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Metacognitive Training Modulates Default-Mode Network Homogeneity During 8-Week Olanzapine Treatment in Patients With Schizophrenia

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Background: Previous studies have revealed the efficacy of metacognitive training for schizophrenia. However, the underlying mechanisms of metacognitive training on brain function alterations, including the default-mode network (DMN), remain unknown. The present study explored treatment effects of metacognitive training on functional connectivity of the brain regions in the DMN.

Methods: Forty-one patients with schizophrenia and 20 healthy controls were scanned using resting-state functional magnetic resonance imaging. Patients were randomly assigned to drug plus psychotherapy (DPP) and drug therapy (DT) groups. The DPP group received olanzapine and metacognitive training, and the DT group received only olanzapine for 8 weeks. Network homogeneity (NH) was applied to analyze the imaging data, and pattern classification techniques were applied to test whether abnormal NH deficits at baseline might be used to discriminate patients from healthy controls. Abnormal NH in predicting treatment response was also examined in each patient group.

Results: Compared with healthy controls, patients at baseline showed decreased NH in the bilateral ventral medial prefrontal cortex (MPFC), right posterior cingulate cortex (PCC)/precuneus, and bilateral precuneus and increased NH in the right cerebellum Crus II and bilateral superior MPFC. NH values in the right PCC/precuneus increased in the DPP group after 8 weeks of treatment, whereas no substantial difference in NH value was observed in the DT group. Support vector machine analyses showed that the accuracy, sensitivity, and specificity for distinguishing patients from healthy controls were more than 0.7 in the NH values of the right PCC/precuneus, bilateral ventral MPFC, bilateral superior MPFC, and bilateral precuneus regions. Support vector regression analyses showed that high NH levels at baseline in the bilateral superior MPFC could predict symptomatic improvement of positive and negative syndrome scale (PANSS) after 8 weeks of DPP treatment. No correlations were found between alterations in the NH values and changes in the PANSS scores/cognition parameters in the patients.

Conclusion: This study provides evidence that metacognitive training is related to the modulation of DMN homogeneity in schizophrenia.

Keywords: metacognitive training, default-mode network, network homogeneity, schizophrenia, olanzapine

INTRODUCTION

Schizophrenia is a chronic disorder with a high functional disability. Previous studies have shown that approximately 20% to 30% of patients with schizophrenia are resistant to antipsychotics (1). Compliance with medication remains low, even during atypical antipsychotic medication (2, 3). Hence, therapy based on pharmacological treatment may not attain satisfactory improvement of social functioning in the patients (4) .

Metacognition is an extensive mental activity that involves contemplation of one's own thinking or others' mental state. Metacognitive deficits have been reported in all phases of schizophrenia (5–7) and are related to poor treatment outcomes. Metacognitive training (MCT), a novel and widely used group intervention for patients with schizophrenia, may enhance patients' self-awareness and insights into these cognitive distortions to alleviate the positive symptoms of psychosis, especially paranoid ideation(8). A systematic review that covered 14 studies showed that MCT effectively decreased cognitive biases and delusions related to schizophrenia and improved insight in the patients with schizophrenia (9). Randomized controlled trials showed that MCT reduced positive symptomatology and influenced insight and social functioning (10, 11). Moritz et al. found that MCT exhibited sustained effects in the decrease of delusions, which were beyond the effects of antipsychotic drugs; meanwhile, the quality of life and self-esteem in the MCT group had a significant improvement after 3 years of treatment (12). However, the potential mechanisms through which MCT executes treatment effects remain unknown.

As the major components of the default-mode network (DMN), medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and precuneus play a key role in metacognition capacity and related cognitive functions, including self-referential tasks (13, 14). The efficient connectivity within the DMN is crucial for high metacognitive capacity (15). Francis et al. discovered substantial resting-state functional connectivity across the precuneus, MPFC, and PCC in patients with schizophrenia with high metacognitive capacity; this finding suggests that disrupted resting-state connectivity is relevant to metacognitive dysfunction in psychosis (15). Baird et al. determined relationships between resting-state functional connectivity in the precuneus, anterior MPFC, and inferior parietal lobule structures/intraparietal sulcus and metacognitive capacity relevant to memory retrieval (16). However, it remains unknown whether MCT can modulate functional connectivity of the DMN.

In the present study, alterations in the DMN homogeneity relative to MCT treatment in patients with schizophrenia were examined using network homogeneity (NH) (17) from a network-based perspective. NH is defined as the mean associations between the time series of a given voxel and the time series of all other voxels inside the network. NH allows an unbiased examination to a network of interest by seeking for brain regions that reveal pathology correlated with alterations in this network. Many clinical studies on psychiatric disorders have used NH, particularly in patients with schizophrenia and their unaffected siblings (18, 19), major depressive disorders (20), attention deficit/hyperactivity disorder (17), and somatization disorder (21). We examined DMN alterations at two time points (baseline and 8 weeks of treatment) in inpatients with schizophrenia at rest. We hypothesized that MCT could modulate DMN homogeneity in patients with schizophrenia, particularly in the MPFC, PCC, and precuneus. Correlations between alterations in the DMN NH values and reductions in symptom severity were also expected in this study. We also hypothesized that the abnormalities of DMN NH at baseline might be applied as underlying image biomarkers for distinguishing patients from controls through the support vector machine (SVM) analyses.

MATERIALS AND METHODS

Participants

We recruited forty-one patients with schizophrenia from the Second Affiliated Hospital of Xinxiang Medical University in China. Twenty patients were allocated to the drug plus psychotherapy (DPP) group, and twenty-one patients were allocated to the drug therapy (DT) group on the basis of the random number list. The assessment was executed by a psychiatrist who was blinded to the patient allocation. Schizophrenia was diagnosed using the Structural Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Illness duration was no more than five years since the onset of the disease, and the total score of the positive and negative syndrome scale (PANSS) was greater than 75. The patients were right-handed and 18–50 years old. They were randomly allocated to the DPP and DT groups. PANSS was applied to assess symptomatic severity at baseline and 8 weeks of treatment. Cognitive function was evaluated through the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery, including Trail-making test, part A (TMT-A); Hopkins verbal learning Test–Revised (HVLT-R); Brief Assessment of Cognition in Schizophrenia Symbol Coding Test (BACS-SC); Brief Visuospatial Memory Test–Revised (BVMT-R); Continuous Performance Test-identical Pairs (CPT-IP); Wechsler Memory Scale Spatial Span (WMS-SS); Neuropsychological Assessment

Battery–Mazes(NAB-M); Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT); and Category Fluency–Animal Naming Fluency (CF–ANF). These tests were used to evaluate processing speed, attention/vigilance, working memory, verbal learning, reasoning, and problem solving in the participants.

Healthy controls unrelated to patients were recruited from the local community. Age, years of education, and sex ratio of the patients and healthy controls were matched. The non-patient version of the Structured Clinical Interview for DSM-IV was used to screen healthy controls. Healthy controls were excluded if they suffered from any medical and neurological illnesses, substance abuse, and psychosis symptoms. They were also excluded if they had a first-degree relative with a history of psychiatric disorders.

