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Targeting disrupted rich-club network organization with neuroplasticity-based computerized cognitive remediation in major depressive disorder patients

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ABSTRACT

Disrupted rich-club organization has been extensively studied in major depressive disorder (MDD) patients. Although data indicate that neuroplasticity-based computerized cognitive remediation (nCCR) can accelerate clinical responses in MDD patients, the mechanisms underlying its antidepressant efficacy are unknown. In this study, all MDD patients underwent two (baseline and week 4) neuropsychological assessments and DTI imaging. Additionally, 17 MDD patients did nCCR for 30 hours spread across 4 weeks. Rich-club organization was calculated with a graph-theoretical approach, and SC-FC coupling was explored. After 4 weeks of treatment, the number of rich-club connections, global efficiency, and SC-FC coupling strength increased significantly and were negatively associated with TMT-B scores. The effects of nCCR on disrupted rich-club organization may partly underlie its efficacy in improving the executive function of patients with MDD. Effects of nCCR on disrupted rich-club organization may partly underlie its efficacy in improving the executive function of patients with MDD.

1. Introduction

Major depressive disorder (MDD) is a chronic psychological disorder with typical clinical features of marked and persistent depression and cognitive dysfunction (Murray et al., 2012; Murray et al., 2015). Neuropsychological studies have shown that some MDD patients may have impairments in executive function (Snyder, 2013), working memory (Jopling et al., 2020) and processing speed (Pan et al., 2019). Cognitive dysfunction is a common and persistent symptom in some MDD patients (Culpepper et al., 2017). It is essential for MDD patients to improve their cognitive function in order to return to a normal psychosocial state (Knight et al., 2018). Approximately 30–50% of MDD patients can improve their mood with pharmacotherapy (Fleurence et al., 2009; Tedeschini et al., 2011), but some MDD patients still have cognitive impairment (Salagre et al., 2017; Vicent-Gil et al., 2019). Therefore, new strategies are needed to address persistent cognitive impairment in MDD patients.

Some nodes with higher degree values in the local cortex of the brain network are often selected as hub nodes, known as rich-club nodes; the connections between rich-club nodes are closer than those between nodes with lower degree values (van den Heuvel et al., 2012; van den Heuvel and Sporns, 2011). Rich-club nodes are mainly involved in efficient information transmission between different brain regions (Pedersen and Omidvarnia, 2016); they help maintain global functional coordination and are associated with higher-order cognitive functions (Griffa and Van den Heuvel, 2018). Substantial neuroimaging evidence has revealed the low connectivity of the rich club in MDD patients (Liu et al., 2021a, 2021b; Mai et al., 2017; Yoon et al., 2016), which may be due to the tighter connections between the rich-club nodes that make them vulnerable to disruption. Disrupted rich-club connections also affect global efficiency, thereby affecting network integration and information exchange (Liu et al., 2021b). Lower rich-club connection strengths were associated with higher depressive symptom severity scores in MDD patients (Yoon et al., 2016). The integrity of rich-club organization is largely dependent on the integration of distributed brain regions (Castellanos et al., 2011; Hillary et al., 2014; Mai et al.,

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2017; van Leijsen et al., 2019; Verhelst et al., 2018). Disrupted rich-club organization leads to decreased executive function, possibly related to impaired white matter integrity (Linke et al., 2013). A 2014 meta-analysis of neuropsychiatric disorders found that rich-club organization is more likely to be disrupted in psychiatric disorders than other network connections in the brain (Crossley et al., 2014; van den Heuvel et al., 2013). Due to the importance of rich-club organization in brain networks and its vulnerability, its disruption may lead to reduced cognitive function. Therefore, non-drug interventions aimed at repairing disrupted rich-club organization are a promising treatment approach for the vast majority of MDD patients with rich-club low connectivity, who generally do not benefit from standard therapy.

