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Effects of psychotherapy on plasma serotonin in obsessive-compulsive disorder

Li-Jing Shi[1†]; Hai-Zhu Zhang[2†]; Chang-Hong Wang[1]; Hong-Zeng Zhao[1]; Zongya Zhao[1]; Jian-Dong Ma[1]; Xunan Wang[4]; Kai-Chen Yue[1]; Chen-Yang He[1]; Ping Huang[5]; Heng-Fen Li[6]; De-En Sang[1]; Shao-Jie Kou[5,7]; Zhi-Rong Li[5]; Hong-Kai Lian[8]; Xian-Zhang Hu[1,7]*

[1]The Second Affiliated Hospital of Xinxiang Medical University, Xinxiang Medical University, Xinxiang City 453003, Henan Province, China.

[2]School of Basic Medical Sciences, Xinxiang Medical University, Xinxiang City 453002, Henan Province, China.

[3]School of Medical Engineering, Xinxiang Medical University, Xinxiang 453002, Henan Province, China.

[4]The People's Hospital of Xuchang, Xuchang City 461000, Henan Province, China.

[5]The Fifth People Hospital of Kaifeng, Kaifeng City 475003, Henan Province, China.

[6]The First Affiliated Hospital of Zhengzhou University, Zhengzhou City 450052, Henan Province, China.

[7]Workstation of Henan Province for Psychiatry experts, Kaifeng City 475003, Henan Province, China.

[8]Zhengzhou Central Hospital, Zhengzhou City, Henan Province, China.

[†]Contributed eually.

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***Corresponding Author:** Xian-Zhang Hua, Second Hospital of Xinxiang Medical University, Xinxiang City 453002, Henan Province, PR China.
E-mail: huxianzhang@xxmu.edu.cn

Abstract

The effects of the treatments on plasma serotonin (5-HT) have been intensively investigated in obsessive-compulsive disorder (OCD). Recently, a novel psychotherapy cognitive-coping therapy (CCT) for OCD has been developed and exhibits a large effect size, which is related to the alteration of resting-state brain function. However, whether CCT affects peripheral 5-HT remains unknown. One hundred and seven individuals with OCD were randomly accepted CCT, pharmacotherapy plus CCT (SSRI+CCT), or SSRIs; and 46 participants donated blood samples. The Yale-Brown obsessive compulsive scale (Y-BOCS), plasma 5-HT, brain-derived-neurotrophic factor (BDNF), and 5-HT transporter (5-HTT) were measured before and after 4-week treatments. The Y-BOCS scores significantly decreased in SSRI+CCT and CCT ($p < 0.001$). Compared with the baseline, the plasma 5-HT level decreased after the treatment of SSRIs and increased after CCT ($p<0.05$). The altered z-value of left amygdala-seeded functional connectivity was significantly correlated with plasma 5-HT in the CCT group. This study provided evidence that CCT was an efficacious intervention for OCD and was associated with the increase of plasma 5-HT, which potentially served as a biomarker reflecting functional brain plasticity in OCD.

Keywords: Obsessive-compulsive disorder, Serotonin, Cognitive-coping therapy, Functional connectivity, Brain-derived neurotrophic factor, Serotonin transporter.

Introduction

Obsessive-compulsive disorder (OCD) is a chronic and debilitating mental illness characterized by recurrently intrusive, distressing, unwanted thoughts (obsessions) and by repetitive behaviors or mental rituals (compulsions) performed in response to an obsession. Currently, selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT) benefit around 60% of OCD patients [1-3]. The remission of symptoms is rare in those with moderate to severe OCD, even with the best treatments. The current first-line treatments are not effective enough because of their time-consuming, 60% of patients without adequate response [4, 5], and relatively high relapse rate. The relapse rates among OCD patients with SSRIs, from 24% in 28 weeks to 89% in seven months, are in part due to differences in study design and definitions of relapse [6-8].

Alteration of the serotonin system in OCD has been inten-

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sively investigated. OCD patients have lower levels of whole blood 5-HT [9, 10], fewer platelet 5-HTT binding sites, and higher platelet IP3 content than healthy controls [10]. Drug-naïve OCD patients exhibit reduced or normal whole blood or platelet 5-HT levels [11 ,12], whereas the binding capacity (Bmax) of the platelet 5-HTT is consistently reduced, both for [3H]-paroxetine [13,14] and [3H]-imipramine [15]. Chronically administration of SSRIs results in platelet 5-HT content being lowered by 66% [16]. Also, SSRI treatment lowers whole blood 5-HT concentration and further decreases the number of 5-HTT binding sites; the magnitude of the decrease is correlated with clinical improvement [12].