The exclusion criteria for all individuals were as follows: any current or past neuropsychiatric disorders; any physical illnesses, such as cardiovascular and liver and kidney diseases; any traumatic brain injury; serious impulsive behavior; seizures; a history of electroconvulsive therapy and olanzapine therapy that were ineffective or tolerable; drug or alcohol addiction; pregnancy; and contraindications for MRI scan.

The study was approved by the local ethics committee of the Second Affiliated Hospital of Xinxiang Medical University, and has been registered in a public trials registry. The number is NCT03451734 from ClinicalTrials.gov. The study was executed in accordance with the Helsinki Declaration. After a complete explanation, the participants provided their written informed consent.

Intervention

Olanzapine with a mean dose of 21.58 and 20.50 mg/day was administered to each patient in the DPP and DT groups, respectively. Olanzapine dosage increased within the first 2 weeks and remained unchanged until the last fMRI scan. The use of other antipsychotic drugs was not allowed. On the basis of the olanzapine treatment, the DPP group received MCT from a trained clinical psychologist who had more than one years of experience with MCT. The DT group was given a non-specific therapeutic procedure involving some recreational activities as executed in the Second Affiliated Hospital of Xinxiang Medical University. The duration of entire program and frequency and duration of the sessions were matched to the MCT program.

MCT consisted of eight sessions. The details of MCT procedure are offered in the **Supplementary Method**.

Image Acquisition and Processing

A 3.0 T Siemens scanner (Germany) was used to scan the subjects. All participants were instructed to lie on the scanner with their eyes closed and stay still. Soft earplugs and foam pads were used to reduce scanner noise and head motion. The parameters were as follows: flip angle = 90°, repetition time/echo time = 2000/30 ms, slice thickness/inter-slice spacing = 4/0.8 mm, field of view = 220 mm × 220 mm, and acquisition matrix = 64×64. Each resting-state fMRI scan contained 240 image volumes.

The resting-state fMRI data were preprocessed by the DPABI software (22). The first 10 volumes were ruled out because of the instability of the initial MRI signal and for the individuals to adapt to circumstances. Subjects with over 2-mm maximal translation in the x, y, or z axis and 2° maximal rotation in each axis were excluded after slice timing and head motion correction. The imaging data were then spatially normalized to a conventional Montreal Neurological Institute (MNI) EPI template and resampled to 3 × 3 × 3 mm. The follow-up images of the patients were coregistered with baseline images before normalization. Finally, the data were temporally band-pass filtered (0.01–0.08 Hz) and linearly detrended to reduce the effect of physiological high-frequency noise and low-frequency drifts. Several covariates, including signals from a ventricular region of interest, signals from a region centered in the white matter, and Friston-24 head motion parameters obtained *via* rigid body correction, were removed. The global signal was not removed as indicated in a previous study (23). Besides, mean framewise displacement (FD) was used to solve the residual effects of motion as a covariate in group analyses. Scrubbing was also used as an aggressive head motion control strategy (removing time points with FD > 0.2mm) to minimize confounding effects of head motion.

DMN Identification

After being preprocessed, the time series of all the groups were examined to construct a DMN mask by using Group ICA with the toolbox GIFT (http://mialab.mrn.org/software/#gica) (24, 25). The details of DMN identification are offered in the **Supplementary Method**.

NH Analyses

NH analyses were performed with an in-house MATLAB script. The details of NH analyses are offered in the **Supplementary Method**.

Statistical Analyses

Data about the demographic characteristics of the three groups were compared by using the Mann–Whitney U-test or the chi-square test when necessary.

Repeated analyses of covariance (ANCOVAs) were conducted to analyze the differences of the three groups on the NH maps, and to assess the interaction effects between time points and groups with age and mean framewise displacement as the covariates. Post hoc t-tests were used to evaluate group differences. Gaussian random field (GRF) theory was used to correct for multiple comparisons at $p < 0.05$ with the REST software (voxel significance: $p < 0.001$, cluster significance: $p < 0.05$).

To assess the treatment effect, the following formula was used to calculate the reduction ratio (RR) of the PANSS total scores.

$$RR = \left(PANSS_{total\_1} - PANSS_{total\_2}\right)/PANSS_{total\_1}$$

$PANSS_{total\_1}$ referred to the PANSS total scores at baseline, whereas $PANSS_{total\_2}$ was the PANSS total scores after 8 weeks of treatment. Similar RRs were calculated for the PANSS positive, negative, and general symptoms subscale scores.

Correlation Analyses

After abnormal NH of the brain clusters were identified, the average NH values from these clusters were extracted. The correlations between abnormal NH and PANSS scores/cognition parameters of the patients at baseline and between NH alterations and changes in PANSS scores/cognition parameters of the patients after treatment were determined using Pearson's correlation analyses with a threshold of $p < 0.05$.

Classification Analysis Using SVM

SVM was applied to test the capability of abnormal NH values in any brain region to distinguish patients from healthy controls by using the LIBSVM software package (http://www.csie.ntu.edu.tw/~cjlin/libsvm/) in MATLAB. The "leave one out" method was used.

Support vector machines (SVM), a popular and well-known supervised learning technique, is used to find a max-margin separator hyperplane to classify data (26). The hyperplane is orientated that it is as far as possible from the nearest data points from each class. These nearest points are called the support vectors (27).

Given a labeled training dataset:

$$(x_1, y_1), \ldots, (x_n, y_n),\ x_i \in R^d \ \text{ and } \ y_i \in (-1, +1),$$

where $X_i \in R^d$ are the training data and $Y_i \in \{-1, 1\}$ are the corresponding labels. The essence of SVM is to find the optimal hyperplane and to divide the two classes of data points with the maximum margin (28):

$$\min_{wb} \frac{1}{2} \| w \|2 + C\sum_{i=1}^{n}\xi i \tag{1}$$

$$s.t.\ Y_i(X_i w + b) \geq 1 - \xi_i$$

$$\xi_i \geq 0,\ i = 0, 1, 2, \ldots, n.$$

Here, C is a tuneable positive scalar and ξ_i is the slack variables. It may be equivalently converted into hinge loss with an $\ell 2$ norm penalty format:

$$\min_{wb} \Sigma_{i=1}^{n} (1 - Y_i(X_i w + b))_+ + \frac{\lambda'}{2}||w||^2 \tag{2}$$

where the loss function $(1 - \cdot)_+ = \max(1 - \cdot, 0)$ is called hinge loss and λ' is positive regularization parameter corresponding to C parameter in problem (1), which helps control the balance between the loss and penalty. A more detailed description about SVM can be found in a previous study (29).

Classification Analysis by Using SVR

Support vector regression (SVR) was used to explore the capability of the extracted NH values in abnormal brain regions to predict treatment response with the LIBSVM software package (http://www.csie.ntu.edu.tw/~cjlin/libsvm/) in MATLAB. SVR was executed for the extracted baseline levels of NH values and each symptomatic domain (PANSS total, positive symptoms, negative symptoms, and general symptom subscale scores) in each patient group.