Neuroplasticity-based computerized cognitive remediation (nCCR), a type of digital neurotherapy (DNT) designed to restore neuronal systems to their normal function (Wexler, 2022), is a novel antidepressant therapy based on cognitive training and games designed to improve cognitive function in MDD patients through a series of exercises targeting single or multiple cognitive domains (Morimoto et al., 2012; Morimoto et al., 2014). These cognitive exercises are designed based on principles of neuroplasticity; they act primarily by altering neural network function and modulating synaptic connections to improve neuroplasticity in the brain (Morimoto et al., 2012). A recent review confirmed that a specific cognitive remediation therapy can be credited with improvement in neurocognition, including executive function (Motter et al., 2015), which suggests that cognitive function may be improved by a compensatory method to restore the cognitive performance of the brain. nCCR can improve cognitive function in patients with MDD and neurodegenerative diseases (Erickson et al., 2007; Kueider et al., 2012; Lampit et al., 2014; Lin et al., 2016; Masurovsky, 2020; Morimoto et al., 2020; Morimoto et al., 2016; Morimoto et al., 2012; Morimoto et al., 2014; Motter et al., 2016; Naismith et al., 2011; Shah et al., 2017; Ten Brinke et al., 2018; Ten Brinke et al., 2017; Ten Brinke et al., 2021; Vicent-Gil et al., 2019; Wykes et al., 2011), and this treatment can also result in increased regional cerebral blood flow, enhanced brain network connectivity, and improved white matter integrity (Chapman et al., 2015). nCCR can stimulate neuroplasticity; enhance the metabolic activity of the brain; and train cognitive functions such as working memory, executive function, and attention in a targeted manner. Through repeated training, cognitive decline can be delayed in MDD patients. Morimoto et al. applied a 4-week, 30-hour nCCR treatment regimen in MDD patients and demonstrated that nCCR could significantly relieve depressive symptoms and improve cognitive function (Morimoto et al., 2020). These MDD patients showed corresponding behavioural changes, including improvements in Montgomery–Asberg Depression Rating Scale (MADRS), Trail Making Test part B (TMT-B) and digit span (DS) scores (Morimoto et al., 2020). Morimoto et al. compared nCCR therapy with escitalopram in 11 patients with MDD and found that nCCR improved executive function significantly more (Morimoto et al., 2014). Lin et al. applied 6 weeks of computerized cognitive training to patients with MDD and found a significant increase within the control network (CON); patients showed corresponding changes in executive function (Lin et al., 2016). Most studies of non-drug interventions for MDD have focused on demonstrating efficacy rather than identifying the specific substrate of the brain's response to the treatment.

So far, the related researches about rich-club organization have mainly focused on the abnormal network connection caused by disease, and the remission of rich-club organization caused by treatment is often overlooked, especially the related changes in rich-club organization caused by nCCR. However, there are also some studies using pharmacotherapy to explore related changes in rich-club organization. Yoon et al. found that the creatine monohydrate augmentation therapy could effectively increase the strength of rich-club connections in MDD patients (Yoon et al., 2016). Tagliazucchi et al. (2016) found that the lysergic acid diethylamide (LSD) significantly increased global connectivity at the expense of rich-club organization in the brain.

In the present study, we applied DTI to assess the effect of nCCR treatment on rich-club organization. The primary goal is to determine how the connectivity strength of rich-club organization changes after nCCR treatment and to examine whether nCCR treatment has a similar effect on rich-club organization as other antidepressant therapy. It also needs to be examined whether nCCR treatment can improve cognitive function to confirm the specific target of nCCR treatment in MDD patients.

2. Materials and methods

2.1. Participants

A total of 45 MDD patients were initially recruited for this study. Twenty patients with MDD presenting for outpatient treatment for depression at Zhongda Hospital volunteered to receive nCCR as part of their treatment in addition to any medication or psychological treatments recommended and agreed upon as part of their standard care, as well as to participate in the DTI and cognitive assessments. Although MRI studies of brain changes in MDD after pharmacotherapy almost universally lack patient control groups, given the high placebo response rate in MDD, we thought it would be valuable to have some comparison to patients not receiving nCCR and created a comparison group of 25 age- and gender-matched controls who had participated in previous fMRI and cognitive assessment studies in our centre (Table 1).

Table 1
Demographic and the treatment group × time interaction of clinical neuropsychological scale information between the control and nCCR groups

Items	nCCR (*n* = 17)	Control (*n* = 23)	Statistic	P values
Age (years)	31.47 (11.89)	30.13(8.93)	-0.390[a]	0.699
Gender(male/ female)	7\10	7\16	0.496[b]	0.481
Education (years)	14.97(2.50)	16.78(3.22)	1.926 [a]	0.062
HAMD			F (1,38) =11.280[c]	**0.002****
baseline	18.35(2.06)	19.49(2.66)		
week 4	11.00(2.32)	16.04(5.00)		
MMSE			F (1,38) =0.829[c]	0.368
baseline	28.35(1.17)	28.30(1.74)		
week 4	29.06(0.75)	28.48(1.24)		
DS			F (1,38) =1.021[c]	0.319
baseline	14.82(2.46)	14.65(2.87)		
week 4	15.88(2.20)	15.13(3.05)		
VFT			F (1,38) =4.745[c]	**0.036***
baseline	22.24(5.82)	22.87(6.17)		
week 4	26.94(7.40)	24.22(6.73)		
TMT-A			F (1,38) =0.370[c]	0.547
baseline	42.09 (14.73)	37.91(13.76)		
week 4	34.55 (14.36)	32.28(15.69)		
TMT-B			F (1,38) =9.635[c]	**0.004****
baseline	104.80 (29.80)	85.48(27.56)		
week 4	77.38 (22.49)	79.68(27.89)		

The data are presented as the mean (with standard deviation, SD). **Abbreviations:** HAMD, Hamilton Depression Scale; MMSE, Mini-Mental State Examination; DS, Digit Span Test; VFT, Verbal Fluency Test; TMT-A, Trail-Making Test A; TMT-B, Trail-Making Test B; nCCR, neuroplasticity-based computerized cognitive remediation. * $p < 0.05$, ** $p < 0.01$.