Theoretically, CBT has potential effects on neuroplasticity including the serotonergic function directly or indirectly. There are few studies about the effects of CBT on 5-HT and its expression regulators in both the central nervous system and whole blood in OCD. It is reported that successful remediation of OCD symptoms is associated with greater serotonergic tone after 12 weeks of CBT or sertraline treatment [17]. CBT increases the N-acetylaspartate in the dorsal and rostral anterior cingulate cortex in OCD [18] and changes 5-HT function in bulimia nervosa [19]. The efficacy of CBT in OCD treatment is associated with the brain-derived neurotrophic factor (BDNF) Val66Met genotype [20] and serotonin transporter-linked polymorphism (HTTLPR) [21]; both of the polymorphisms are functional mutations and affect their protein expression. 5-HTT is a key feature of the serotonin system, providing the primary mechanism for the inactivation of 5-HT after its release into the synaptic cleft. Its function is dependent on the BDNF [22] and BDNF along with the 5-HTTLPR [23]. Previously, functional brain plasticity has been reported to be involved in the effectiveness of psychotherapies in OCD treatment [24, 25]. BDNF improves neural plasticity. It is reported that BDNF-induced improvement in neural plasticity in hippocampal cells [26].

Recently, based on cognitive theory and stress-coping theory, novel psychotherapy termed cognitive-coping therapy (CCT) for OCD has been developed and exhibits a large effect size in short-term (four weeks) treatment [27-31]. Four-week CCT can alter the amplitude of low-frequency fluctuation (ALFF) in resting-state functional magnetic resonance imaging (rs-fMRI) in brain regions, including the left insula, the right occipital, and the right lingual gyri, and decrease the left amygdala-seeded functional connectivity (LA-FC) with the left occipital and the left parietal [24]. These neuroimaging findings indicate that the novel psychotherapy induces functional brain plasticity. However, whether the CCT for OCD affects the 5-HT function system and whether there is an association between functional brain plasticity and peripheral 5-HT remains unknown.

In the present study, to better understand the potential mechanism underlying the CCT for OCD, we investigated the effects of CCT on different levels, including the alteration of symptom severity, and the peripheral concentrations of 5-HT, 5-HTT, and BDNF. We also sought to examine the correlation between the blood levels of 5-HT, 5-HTT, or BDNF and functional brain plasticity after SSRI+CCT and CCT. We hypothesized that pharmacotherapy and CCT had different effects on the plasma levels of 5-HT, 5-HTT, and BDNF and that the LA-FC was associated with 5-HT, 5-HTT, and BDNF.

Method

Participants: Participants were recruited from the Second Affiliated Hospital of Xinxiang Medical University and referred by collaborators from other hospitals from May 2013 to April