Detecting a multivariate regression function f(x) based on X through a sample spectrum is to predict a desired output feature. The SVR equation has been clearly clarified in the literature (30, 31).

RESULTS

Demographic and Clinical Characteristics

A total of 41 patients with schizophrenia and 20 healthy controls were enrolled in the study. However, two patients (one in the DPP group and one in the DT group) were excluded due to excessive head movement. A total of 39 patients with schizophrenia (19 in the DPP group and 20 in the DT group) were included in the analysis (**Figure 1**). No substantial differences were observed in the age, sex ratio, and years of education across the three groups. The mean dosage of olanzapine did not significantly differ between the DPP and DT groups (**Table 1**). No significant differences were found in the negative and general symptoms subscale scores of PANSS between the two groups, except the positive symptoms subscale score ($p < 0.05$) at baseline.

Clinical Symptoms After 8 Weeks of Treatment

There are significant interactions of group × time for PANSS total scores, positive, and general symptoms subscale scores. By contrast, the interaction of group × time was not significant for PANSS negative symptoms subscale scores. DPP group and DT group showed significant improvement in PANSS total scores, positive symptoms subscale scores, negative symptoms subscale scores, general symptoms subscale scores, and cognitive function tests after 8 weeks of treatment compared to the baseline values (**Figure 2**) ($p \leq 0.001$). After 8 weeks of treatment, the PANSS total, positive symptoms, and general symptoms subscale scores in the DPP group became considerably lower than those in the DT group (46.64 ± 7.97 VS 56.05 ± 12.08;9.63 ± 2.24 VS 12.3 ± 3.85; 24.95 ± 4.08 VS 29.2 ± 5.51, respectively) ($p < 0.05$). The CF-ANF and BACS-SC scores in the DT group were also substantially lower than those in the DPP group (17.95 ± 2.26 vs 19.53 ± 2.25; 44.25 ± 11.02 vs 49.89 ± 7.10, respectively) ($p < 0.05$) (**Table 2**). Besides, the BACS-SC, HVLT-R, WMS-SS, CF-ANF scores showed interactions of group × time.

DMN Mask

The group ICA approach was applied to generate a DMN mask for all subjects. The DMN included MPFC, precuneus, PCC, lateral parietal and temporal gyri, and cerebellum Crus II. The obtained DMN mask was used in the following NH analysis.

Repeated ANCOVA Results

Compared with the controls, the patients (both DPP and DT groups) at baseline showed decreased NH in the bilateral ventral

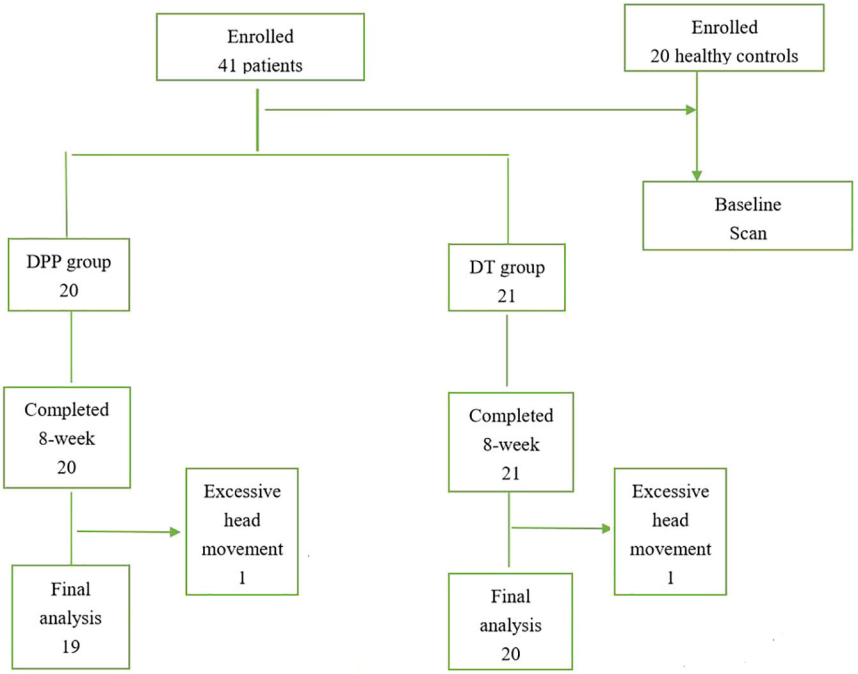

FIGURE 1 | The consort flow diagram for the present study.

TABLE 1 | Demographic characteristics of the subjects.

	DPP(n = 19)	DT (n = 20)	Controls (n = 20)	F/χ^2	p
Sex (male/female)	12/7	15/5	14/6	0.648	0.723[a]
Age (years)	26.05 ± 5.81	22.75 ± 4.38	25.70 ± 4.90	5.667	0.059[b]
Years of education (years)	11.63 ± 3.75	10.65 ± 2.50	12.75 ± 2.95	4.120	0.127[b]
Dose of olanzapine (mg/day)	21.58 ± 3.75	20.50 ± 1.54		0.459	0.498[b]

[a]*The p values for sex distribution were obtained by a chi-square test.*
[b]*The p values were obtained by Mann-Whitney U test.*
DPP, drug plus psychotherapy; DT, drug therapy.

MPFC, right PCC/precuneus, and bilateral precuneus and increased NH in the right cerebellum Crus II and bilateral superior MPFC (**Table 3** and **Figures 3** and **4**). Compared with the baseline parameters, the DPP group showed increased NH in the right PCC/precuneus after treatment (**Table 3**, **Figures 4** and **5**), whereas the DT group showed no remarkable difference in the NH values after 8 weeks of treatment. After treatment, patients in the DPP group showed increased NH in the bilateral precuneus compared with those in the DT group (**Table 3**, **Figure 5**). At baseline, no significant difference in the NH values was found between the two groups. Besides, the significant group × time interactions on NH are presented in the **Supplemental Figures** and **Tables**.

Correlation Results

The NH value of the bilateral precuneus, which was different in this brain regions between DPP group and DT group after 8 weeks of treatment, was negatively correlated with BVMTR in the DPP group (r=-0.503, p=0.028) (**Figure 6**). There were no significant correlations between alterations in the NH values and changes in the PANSS scores/cognition parameters in the DPP group and DT group, respectively, and no significant correlation was observed between abnormal NH and symptomatic severity in the DPP group and DT group, respectively.

Discriminating Patients From Controls

Table 4 presents the detailed information of the SVM results for DPP and DT groups.