[a] Statistical comparison was performed using two-sample t-test

[b] Statistical comparison was performed using a chi-square test. [c]Statistical comparison was performed using analysis of variance.

All patients met the following inclusion criteria: (1) fulfilment of the diagnostic criteria for MDD in the DSM-V (Wakefield, 2016) and a 17-item Hamilton Depression Rating Scale (17-HAMD) score > 17 (Williams, 1988); (2) an age range of 18 to 70 years old; (3) right-handedness, normal colour vision, and normal or corrected-to-normal visual acuity; (4) use of conventional antidepressant therapy without significant relief; and (5) no suicidal tendencies, stable condition in the short term, and medication remaining unchanged. The exclusion criteria were as follows: (1) history of other mental illnesses that may lead to changes in brain function or structure, such as bipolar disorder, panic attacks, schizophrenia, etc.; (2) severe brain injury, epilepsy, cerebrovascular disease, brain history of long-term neuropsychiatric complications such as tumours; and (3) a history of alcohol or drug abuse. The study was approved by the responsible Human Participants Ethics Committee of the Affiliated Zhongda Hospital, Southeast University, and written informed consent was obtained from each participant.

We recruited patients according to the principle of monthly rotation: we recruited the treatment group one month and then recruited the control group the next month. All MDD patients were divided into the nCCR group and the control group. The nCCR group used computerized cognitive function training, and the control group did not receive intervention. All MDD patients in the nCCR and control groups remained on their pre-enrolment drug regimen throughout the study period. All patients underwent neuropsychological testing, DTI, and resting-state fMRI scans at baseline and at week 4. The neuropsychological assessments included the Mini-Mental State Examination (MMSE) (Folstein and McHugh, 1975), 17-HAMD (Williams, 1988), Digit Span Test (DS) (Heilbrun, 1958), Verbal Fluency Test (VFT) (Hooper, 1999), and Trail-Making Test parts A and B (TMT-A and B) (Gordon, 1972). See Supplementary Materials for a detailed description.

2.2. Neuroplasticity-based computerized cognitive remediation (nCCR)

The nCCR consisted of a computerized cognitive training program called "Catch the Ball", designed by Bruce Wexler at Yale University and programmed by one of the authors (JL) (Morimoto et al., 2020; Morimoto et al., 2016; Morimoto et al., 2012; Morimoto et al., 2014). Special algorithms individualize training, moving patients according to their individual performance through a series of levels with incremental changes in difficulty and combinations of required cognitive functions including visual attention, working memory, cognitive flexibility, multi-task performance, and inhibition of dominant response. In this program, different numbers of yellow balls move and change colour (blue or red) randomly on the screen, and the patient presses buttons according to the corresponding rules displayed on the screen (Fig. 1). Participants in the nCCR group completed 30 hours of computerized cognitive remediation over 4 weeks of 2-3hour sessions 4-5 times per week on a computer in a private treatment room at the Affiliated ZhongDa Hospital, Southeast University.

2.3. Image acquisition and processing

2.3.1. Image acquisition

All MRI data were acquired using a Philips Ingenia II 3.0 T scanner with a 16-channel head coil at ZhongDa Hospital Affiliated with Southeast University. The diffusion tensor imaging (DTI) sequences had the following parameters: repetition time (TR)/echo time (TE) = 5825.5/106.6 ms; flip angle = 90°; field of view (FOV) = 256 × 256 mm^2; matrix = 128 × 128; 32 diffusion-weighted directions with b = 1000 s/mm^2 and one additional non-dispersion-weighted scan with b = 0; slice thickness = 2 mm; slice number (interleaved axial) = 75. The resting-state fMRI data adopts echo-plane imaging sequence, and the scan parameters are as follows: TR/TE = 2000/35 ms; flip angle = 90°; FOV = 230 × 230 mm^2; matrix = 64 × 64; slice thickness = 3.6 mm; intersection gap = 0.6 mm; number of slices = 33. T1 images with the following parameters: TR/TE = 1800/20 ms; flip angle = 9°; FOV = 230 × 230 mm^2; matrix = 480 × 480; slice thickness = 0.48 mm; and number of slices = 33.