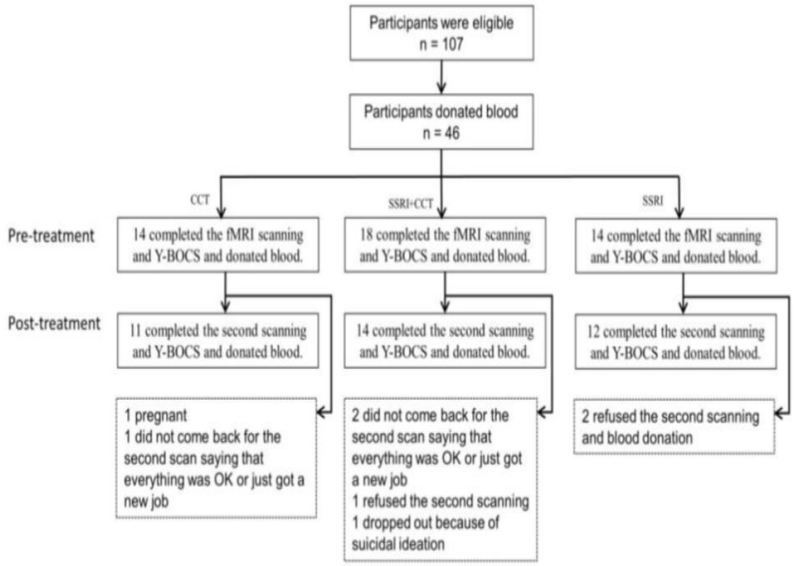


Figure 1: *Chart flow of participants.*

2020. All participants met the DSM-IV diagnostic criteria for OCD. All potential recruits undertook a semi-structured clinical interview to screen for current disorders. Individuals aged ≥18 years old were recruited based on an OCD diagnosis and a Yale-Brown obsessive-compulsive scale (Y-BOCS) score ≥16. Those with schizophrenia, substance abuse, developmental disabilities, or severe cognitive dysfunction were excluded. All participants provided written informed consent before participation, were right-hand dominant, and reported no history of head trauma, neurological disease, or contraindications for MRI. The study was approved by the Committee on Human Research at Xinxiang Medical University.

In this study, 107 OCD patients who completed the first rs-fMRI scan were randomly assigned to the treatments of CCT (n=37), SSRI+CCT (n=36), and SSRIs (n=34) (Figure 1). Before treatment, the Y-BOCS symptom checklist and demographic information were collected. The Y-BOCS evaluation and rs-fMRI scan were performed again after a four-week treatment. The investigators who were responsible for these measurements were blind to group allocation.

Cognitive-coping therapy: CCT is a novel emotion- and motivation-focused psychotherapy for OCD treatment, as described in previous publications [27, 28, 31, 32]. Briefly, each session of CCT repeats the following four steps. Step 1 is to collect information, including demographic information, symptoms, the severity of symptoms, and the changes in the severity of symptoms, etc. Step 2 is to identify fear/worry of negative events and to cope with the fear/worry (e.g. rationale). Step 3 is to cope with obsessions, but without using exposure and response prevention (ERP). Step 4 is to cope with urges to perform neutralizing behaviors (e.g. sublimation), eliminate over or covert compulsions, and increase the social-occupational functions. When an individual with OCD reached clinical remission, there will be a session to aim at how to prevent the relapse of symptoms.

Our patients received 2-3 sessions per week and each session took about 40 min. No standard number of sessions was assigned in CCT. In each session of CCT, the standard procedure was gone through. The total number of sessions varied between individuals until the OCD patient learned successfully how to cope with their fear of negative events, obsessions, and compulsions.

Pharmacotherapy: Before the clinical trials, 12 out of 14 blood donors in pharmacotherapy, and 17 out of 18 blood donors in SSRI+CCT were drug naive and donated 10 ml forearm vein blood. In the pharmacotherapy and SSRI+CCT groups, patients were prescribed either clomipramine or one of the selective serotonin reuptake inhibitors (SSRIs) by their psychiatrists, who were unaware of the group assignment. The present study did not interfere with the psychiatrists' medication prescriptions for individual treatment. To standardize the dosages, the amounts of clomipramine and SSRIs were converted to an equivalent dosage of fluoxetine [33].

Blood sample collecting: Blood samples (5 ml) were collected from the arm vein of participants using EDTA tubes before and after the 4-week treatment (Shans Medical, Zhengzhou China). The blood sample was allowed to stand at room temperature for no longer than 30 minutes before they were centrifuged at 800 x g for 15 minutes at 4ºC. The supernatant (platelet-rich plasma) was removed to a fresh tube and centrifuged at 1200 x g for 15 minutes at 4ºC. The supernatant (plasma without platelet) was immediately aliquoted to fresh tubes and was stored at -80ºC.

Measurement of plasma levels of 5-HT, 5-HTT, and BDNF: The sandwich enzyme-linked immunosorbent assay (ELISA) was used to measure plasma levels of the 5-HT, 5-HTT, and BDNF in 46 OCD patients who donated blood before the 4-week treatment and 37 patients who donated blood after. The ELISA was carried out using Assay kits from Cloud-Clone Co (China) following the manufacturer's protocol. All samples were measured in triplicate.