For the DPP group, the results showed that the NH values in the right PCC/precuneus exhibited an accuracy of 89.74%, a sensitivity of 84.21%, and a specificity of 95% to distinguish patients from healthy controls (**Figure 7**). The NH values in the bilateral ventral MPFC showed an accuracy of 79.49%, a sensitivity of 73.68%, and a specificity of 85% (**Figure 8**). The

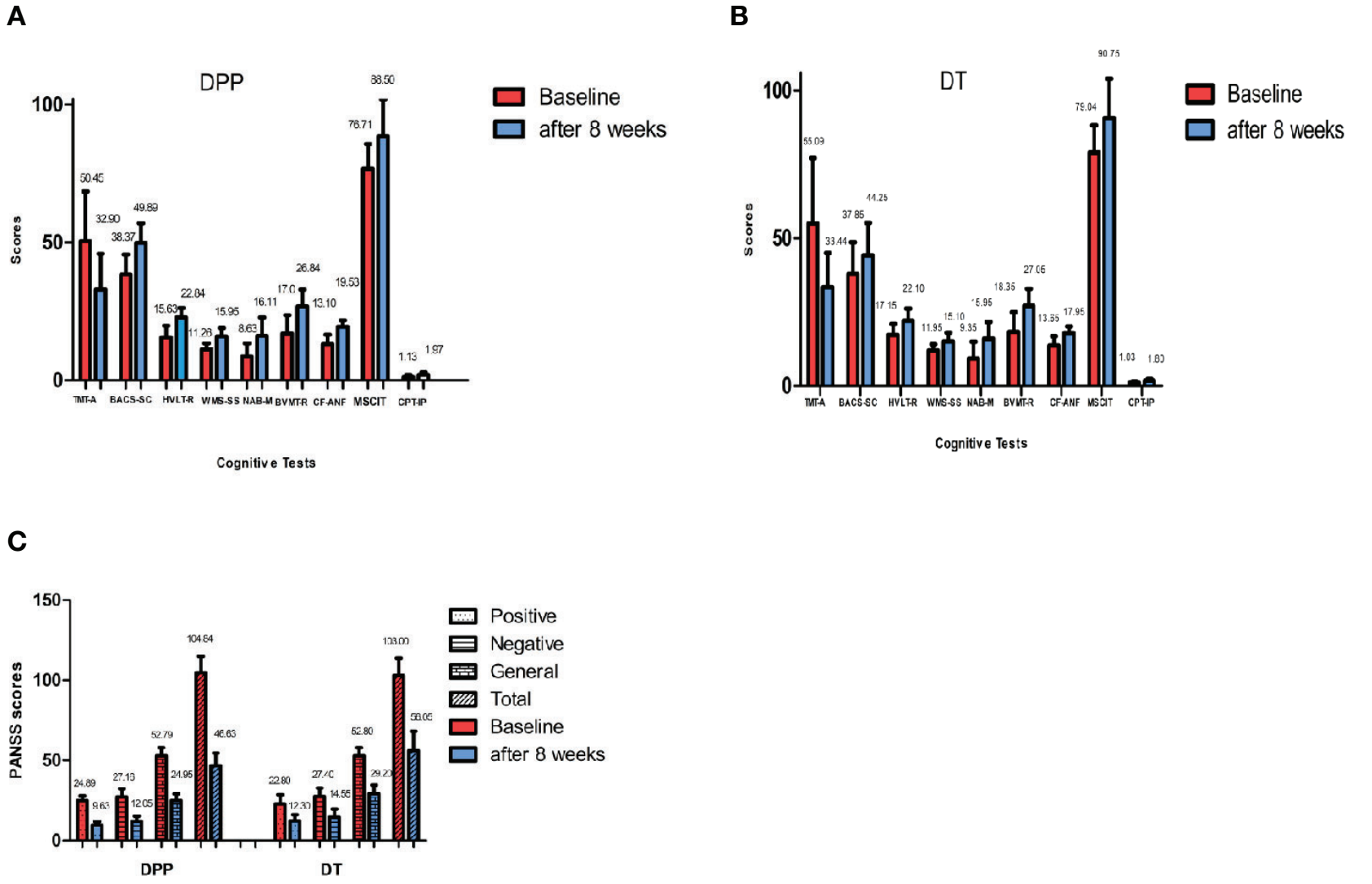

FIGURE 2 | PANSS and cognitive tests results across different time points. Values above histogram bars represent related group means. Bars represent related SD. PANSS, Positive and Negative Syndrome Scale; TMT-A, Trail Making Test, part A; BACS-SC, Brief Assessment of Cognition in Schizophrenia Symbol Coding Test; HVLT-R, Hopkins Verbal Learning Test-Revised; WMS-SS, Wechsler Memory Scale Spatial Span; NAB-M, Neuropsychological Assessment Battery-Mazes; BVMT-R, Brief Visuospatial Memory Test-Revised; CF-ANF, Category Fluency-Animal Naming Fluency; MSCIT, Mayer-Salovey-Caruso Emotional Intelligence Test; CPT-IP, Continuous Performance Test-identical Pairs. **(A)** Cognitive results across different time points in the DPP group. **(B)** Cognitive results across different time points in the DT group. **(C)** PANSS total scores and subscale scores across different time points in the two groups.

TABLE 2 | Comparison of the clinical characteristics between the DPP group and the DT group.

			Baseline		Z	P	Z^a	8 weeks		Z	P	Z^b
	Test Statistic	P	DPP group	DT group				DPP group	DT group			
PANSS		0.000	104.84 ± 9.96	103.0 ± 10.79	-0.394	0.708	-3.898	46.64 ± 7.97	56.05 ± 12.08	-2.169	0.03	-3.922
Time	F= 829.876	0.0038										
Group × Time	F= 9.515											
Positive		0.000	24.89 ± 3.09	22.80 ± 5.82	-2.003	0.047	-3.826	9.63 ± 2.24	12.3 ± 3.85	-2.426	0.015	-3.886
Time	F=281.287	0.0037										
Group × Time	F=9.615											
Negative		0.000	27.16 ± 5.19	27.4 ± 5.42	0.000	1.0	-3.825	12.05 ± 3.19	14.55 ± 5.12	-1.27	0.241	-3.929
Time	F= 221.783	0.237										
Group × Time	F= 1.443											
General		0.000	52.79 ± 5.13	52.8 ± 5.11	-0.014	0.989	-3.828	24.95 ± 4.08	29.2 ± 5.51	-2.439	0.014	-3.921
Time	F= 980.166	0.014										
Group × Time	F= 6.665											
TMT-A		0.000	50.45 ± 18.13	55.09 ± 22.11	-0.72	0.496	-3.823	32.90 ± 13.08	33.44 ± 11.54	-0.267	0.792	-3.92
Time	F=68.759	0.392										
Group × Time	F=0.751											
BACS-SC		0.000	38.37 ± 7.28	37.85 ± 10.79	-1.17	0.247	-3.729	49.89 ± 7.10	44.25 ± 11.02	-2.293	0.021	-3.929
Time	F=78.836	0.015										
Group × Time	F=6.447											
HVLT-R		0.000	15.63 ± 4.19	17.15 ± 3.79	-1.03	0.309	-3.831	22.84 ± 3.39	22.1 ± 4.09	-0.339	0.749	-3.84
Time	F=173.030	0.019										
Group × Time	F=5.979											
WMS-SS		0.000	11.26 ± 2.1	11.95 ± 2.65	-0.575	0.588	-3.832	15.95 ± 3.08	15.1 ± 2.94	-1.018	0.322	-3.947
Time	F=134.380	0.029										
Group × Time	F=5.154											
NAB-M		0.000	8.63 ± 4.78	9.35 ± 5.66	-0.042	0.967	-3.828	16.11 ± 6.67	15.95 ± 5.71	-0.07	0.945	-3.929
Time	F=95.522	0.548										
Group × Time	F=0.368											
BVMT-R		0.000	17.0 ± 6.68	18.35 ± 6.62	-0.451	0.667	-3.828	26.84 ± 6.06	27.05 ± 5.81	-0.183	0.857	-3.924
Time	F=127.686	0.491										
Group × Time	F=0.484											
CF-ANF		0.000	13.10 ± 3.40	13.65 ± 3,22	-0.82	0.428	-3.833	19.53 ± 2.25	17.95 ± 2.26	-2.163	0.033	-3.932
Time	F=214.891	0.006										
Group × Time	F=8.411											
MSCIT		0.000	76.71 ± 9.01	79.04 ± 9.19	-0.843	0.411	-3.823	88.50 ± 13.25	90.75 ± 13.28	-0.702	0.496	-3.92
Time	F=69.445	0.979										
Group × Time	F=0.001											
CPT-IP		0.000	1.13 ± 0.89	1.03 ± 0.56	-0.098	0.923	-3.823	1.97 ± 0.97	1.80 ± 0.54	-0.759	0.461	-3.92
Time	F=72.904	0.685										
Group × Time	F=0.167											

