 1.903$, $df = 1$, TLI = 0.950, RMSEA = 0.077, CFI = 0.992, GFI = 0.994, and the Cronbach's α is 0.762.

2.2.3. Cognitive Reappraisal. Cognitive reappraisal was measured by the Chinese version of the Emotion Regulation Questionnaire. The scale includes 6 items, with each item scoring from 1 to 7 (1 means "strongly disagree" and 7 means "strongly agree"). A higher score indicates more frequently emotional regulation strategies. The Chinese version of the scale has been wildly used in Chinese college students' samples and shows great reliability and validity. Cronbach's alpha of the ERQ subscale was 0.78.

2.2.4. Sleep Quality. Pittsburgh Sleep Quality Index (PSQI) was used to measure the sleep quality. The questionnaire includes 7 factors and 19 items. The 7 factors include sleep latency, sleep duration, sleep disturbance, sleep efficiency, daytime dysfunction due to sleepiness, as well as sleep medication use, and overall sleep quality. Each item was scored with 0-3, with high scores indicating worse sleep. This questionnaire is widely used in China and shows good validity and reliability. 0.87 was the Cronbach's alpha for this study.

2.2.5. Procedures. Paper-and-pencil-based questionnaires were used in this study, and the investigation was done in 30-60 student classes. The investigation was done during the middle semester and excluded stressful events such as examinations. The test lasted for about 30 minutes. SPSS20.0 and SPSS macro PROCESS were used for the statistics.

3. Results

3.1. Preliminary Analyses. We first checked the normality, using the asymptotically distribution-free procedure, and the results showed that the data are univariate normality. Then, we evaluated the common method variance using the Harman's single-factor test and found that the maximum component explained only 19.36% of total variance, which suggested that no single factor can explain majority of variance.

The means and standard deviations, as well as correlations among all variables, are shown in Table 1. The mean PSQI score was 6.37 ± 2.72 among 755 students, and 223

Table 2: Multiple regression analyses for the indirect effect of sleep.

Regression		Fix index			Significance of regression coefficient			
Dependent variable	Independent variable	R	R^2	F	β	*LLCI*	*ULCI*	t
Sleep quality	Avoidance	0.24	0.06	23.76^{***}	0.32	0.69	5.28^{***}	2.68^{**}
	Anxiety				0.51	0.32	0.69	5.28^{***}
Depression	Avoidance	0.36	0.14	61.34^{***}	0.12	0.23	7.78^{***}	2.79^{*}
	Anxiety				0.22	0.18	0.27	9.94^{***}
Reappraisal	Avoidance	0.31	0.09	26.25^{***}	0.27	0.04	0.50	2.29^{*}
	Anxiety				0.32	0.12	0.52	3.21^{**}
Sleep quality	Depression				0.64	0.63	1.04	4.92^{***}

Note: $n = 755$. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Continuous variables in the regression equation have been normalized. *LLCI* and *ULCI* represent the lower and the upper limitations of 95% bootstrap confidence interval, respectively.

Table 3: Multiple regression analyses of the moderate effect of cognitive reappraisal.

Regression		Fit index			Significance of regression coefficient			
Dependent variable	Independent variable	R	R^2	F	β	*LLCI*	*ULCI*	t
Depression	Avoidance	0.45	0.18	38.69^{***}	0.08	0.09	0.17	2.64^{*}
	Anxiety				0.23	0.18	0.28	10.82^{***}
	Reappraisal				-0.04	-0.01	0.08	1.62
	Anxiety × **reappraisal**				-0.08	0.04	0.12	3.81^{***}
Sleep quality	Avoidance	0.31	0.10	16.14^{***}	0.28	0.05	0.52	2.35^{*}
	Anxiety				0.31	0.11	0.51	3.08^{**}
	Depression				0.85	0.58	1.67	7.83^{***}
	Reappraisal				-0.07	-0.13	0.26	0.67
	Anxiety × **reappraisal**				-0.11	-0.06	0.29	1.26

Note: $n = 755$. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Continuous variables in the regression equation have been normalized. LLCI and ULCI represent the lower and the upper limitations of 95% bootstrap confidence interval, respectively.

students (97 males, 126 females) showed sleep disturbance (PSQI scores ≥ 8), with no difference between male and female ($t = 0.61$, $p = 0.54$). The average score for depression was 3.83 ± 0.59. Correlation analysis showed that insecure attachment is positively related with depression ($R_2 = 0.33$), and also with sleep quality ($R_2 = 023$). Depression is also correlated with sleep quality ($R_2 = 027$). However, reappraisal is negatively correlated with attachment anxiety.

3.2. Mediation Analyses. The indirect effect of sleep on the relationship between insecure attachment and depression was examined using the SPSS 20.0 PROCESS procedure. The results show that insecure attachment positively predicted depression ($\beta = 0.22$, $p < 0.001$); and insecure attachment also affected sleep quality (Table 2, $\beta = 0.51$, $p < 0.001$). If both attachment anxiety and sleep quality are taken as predictors, their effects on depression are significant ($\beta = 0.32$, $p < 0.01$ and $\beta = 0.84$, $p < 0.001$).