The rs-fMRI scanning, data preprocessing, Seed-based functional connectivity analysis: The rs-fMRI scanning and data preprocessing have been published somewhere else [34]. Briefly, all scannings were done on a 3 T MR imaging system (TIM Verio, Siemens, Germany). After a conventional localizer scan and T2 anatomic scan, resting-state functional images were acquired using an echo-planar imaging (EPI) sequence. Foam pads were used to position and immobilize the subject's head within the coil. Each patient completed rs-fMRI scanning before and after the 4-week treatment. During the scanning, participants were instructed simply to remain relaxed, eyes closed, and to think of nothing in particular. Data preprocessing was performed using the Data Processing and Analysis of Brain Imaging (DPARSF) toolbox [35]. Seed-based functional connectivity (FC) analysis was performed using the DPARSF software. Seed regions corresponding to the bilateral amygdala were defined as 8-mm-diameter spherical regions of interest (ROIs) centered on the x-y-z MNI coordinates from a meta-analysis (Left amygdala:-20,0,-20; Right amygdala: 28,-2,-12).[36] For each subject and each seed region, Pearson's correlation coefficients between the mean time series of each ROI and the time series of each voxel in other brain areas were generated and converted to z-values by using Fisher's Z-transform to improve data normality.

Data analysis: All analyses were performed using SPSS 25. One-way ANOVA with LSD Post Hoc was performed for parameter variables including age, age at onset of OCD, education, Y-BOCS score, and the plasma levels of 5-HT, 5-HTT, and BDNF. The $\chi 2$ test or Fisher's exact test was used to analyze the categorical data. ANCOVA with repeated measures was performed to test the effects of the treatment, time, and interaction on the Y-BOCS-SR score. Cohen's d (M1 - M2 / spooled, where spooled = [(s 12+ s 22) / 2]1/2) was calculated to show the effect sizes of the treatment for OCD. In our previous study on the seed-based FC, decreased LA-FCs with right cingulate/left paracentral/parietal after SSRI+CCT, and with occipital/parietal after CCT was found. The bivariable correlation was performed to investigate the correlation of the z-value of LA-FC with the plasma 5-HT, 5-HTT, and BDNF.

Results

Demographic and clinical character: Among participants in pharmacotherapy (n=14), pharmacotherapy plus CCT (n=18), and CCT only (n=14), who donated blood pre-treatment with rs-fMRI scans, no difference was found in age, age at OCD onset, education, duration of illness, pre-treatment Y-BOCS score, and the distributions of gender, marital status, the symptom of OCD, and subtypes (covert vs overt compulsions). The average dose of SSRIs (equivalent to fluvoxamine) was higher in pharmacotherapy than in SSRI+CCT (P<0.01) (Table 1).

Effectiveness of treatment: After 4-week treatment, there was no difference in the Y-BOCS scores between SSRI+CCT (7.1 ± 5.4) and CCT (6.5 ± 6.9), but the mean scores in the two groups were significantly lower than that in pharmacotherapy (25.4 ± 5.8; p < .001). Compared to baseline, the Y-BOCS score was significantly reduced in post-SSRI+CCT (24.3 ± 8.2 vs 7.1 ± 5.4) and post-CCT (25.4 ± 6.6 vs 6.5 ± 6.9) (p < .001), but not in post-pharmacotherapy (27.2 ± 5.6 vs 25.4 ± 5.8) (Table 1). The effect sizes (Cohen's d) were 0.3, 2.5, and 2.8 for pharmacotherapy, SSRI+CCT, and CCT, respectively.

The alteration of plasma levels of 5-HT, 5-HTT, and BDNF: First, no differences in the plasma levels of 5-HT, 5-HTT, and BDNF were found among the three treatment groups at baseline. Second, compared post-treatment to baseline using the ANCOVA with repeated measures in paired samples, the plasma level of 5-HT was decreased significantly (p < 0.05 and p < 0.01, respectively) in pharmacotherapy. The plasma 5-HT level in those accepted CCT was significantly increased (p < 0.057). No different plasma levels of 5-HT were found in SSRI+CCT. No differences in the plasma levels of 5-HTT and BDNF were found, compared post-treatment to pre-treatment among the three treatment groups. Last, the differences between pre- and post-treatment in the plasma levels of 5-HT BDNF, and HTT were examined. After four-week treatments, significant differences in the plasma level of 5-HT, but not 5-HTT and BDNF, among the three treatments were observed (F(2)=6.7, p = .003) (Table 2).

The plasma concentration of the contents is ng/ml. All the data is shown in the way of mean ± sd.

Regression analysis did not show any correlation among the plasma levels of 5-HT, 5-HTT, and BDNF and the improvement of OCD symptoms, which was evaluated using the reduction of the Y-BOCS score.