Z: The comparison between the DPP group and the DT group using Wilcoxon test of two independent samples.

Z^a: The comparison from baseline to 8weeks within DPP group using Pairs Sample Wilcoxon test.

Z^b: The comparison from baseline to 8weeks within DT group using Pairs Sample Wilcoxon test.

TMT-A, Trail Making Test, part A; BACS-SC, Brief Assessment of Cognition in Schizophrenia Symbol Coding Test; HVLT-R, Hopkins Verbal Learning Test-Revised; WMS-SS, Wechsler Memory Scale Spatial Span; NAB-M, Neuropsychological Assessment Battery-Mazes; BVMT-R, Brief Visuospatial Memory Test-Revised;CF-ANF, Category Fluency-Animal Naming Fluency; MSCIT, Mayer-Salovey-Caruso Emotional Intelligence Test; CPT-IP, Continuous Performance Test-identical Pairs.

TABLE 3 | Alterations of DMN NH across patients (at baseline, after 8 weeks of treatment) and controls.

Cluster location	Peak coordinate			Cluster (voxel)	*T* value
	x	y	Z		
DPP group at baseline vs controls					
Right Cerebellum Crus II	24	-75	-39	20	3.661
Bilateral ventral MPFC	0	54	-6	58	-3.3422
Right PCC/Precuneus	15	-48	3	65	-6.3186
Bilateral superior MPFC	-3	48	54	26	3.4227
DT group at baseline vs controls					
Bilateral ventral MPFC	-3	54	-9	53	-3.8297
Right PCC/Precuneus	9	-45	9	38	-4.1595
Bilateral Precuneus	3	-63	51	75	-3.7244
Bilateral superior MPFC	-3	42	51	23	3.1693
DPP group after 8 weeks vs at baseline					
Right PCC/Precuneus	15	-48	6	21	3.1264
DT group after 8 weeks vs at baseline					
No cluster					
DPP group vs DT group after 8 weeks					
Bilateral Precuneus	3	-66	51	24	3.3257
DPP group vs DT group at baseline					
No cluster					

The significance level was set at $p < 0.05$ corrected by the Gaussian random field (GRF) theory (voxel significance: $p < 0.001$, cluster significance: $p < 0.05$) for multiple comparisons with the REST software (age and mean FD as covariates). MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; FD, framewise displacement.

NH values in the right Cerebellum Crus II showed an accuracy of 74.36%, a sensitivity of 68.42%, and a specificity of 80%. The NH values in the bilateral superior MPFC showed an accuracy of 79.49%, a sensitivity of 68.42%, and a specificity of 90%.

For the DT group, SVM results showed the accuracy, sensitivity, and specificity for distinguishing patients from healthy controls were more than 0.7 in the bilateral ventral MPFC, right PCC/precuneus, bilateral precuneus, and bilateral superior MPFC.

SVR Analyses

At $p < 0.05/16 = 0.003125$ level (Bonferroni correction), there were significantly positive correlations between baseline NH values in the bilateral superior MPFC and RR of the PANSS negative symptoms subscale scores ($r=0.963$, $p < 0.0001$) and general symptoms subscale scores ($r=0.830$, $p < 0.0001$) in the DPP group (**Figure 9**).

For the DT group, SVR results showed significantly positive correlations between baseline NH value in the bilateral superior MPFC and RR of PANSS total scores ($r=0.887$, $p < 0.0001$), positive symptoms subscale scores ($r=0.838$, $p < 0.0001$), and negative symptoms subscale scores ($r=0.841$, $p < 0.0001$). The details of related data are provided in the **Supplemental Figures**.

DISCUSSION

To our knowledge, this longitudinal study is the first to compare DMN homogeneity alterations with MCT and olanzapine therapy in schizophrenia. The results revealed that NH values in the right PCC/precuneus increased in patients in the DPP group after 8 weeks of treatment. By contrast, no significant difference in the NH values was found in patients in the DT group from baseline to 8 weeks. Patients in the DPP group showed increased NH in the bilateral precuneus compared with patients in the DT group after 8 weeks of treatment. At baseline, no significant difference in the NH values was found between the two groups.

Our findings show that MCT modulates DMN homogeneity in patients with schizophrenia. DPP treatment increased NH in the right PCC/precuneus, and decreased NH became almost normal after 8 weeks of treatment. By contrast, no significant difference in the NH values was found in patients in the DT group within 8 weeks, suggesting that the effects of normalization of the DMN NH values were associated with MCT. This finding

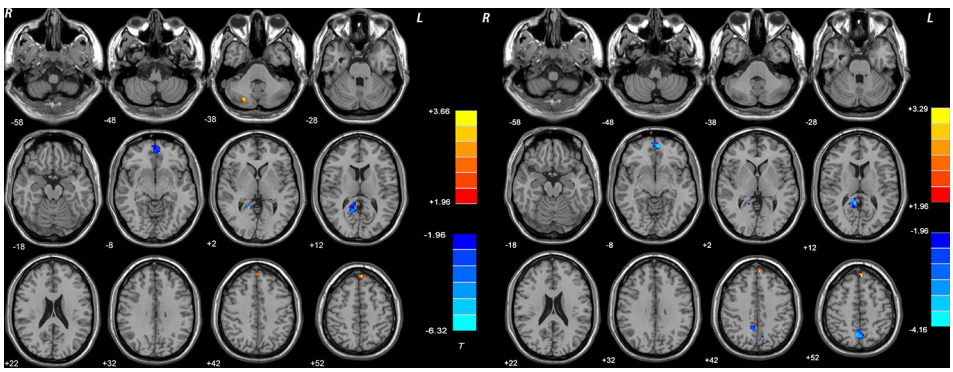

FIGURE 3 | Brain regions with significant difference in DMN NH between patients and healthy controls at baseline. The color bar represents the t values of the group analysis of NH. Left: DPP group vs healthy controls. Brain regions with significant difference were observed in the right Cerebellum Crus II, bilateral ventral MPFC, right Precuneus/PCC, and bilateral superior MPFC. Right: DT group vs healthy controls. Brain regions with significant difference were observed in the bilateral ventral MPFC, right Precuneus/PCC, bilateral Precuneus, and bilateral superior MPFC. DPP, drug plus psychotherapy; DT, drug therapy; DMN, default-mode network; NH, network homogeneity; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex.