In order to further test the indirect effects between them, we created 1,000 bootstrap samples, and the results are shown in Table 2. The indirect effect for sleep quality was statistically significant (indirect effect = 0.18, 95%CI = 0.11 -0.27), and the ratio of indirect to total effect was 36.56%, which means sleep quality serves a partial mediating function in the relation between insecure attachment and depression. Later, we tested the indirect effects of reappraisal on the attachment avoidance and depression, and the result indicated that sleep did not serve as mediating role (95%CI = 0.00-0.11).

3.3. Moderation Analysis. Then, we used SPSS 20.0 PROCESS analysis to test the moderation effects of reappraisal on the links between attachment and depression through sleep quality. It was found that attachment anxiety positively predicts sleep quality (Table 3, $\beta = 0.21$, $p < 0.001$), and sleep quality positively predicts depression ($\beta = 0.80$, $p < 0.001$). In addition, the standardized regression coefficient of "attachment anxiety × cognitive reappraisal" negatively predicts sleep quality ($\beta = -0.08$, $p < 0.001$) and cannot predict depression, which implies that the indirect effect from attachment anxiety to depression is moderated by the level of cognitive reappraisal, and cognitive reappraisal has no moderating effect on the direct effect of attachment anxiety on depression.

We further investigated with moderation effects using a simple slope analysis and found that there is a stronger positive relationship between attachment anxiety and depression

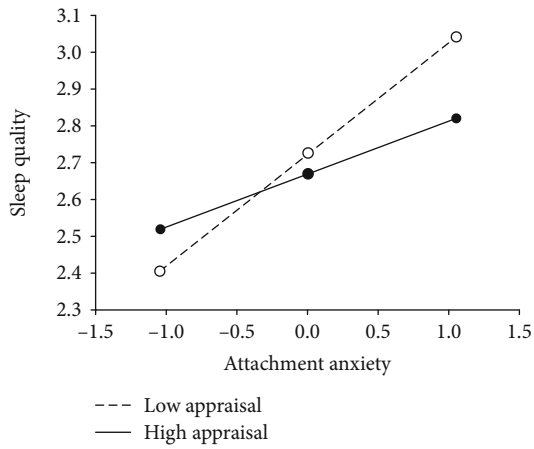

Figure 2: Simple slope analyses of the moderating effect of cognitive reappraisal.

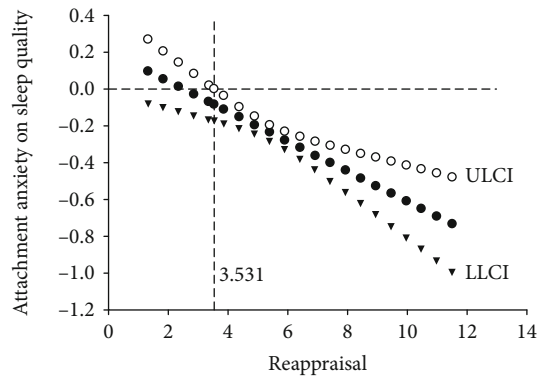

Figure 3: Effects of attachment anxiety on sleep quality moderated by cognitive reappraisal (*LLCI* and *ULCI* represent the lower and the upper limitations of 95% bootstrap confidence interval, respectively).

Table 4: The indirect effects at different levels of cognitive reappraisal.

Cognitive reappraisal	Indirect effect	*LLCI*	*ULCI*
M − *SD*	0.31	0.25	0.36
M	0.22	0.18	0.27
M + *SD*	0.14	0.08	0.21

Note: *LLCI* and *ULCI* represent the lower and the upper limitations of 95% bootstrap confidence interval, respectively.

in individuals with lower levels of cognitive reappraisals (Figure 2 and Table 4). In contrast, individuals with higher levels of cognitive reappraisal tend to show a weaker positive relationship between attachment anxiety and depression.

To explore the boundary value of the moderating effect, we used the Jonson-Neyman technique (J-N technique) [25]. And the data showed that attachment anxiety affects depression less dramatically with the increasing cognitive reappraisal and became statistically significant for participants whose scores were over 3.53, which contained 94.70% participants in this study (Figure 3). The results indicate that for most individuals, the moderating effect of reappraisal is significant. Of note, 95% confidence interval is required in the J-N technique, which suggests that "0" means there is no association between attachment anxiety and sleep quality (Figure 3).

4. Discussion

Tons of studies have suggested that insecure attachment are related to stress-induced depression [27–28]; however, the underlying neural mechanisms are not clear [29]. We proposed that the neuromodulators are the major substrate for emotions, also for sleeps and attachments [30]. Thus, we propose that insecure attachment positively predicts depression and poor sleep quality mediates the process. Insecure attachment positively predicts poor sleep quality, and poor sleep quality can induce bad emotions, such as depression. Consistently, our previous work showed that depressive people showed characteristic EEG recordings [31]. The data in this study which are collected from 755 college students in the Jiangsu, province of China, support our model.