Correlate coefficient between the z-value of LA-FC and the plasma levels of 5-HT, 5-HTT, and BDNF: We did not observe the alteration of LA-FC in the pharmacotherapy group. In SSRI+CCT-treated patients, LA-FC with two clusters significantly decreased after treatment, named cluster 1 and cluster 2. Cluster 1 included the right cingulate and cluster 2 included the left paracentral/parietal lobules. In CCT-treated patients, LA-FC with the left occipital/parietal lobules (cluster 3) was significantly decreased (Figure 2A). The alteration of the z-value of LA-FC cluster 1 and cluster 2 was not correlated to 5-HT, 5-HT, or BDNF in both pre-SSRI+CCT and post-SSRI+CCT. In the CCT group, the alteration of the z-value of LA-FC cluster 3 was negatively correlated to the plasma 5-HT (p < .05), but not the plasma BDNF and 5-HTT, before treatment and after treatment (Figure 2B).

Panel A presents the brain regions that the left amygdala-seeded functional connectivity (LA-FC) with three brain regions, compared post-treatment to pre-treatment. No significantly altered amygdala-seeded FC was found in SSRI-treated patients. Clusters 1 (LA-FC with right cingulate) and 2 (LA-FC with the left paracentral/parietal lobules) were found in SSRI+CCT-treated patients, and cluster 3 (LA-FC with the left occipital/parietal lobules) was found in CCT-treated patients.

Panel B shows the bivariable correlation. Δz of LA-FC 1 denotes the alteration (difference between pre-treatment and post-treatment) of the z-value of left amygdala-seeded functional connectivity (LA-FC) with the right cingulate in SSRI+CCT-treated OCD patients. Δz of LA-FC 2 denotes the alteration of the

Table 1: *Demographic and clinical characteristics.*

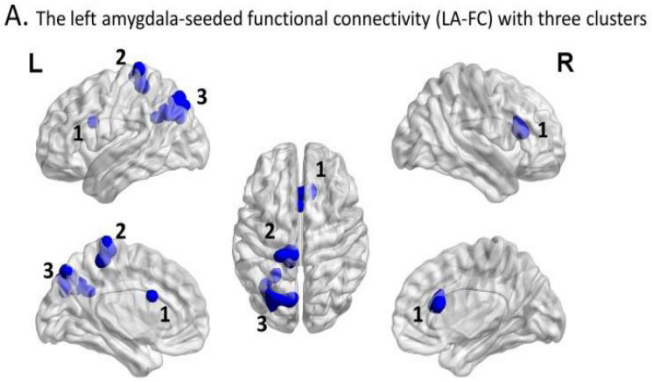
Gender			
Female	9 (64.3)	8 (44.4)	7 (46.7)
Male	5 (35.7)	10 (55.6)	8 (53.3)
Marriage status			
Single	8 (57.1)	9 (50.0)	9 (60.0)
Married	5 (35.7)	9 (50.0)	5 (33.3)
Divorce	1 (7.1)	0 (0.0)	1 (6.7)
Age	30.1 ± 12.7	28.5 ± 9.9	27.9 ± 10.1
Age of onset of OCD	22.6 ± 11.5	22.4 ± 10.0	20.0 ± 7.4
Education (years)	12.5 ± 3.2	12.67 ± 2.9	14.1 ± 2.3
Duration of illness (years)	7.7 ± 7.7	6.1 ± 5.1	8.4 ± 8.5
Y-BOCS score before treatment	27.2 ± 5.6	24.3 ± 8.2	25.8 ± 6.4
Y-BOCS score after 4-week treatment	25.4 ± 5.8	7.1 ± 5.4***	6.4 ± 6.8 ***
Medications (mg/D, equivalent to) Fluvoxamine	74.6 ± 23.4	45.0 ± 24.7**	
Symptom of OCD, No (%)			
Obsessions			
Contamination	7(50.0)	9 (50.0)	6 (42.9)
Aggressive	1 (7.1)	1 (5.6)	2 (14.3)
Sex	1 (7.1)	2 (11.2)	3 (21.4)
Religion	2 (14.2)	0 (0.0)	1 (7.1)
Hoarding	0 (0.0)	0 (0.0)	0 (0.0)
Pathological doubt	8 (57.1)	5 (27.8)	5 (35.7)
Symmetry	2 (14.2)	2 (11.2)	2 (14.2)
Other	5 (35.7)	2 (11.1)	4 (28.6)
Compulsions			
Washing	6 (42.9)	8 (44.4)	4 (28.5)
Checking	8 (57.1)	5 (27.8)	8 (57.1)
Repeating rituals	2 (14.2)	2 (11.2)	6 (42.9)
Hoarding	0 (0.0)	0 (0.0)	0 (0.0)
Order	1 (7.1)	1 (5.6)	2 (14.3)
Other	3 (21.4)	2 (11.2)	5 (35.7)