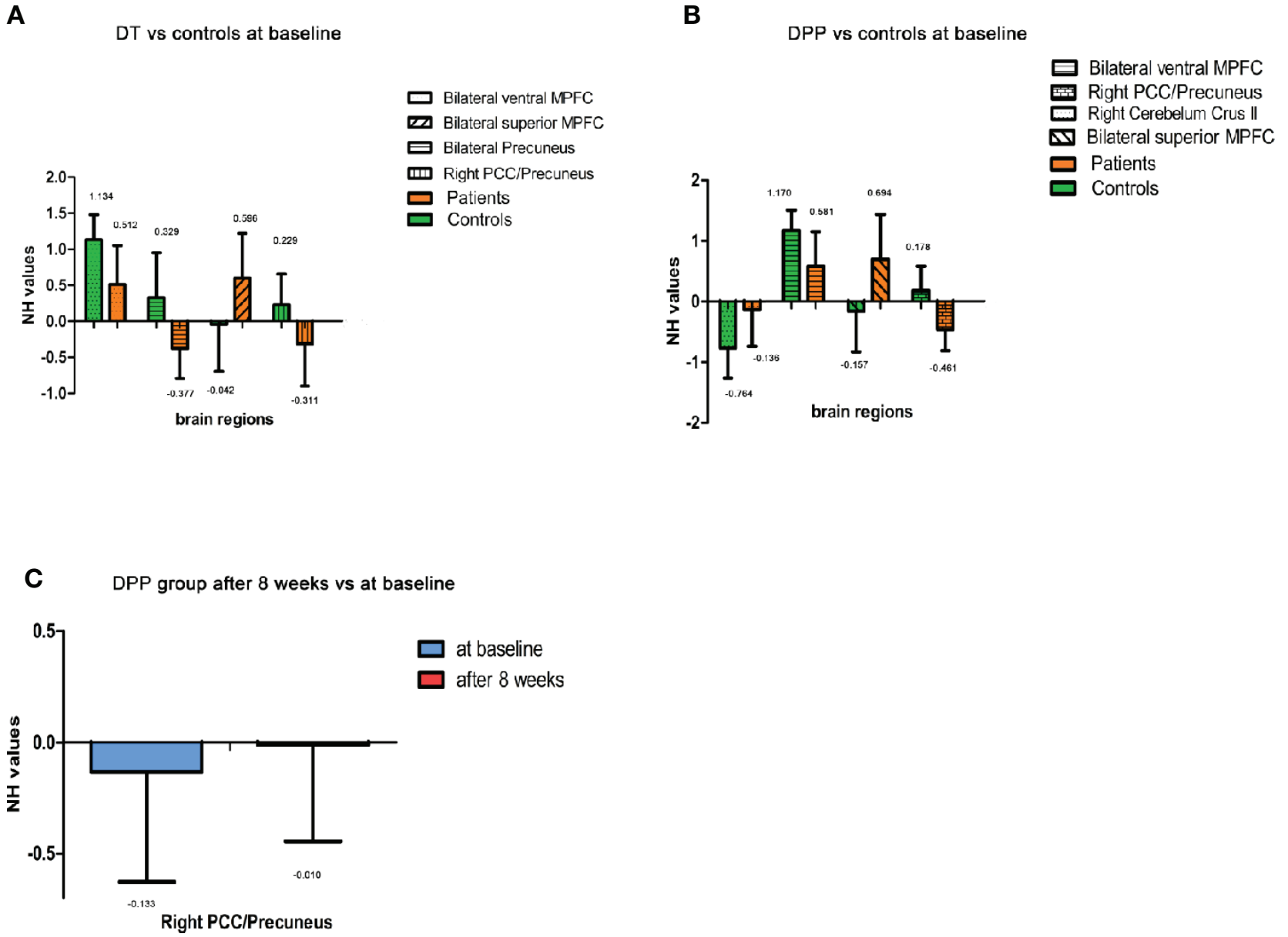

FIGURE 4 | Imaging results across different time points. Values above histogram bars represent related group means. Bars represent related SD. **(A)** The NH values of brain regions across patients in the DT group and controls at baseline. **(B)** The NH values of brain regions across patients in the DPP group and controls at baseline. **(C)** The NH values of brain regions in the DPP group from baseline to 8 weeks.

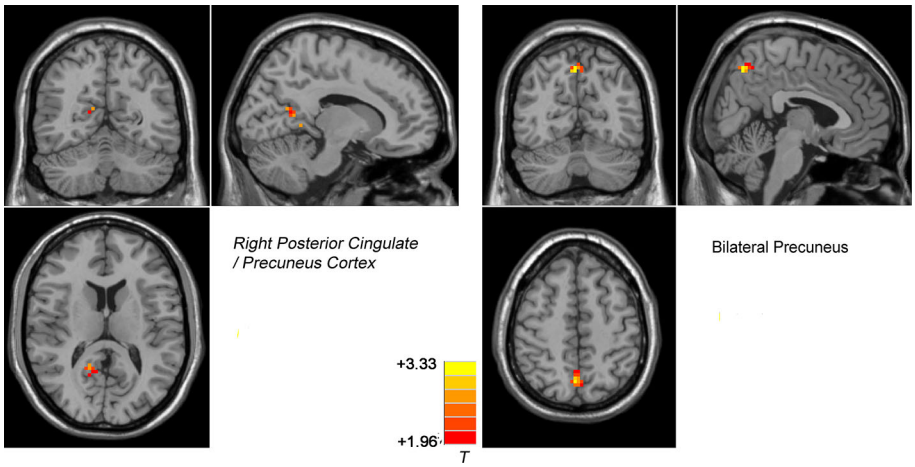

FIGURE 5 | Treatment effects of DMN NH across patients at two point (at baseline and after 8 weeks of treatment). The color bar represents the t value of the group analysis of NH. Left: DPP group from baseline to 8 weeks. Brain regions with significant difference in the NH values were observed in the right Precuneus/ PCC. Right: DT group vs DPP group at 8 weeks. Brain regions with significant difference in the NH value were observed in the bilateral Precuneus.