First, the current study illustrates the relationship among adult attachment anxiety and sleep quality as well as depression. Similar to the attachment in kids, insecure attachment in adults is also related to emotional disorders, such as depression. The results showed that insecure attachment (represented by high level of attachment avoidance and/or high level of attachment anxiety) reported poorer sleep quality than those with secure attachment, which means self-reported sleep problems are positively associated with insecure attachment. This finding was consistent with previous studies with adult samples [32]. According to attachment theory, individuals with insecure attachment often meet social relationship problems. Individuals with attachment anxiety tend to be stressful and have HPA axis activated and tend to experience sleep disorders [33]. In addition, individuals with attachment avoidance usually have the amygdala activated to have fearful emotions, and thus downplay their close relationships, and they are not successful in using good social support and do experience emotional arousal [34].

Secondly, the data also show the effect that attachment anxiety positively affects poor sleep quality which is moderated by an individual's cognitive reappraisal level. Or put it another way, attachment anxiety affects sleep quality less in individuals with higher cognitive reappraisal compared with those individuals with low cognitive reappraisals [35–36]. Our data from the J-N analysis confirmed this point that reappraisal plays an important role between attachment anxiety and sleep quality. We suppose that both forms of insecure attachment can predict sleep problem by this mechanism, but the results do not support this. Consistently, the attachment theory proposed that avoidant individuals would not trust others and believe they cannot depend on others either [37].

Finally, the results in this study would shed some lights on the mechanism about how insecure attachment styles induce emotional disorders through affecting sleep. Sleep

plays an important mediating role between attachment anxiety and depression, so we should pay attention to sleep quality and its related factors such as attachment and reappraisal, and methods should be taken to help create a supportive environment and improve students' sleep quality. In addition, our study suggested that poor sleep quality moderates insecure attachment with depression. Many previous studies have reported about insecure attachment with depression [38–39]; however, no previous study reported about the mediation role of poor sleep in the process. Poor sleep and lower level of cognitive reappraisal play a moderate role from insecure attachment to depression.

Cognitive reappraisal is a kind of emotional regulation that helps us to keep calm at stressful events. Emotion starts at the individual's perceiving a stimulus with a context and attending to its features. Every stimulus has two features: whether it happens as expected and whether it fits in our needs [40]. The individual appraises these two features of stimulus and triggers an affective, physiological, and behavioral response. The cognitive appraisal is a kind of emotional regulation strategy that helps the individual changing his interpretations or appraisal of the stimulus. The reason for its popularity in emotional regulation is that it is highly effective at regulating affect and physiological arousal without any physiological costs, and it has longer lasting effects than attention-focused strategies [41]. Thus, many studies have begun applying insights from behavioral and brain imaging research on reappraisal [42]. Here, our data showed that cognitive reappraisal might work as a buffer to help good sleep at stressful life events. Finally, as long as cognitive reappraisal acts as a buffer between attachment-related anxiety and depression as well as sleep quality, it is feasible to solve emotional problems by improving reappraisal level [43].

5. Limitation and Future Research Directions

Although the results of this study are interesting and will shed some light on the depression and sleep problems in college students, the results should be assessed with care, and the conclusions should be limited. First, our studies only provide a relationship study; it is hard to see the causal relationship. Second, our data were collected at only one single point; we are expecting a longitudinal study. Third, our study depends on self-reported questionnaire; we hope to have more reliable way to collect data or use animal studies in the future. In addition, neurobiological measurement can be detected in the brain, particularly in areas related to sleep quality and emotional disorders, including control of stress and emotions [44].

In conclusion, our study clarifies the relationship among insecure attachment and depression, through sleep problems. Previous studies about *monoamine theory for basic emotions* suggested that the monoamine neurotransmitters, including norepinephrine (NE), serotonin (5-HT), and dopamine (DA), as well as the cortisol system might be the major reason for emotional arousal and sleep disorders [45]. In our previous papers, we also proposed that the dopamine and norepinephrine are neural substrates for emotional arousal, which is the reverse of sleep [46]. Here, we suggested that sleep plays an important role in insecure attachment-induced emotional disorders, which might suggest that insecure attachment might also relate to the monoamines. In addition, we also found that sleep partially mediated the relationship between insecure attachment and depression. In all, we can make a conclusion that sleep quality can be predicted by insecure attachment directly, and sleep quality in turn can predict the depressive emotional problems. Our findings suggest that sleep quality and cognitive reappraisal play very important roles in depressive emotions.

Data Availability

We will be very glad to share all the data underlying the findings of our manuscripts, in order to verify the results of an article, replicate the analysis, and conduct secondary analyses.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

SG, LYi, LH, and XY planned the study and YLa, WZ, XZ, and LYu collected the questionnaires; LYi, WZ, LYu, SJ, ZH, and NL did the analysis; GS, LYa, and EW did the writing. Liu Yige, Li Hongfan, and Xu Xiayue contribute equally to this work.

Acknowledgments

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