Table 2: *Comparison of the plasma levels of 5-HT, DBNF, and 5-HTT.*

	SSRI		SSRI+CCT		CCT	
	Pre	Post	Pre	Post	Pre	Post
	(n=11)	(n=11)	(n=14)	(n=14)	(n=12)	(n=12)
5-HT	63.6 ± 35.8	28.5 ± 31.3 *	64.0 ± 35.4	59.7 ± 40.3	57.8 ± 36.3	95.6 ± 36.8 *†
BDNF	6.6 ± 4.1	7.4 ± 3.4	4.9 ± 3.6	3.4 ± 2.7	5.1 ± 2.8	4.2 ± 3.2
5-HTT	1.1 ± 0.4	1.0 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.1	1.0 ± 0.4

** p < 0.05 for the comparison of post-treatment to baseline.*

†: p < 0.01 for the comparison of post-treatment among the three groups.



B. Correlation coefficient (r) matrix between LA-FC and plasma levels of 5-HT, 5-HTT, and BDNF

		Pre-treatment			Post-treatment		
		5-HT	BDNF	5-HTT	5-HT	BDNF	5-HTT
PCCT	Δz of LA-FC 1	-0.33	-0.41	0.36	-0.12	-0.36	0.37
	Δz of LA-FC 2	-0.01	-0.21	-0.37	-0.28	-0.32	-0.5
CCT	Δz of LA-FC 3	-0.80*	-0.27	-0.13	-0.77*	-0.25	-0.23

Figure 2: *The LA-FCs clusters in SSRI+CCT and CCT.*

z-value of LA-FC with the left paracentral/parietal lobules in SSRI+CCT-treated OCD patients. Δz of LA-FC 3 denotes the alteration of the z-value of LA-FC with the left occipital/parietal lobules in CCT-treated OCD patients, which was significantly correlated with the plasma levels of 5-HT at both baseline and post-treatment.

* p<0.05

Discussion

In this before-and-after study, we found that those who underwent SSRI+CCT or CCT had significantly reduced Y-BOCS scores. However, a four-week pharmacotherapy (SSRI) did not show significant improvement in OCD symptoms. Compared to the baseline, after 4 weeks of treatment, the plasma 5-HT level decreased in SSRI-treated patients, increased in CCT-treated patients, and did not significantly change in SSRI+CCT-treated patients. Additionally, we observed a correlation between altered z-value of left amygdala-seeded functional connectivity and plasma 5-HT levels in patients who underwent CCT.

As expected, we found that the individuals with OCD who received CCT and SSRI+CCT reached a better clinical outcome than those who received SSRI. Generally, pharmacotherapy is thought to be delayed and takes longer than 12 weeks to obtain a significant clinical response [5, 37]. Interestingly, both SSRI+CCT and CCT treatments significantly reduced the severity of OCD symptoms on the Y-BOCS score after four weeks, with large effect sizes. These findings suggested that a lower dose of SSRI combined with CCT could have an impact on improving OCD symptoms. The efficacy of CCT for OCD might be related to several factors. First, OCD is a situation-invoked mental disorder. In other words, individuals are presenting OCD symptoms only under a specific OCD-invoked situation. Whenever they discard the effects of the situation or the fear/worry induced by the situation, they do not necessarily feel distressed and perform compulsive rituals. Second, in each CCT session, patients with OCD are taught to cope with a fear of negative events, which is hypothesized to play a pivotal role in the development of OCD. Third, the OCD-invoked situation, obsessions, fear, and compulsion are considered stressors in CCT. The psychological and physiological effects of these stressors on OCD patients can be eliminated by using proper coping strategies, including appraisal-focused, adaptive behavioral, and emotion-focused coping strategies. Fourth, accompanied by learning coping strategies, functional brain plasticity is involved in the neurophysiological mechanism [24, 34].