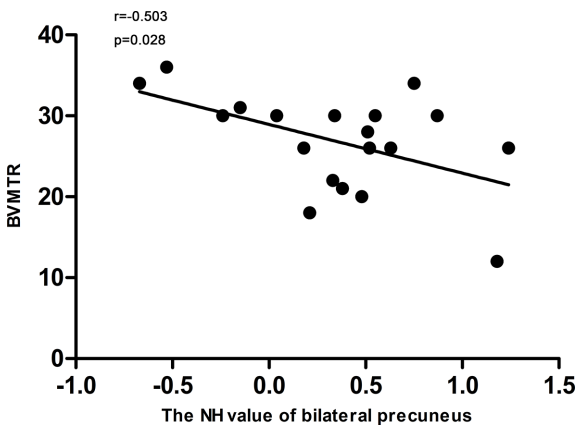

FIGURE 6 | Correlations between the NH values of the bilateral Precuneus and the BVMTR scores in patients after 8 weeks of treatment.

is inconsistent with the results of several previous studies, which showed that olanzapine treatment was related to the modulation of DMN connectivity (32, 33) . This inconsistency may be due to the differences of studied populations. Our study selected inpatients, and no distinction was made between first-episode and recurrent patients. The illness duration of these patients was five years or below, and the treatment period in the current study (8 weeks) was shorter than that in a previous study (33).

The precuneus and PCC play important roles in episodic memory retrieval, self-referential tasks, visuospatial imagery, and consciousness (19, 34). Previous studies have revealed that PCC is hyperactivated in patients with schizophrenia when examining themselves and others (35, 36), whereas other studies have shown decreased PCC activation in the similar conditions (37). The metabolism of the PCC region is also responsive to the cognitive state (38). Although the NH values in the right PCC/ precuneus of the patients after 8 weeks of treatment were lower than those of the controls, the improvement of NH in the right PCC/precuneus might be related to the beneficial effect of MCT treatment.

DPP treatment for 8 weeks increased NH in the bilateral precuneus compared with DT treatment. At baseline, no significant difference in the NH values was found between the two groups. Increased NH in the bilateral precuneus may reflect an enhanced interaction between the precuneus and the entire DMN. This effect may intensify the processes of self-reference and introspection in the patients. Previous study revealed that patients with schizophrenia exhibited less activation in the precuneus while working on self- and other-reflectivity tasks compared with controls (37). Functional neuroimaging study found that the precuneus activation was related to vividness of judgments during episodic memory retrieval (39). Accumulated evidence has revealed the important role of the precuneus in memory metacognition (40, 41). Baird et al. discovered a strong connectivity between the precuneus and anterior MPFC for memory metacognitive efficiency in resting-state functional connectivity (20). Francis et al. found that patients with early-phase psychosis who had high metacognitive capacity could bilaterally gain substantial functional connectivity of the resting state among MPFC, PCC, and precuneus (17). Our study only shows increased NH in the bilateral precuneus after DPP treatment compared with DT treatment and suggests the potential neurological mechanism of modulating DMN of MCT.

Previous studies have reported that alterations in brain function and symptomatic improvement are significantly correlated in patients with schizophrenia (42, 43). However, no significant correlation was found between altered NH and decreases in PANSS scores in the present study. Fabio et al. (32) explained

TABLE 4 | Discriminating patients from healthy controls by the SVM analyses.

Brain region	Accuracy	Sensitivity	Specificity
DPP group			
Right PCC/Precuneus	89.74%	84.21%	95.00%
Right Cerebellum Crus II	74.36%	68.42%	80.00%
Bilateral ventral MPFC	79.49%	73.68%	85.00%
Bilateral superior MPFC	79.49%	68.42%	90.00%
DT group			
Bilateral ventral MPFC	80.00%	90.00%	70.00%
Right PCC/Precuneus	80.00%	70.00%	90.00%
Bilateral Precuneus	77.50%	80.00%	75.00%
Bilateral superior MPFC	72.50%	75.00%	70.00%

PCC, posterior cingulate cortex; SVM, support vector machine.

that the lack of correlation might be due to the usual trajectory of reduced severity of early symptoms. After the initial treatment, the PANSS scores showed a significant downward trend in the first week of treatment. The PANSS scores declined gradually over the following weeks of treatment. Abbott et al. reported that gradual decrements in PANSS scores might mask the correlations between clinical symptoms and fMRI correlates (44).

The sensitivity or specificity of greater than 0.7 is beneficial to establish diagnostic indicators (45), whereas the sensitivity or specificity of less than 0.6 may indicate poor establishment of diagnostic indicators (46). SVM has been widely used in extensive biomedical applications for diagnosis purposes. The present SVM analyses showed that the accuracy, sensitivity, and specificity for distinguishing patients from healthy controls were more than 0.7 in the right PCC/precuneus, bilateral ventral MPFC, bilateral superior MPFC, and bilateral precuneus regions. Hence, NH in these brain regions can serve as potential image markers for distinguishing patients from controls.

Further SVR results revealed that the high NH levels at baseline in the bilateral superior MPFC could predict symptomatic improvement of PANSS after 8 weeks of DPP treatment. Previous studies revealed that the orbital frontal cortex and dorsal MPFC were related to predicting the long-term clinical outcome in the post-traumatic stress disorder (47). The hemodynamic activities of the frontotemporal cortex may predict treatment response to selective serotonin reuptake inhibitor in MDD (48). Jiang et al. found that the precuneus and left

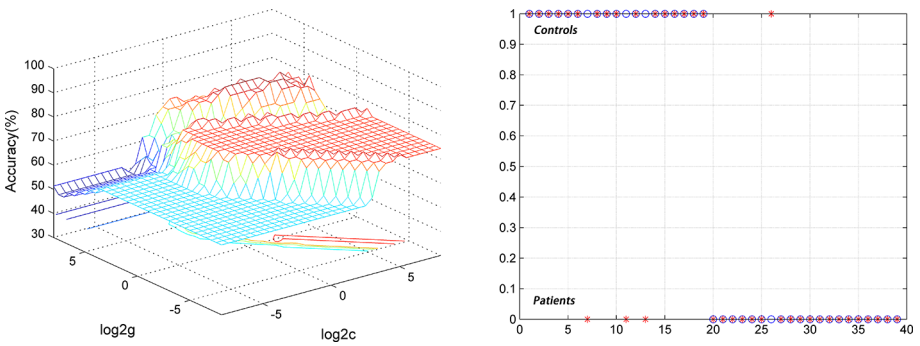

FIGURE 7 | Using decreased NH values in the right PCC/precuneus to differentiate the patients (DPP group) from the controls. Visualization of classifications through support vector machine (SVM) using the NH values in the significantly different regions. Left: SVM parameters selection result of 3D view; Right: Classified map of the NH values in the right PCC/precuneus. SVM, support vector machine.

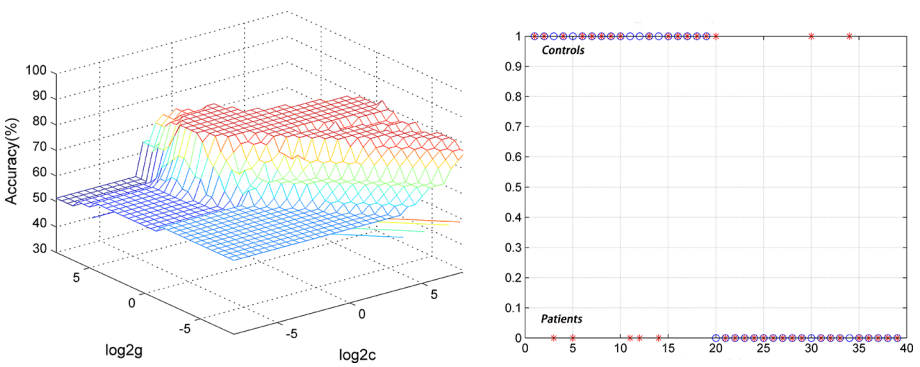

FIGURE 8 | Using decreased NH values in the bilateral ventral MPFC to differentiate the patients (DPP group) from the controls. Visualization of classifications through support vector machine (SVM) using the NH values in the significantly different regions. Left: SVM parameters selection result of 3D view; Right: Classified map of the NH values in the bilateral ventral MPFC.

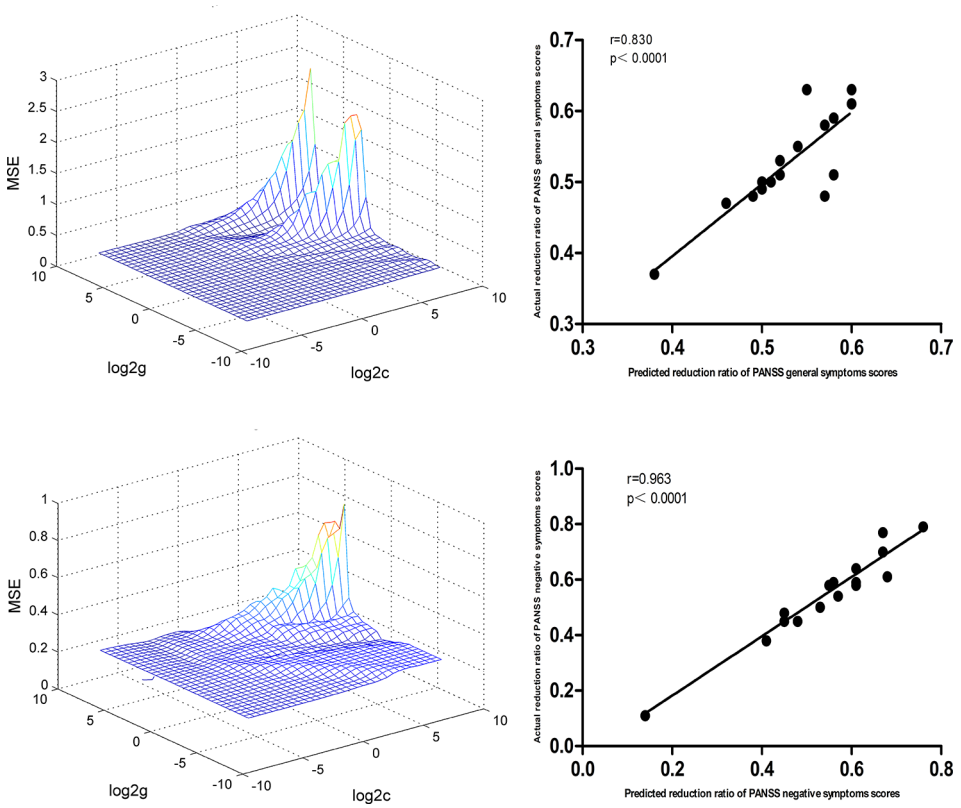

FIGURE 9 | SVR results suggested that the high NH levels at baseline in the bilateral superior MPFC could predict therapeutic response in the DPP group. Left: SVR parameter selection results (3D visualization); Right: The positive correlations between predicted and actual RR of the PANSS general symptoms subscale scores (r=0.830, p < 0.0001) and negative symptoms subscale scores (r=0.963, p < 0.0001) of the individual patients after 8 weeks of DPP treatment. PANSS, Positive and Negative Syndrome Scale; RR, reduction ratio.

postcentral gyrus were associated with the treatment response of electroconvulsive therapy in MDD (49). Consistent with these studies, our findings that the high NH levels in the bilateral superior MPFC can predict clinical treatment response, highlight the importance of this regions in MCT and contribute to interpret clinical symptomatic improvement in psychiatric disorders.

The majority of patients with schizophrenia display neurocognitive deficits. In the present study, the CF-ANF and BACS-SC scores were significantly high in the DPP group after 8 weeks of treatment relative to those in the DT group. The changes in the scores of the BACS-SC, HVLT-R, WMS-SS, and CF-ANF were also considerably higher in the DPP group than in the DT group, suggesting that MCT exerted a beneficial effect on symptomatic parameters and several cognitive functions, including attention and memory. These results are consistent with several previous findings, which revealed that MCT was related to improvement in multiple neurocognitive components. Lam et al. found that MCT improved cognitive insight in patients with schizophrenia using a Chinese sample (50). Furthermore, memory delusion distress and social quality of life were improved by MCT in patients with schizophrenia, suggesting that MCT had beneficial effects on symptomatic parameters and several cognitive functions (51). They also showed that patients with schizophrenia who received MCT exhibited a significant positive change in attitude toward their illness compared with the active control condition and enhanced meaning-making in patients (52). A systematic review showed that MCT was effective in reducing cognitive biases and delusions and improving insights and several aspects of neurocognitive functions in schizophrenia (9).

The present study has several limitations aside from its small sample size. First, this study focused on alterations in the DMN associated with antipsychotic and psychotherapy. Emphasizing the neurobiological contributions of the DMN at the time of therapy would be helpful. For the same reason, some meaningful changes in other brain regions may have been disregarded. Second, only 8 weeks of MCT was considered in the study. Thus, the long-term efficacy of MCT in patients with schizophrenia was not evaluated. Third, healthy controls were only scanned once at baseline. However, the data from healthy controls were used twice in the analyses. Hence, the effect of time may be not excluded in the present study. Fourth, SVM was not performed in a completely new and independent sample of patients, which might induce overoptimistic biases on the accuracies. Lastly, this study was performed at rest. The resting state of patients may be affected by symptoms. For instance, the resting state of someone experiencing auditory hallucinations is different from the resting

state of someone who is inattentive. Hence, interpretation of the results must be performed with caution.

In conclusion, this present study is the first to evaluate DMN homogeneity associated with MCT in patients with schizophrenia. MCT modulates DMN homogeneity in schizophrenia. Increased NH in the bilateral precuneus and increased NH in the right PCC/precuneus may be associated with substantial symptomatic improvement in schizophrenia induced by MCT. By contrast, no significant changes in NH are observed in patients administered with olanzapine within 8 weeks, which may be associated with poor treatment outcomes for schizophrenia. Hence, the findings contribute to the understanding of the treatment effects of MCT on brain functions in schizophrenia.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ **Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by local ethics committee of the Second Affiliated Hospital of Xinxiang Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to and approved the final manuscript. WG and YH designed the study. XS, RL, YO, and YD collected the original imaging data. WG, JZ, JC, and FL managed and analyzed the imaging data, and XS wrote the first draft of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00234/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.