This study also demonstrated that plasma 5-HT decreased after four weeks of pharmacotherapy, while it increased after four weeks of CCT. After four weeks of treatment, the plasma 5-HT was lower in the SSRI group but higher in the CCT group, compared to the SSRI+CCT group. Previous studies have suggested that untreated OCD patients have either reduced or normal plasma 5-HT levels [9, 10, 12] and that the administration of SSRIs can lower plasma 5-HT levels in both OCD [12] and depression patients [38]. Plasma 5-HT has also been reported as a potential biomarker for treatment response, where a higher plasma 5-HT level is associated with better improvement over SSRI treatment for OCD and depression [12, 38]. Consistent with previous findings, our data demonstrated that the plasma level of 5-HT significantly decreased after SSRI treatment. However, we did not observe the association between the pre-treatment plasma 5-HT level and the improvement of OCD symptoms in the three treatment groups, respectively. Therefore, our findings did not support that plasma 5-HT was not a predictor for response to these treatments but suggested that the lower plasma 5-HT level might be a biomarker of OCD symptoms.

The potential mechanism underlying the increase of the plasma level of 5-HT in CCT-treated patients remains unknown. The amygdala plays a pivotal role in the mediation of fear and anxiety [39]. Increased fear learning in mice leads to a deficiency of 5-HT synthesis in the amygdala [40,41]. Previously, the LA-FC with the right cingulate (cluster 1) and the left

paracentral/parietal lobules (cluster 2) in SSRI+CCT-treated patients and the LA-FC with the left occipital/parietal lobules (cluster 3) in CCT-treated patients were decreased [42]. Here, we found the decreased z-value of LA-FC of cluster 3 was associated with the higher plasma 5-HT. Our findings suggested that CCT potentially invoked functional and neuronal plasticity and subsequently resulted in the alteration of the central nervous system and peripheral network. Also, the alteration of the plasma level of 5-HT might serve as a marker of functional and physiological brain plasticity and/or a status marker for OCD.

There could be two pathways in which regulation of the plasma 5-HT occurs. The direct pathway that regulates the 5-HTT function in platelets [43], and the indirect pathway that affects the 5-HT system in the brain. Previous studies have shown that the interaction of 5-HTT and BDNF had effects on serum 5-HT levels [44]. In rats, chronic restrain stress results in decreases in BDNF expression in the hippocampus. These effects can be prevented by administering Escitalopram, ibuprofen, or ESC+IBU, indicating these effects were associated with the upregulation of BDNF expression [45]. The function of 5-HTT is reported to be dependent on the BDNF [22]. In this study, we did not find that the plasma levels of BDNF and 5-HTT were significantly affected by the treatments of SSRIs, SSRI+CCT, or CCT. These results suggested that the plasma 5-HT under SSRIs was regulated via a direct pathway, which is associated with the interfer of 5-HTT function. The correlation between the z-value of LA-FC of cluster 3 and the plasma 5-HT level suggested that the plasma 5-HT under CCT was regulated via an indirect pathway, which is associated with brain functional plasticity.

The strength of the present study is the before-and-after design, allowing us to investigate the different effects of SSRI and the efficacious psychotherapy on plasma 5-HT. However, there were several limitations. First, the sample size was relatively small. Although the statistical power was great enough for the comparison of plasma levels of components, the sample size limited our ability to do further analysis across groups. Second, plasma 5-HT is affected by many factors, including dietary intake [38], blood pressure, the activity of monoamine oxidase [46], and the properties of platelet 5-HTT [47]. Third, the comorbidity of depression or anxiety was not controlled. The comorbidity issue is common in clinical psychiatric diagnoses. Fourth, the standardized SSRI doses were higher in the SSRI alone group than in the SSRI+CCT group. The different SSRI doses might be involved in the difference in the plasma 5-HT between pharmacotherapy and SSRI+CCT. Studies with larger sample sizes and carefully controlled ones are warranted in future studies.

In summary, this study provided further evidence that CCT or SSRI+CCT were efficacious treatments for OCD and demonstrated the different effects of SSRIs, SSRI+CCT, and CCT on plasma 5-HT. The plasma 5-HT was associated with functional brain plasticity under the treatment of CCT. These findings yielded new insight into the OCD treatments and indicated 16

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Declaration of interest

The authors have no conflicts of interest to declare.

that CCT potentially increased the plasma 5-HT, which potentially served as a status marker reflecting functional brain plasticity in OCD.

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