2.3.2. The preprocessing of DTI data

The preprocessing of DTI data was performed using the PANDA toolbox (Cui et al., 2013) based on FSL 5.0. The steps of DTI data processing were as follows: the detailed processing steps of the PANDA toolbox were explained in detail by Cui et al. (2013). The raw DTI data were corrected for head movement and eddy current distortions. All participants with a maximum displacement of head movement in any direction of more than 3 mm or a rotation angle of more than 3° were

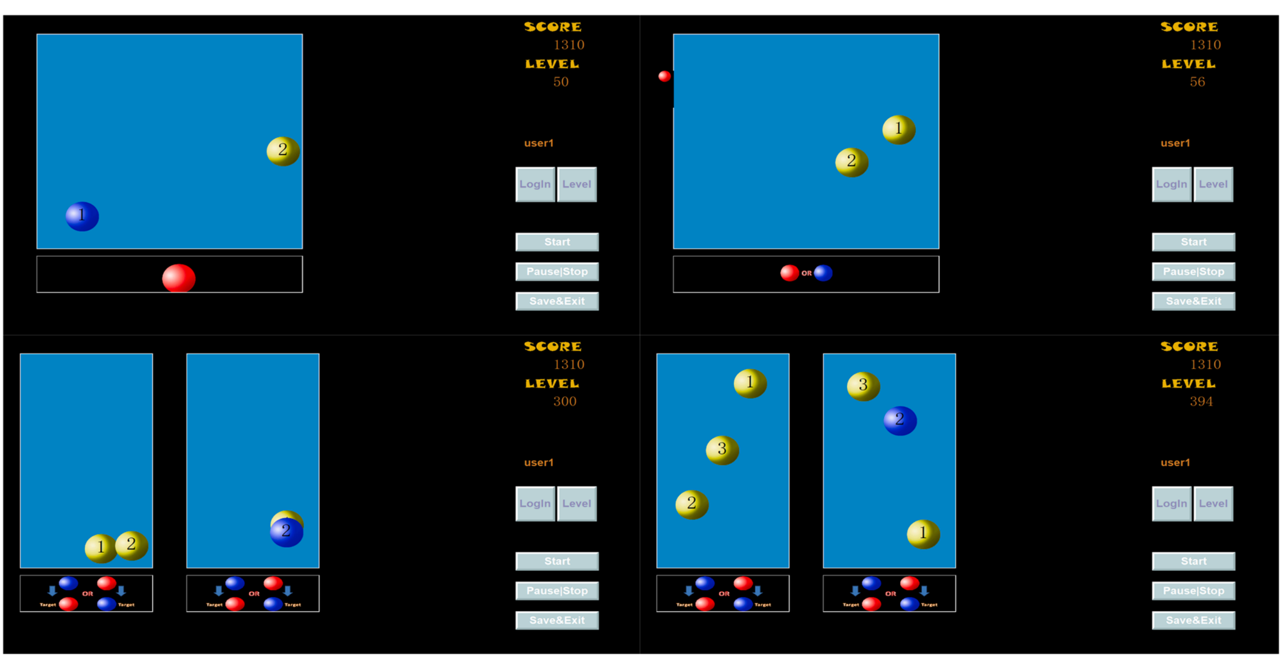

Fig. 1. Neuroplasticity-based computerized cognitive remediation (nCCR) program - “Catch the Ball”.

removed. The Automated Anatomical Labeling (AAL) atlas, which divides the entire brain into 90 regions of interest (ROIs), was used to construct the brain network of each participant. Then, the fractional anisotropy (FA) of each voxel was calculated. Each ROI in the AAL90 atlas represented a node of a structural brain network. The white matter pathways were the edges of the structural brain network, which were reconstructed by using deterministic tractography for each subject with the Fiber Assignment by Continuous Tracking (FACT) algorithm (Mori et al., 1999). The WM deterministic fibre tracking was terminated when the trajectory angle of the streamline exceeded 60 degrees or the streamline reached a voxel with an FA value lower than 0.2 (van den Heuvel and Sporns, 2011; van den Heuvel et al., 2013). Finally, the 90 × 90 structural connectivity (SC) matrix for each subject was reconstructed.

2.3.3. Preprocessing of fMRI data

Resting-state fMRI data preprocessing was performed with the GRETNA toolbox (Wang et al., 2015) based on MATLAB. The first 5 volumes of each data point were discarded to reduce the instability of the initial signals. Corrections for slice timing and head motion were applied to the remaining 235 volumes. All participants with a maximum displacement of head movement in any direction of more than 3 mm or a rotation angle of more than 3° were removed. Then, images were normalized into Montreal Neurological Institute (MNI) space using the high-dimensional diffeomorphic anatomical registration through exponentiated Lie algebra (DARTEL) algorithm (Ashburner, 2007) and then resampled to $2 \times 2 \times 2\ mm^3$ voxels. A 4 mm full width at half maximum (FWHM) Gaussian kernel was applied to smooth the data. Several nuisance signals, such as head motion signals (Original 6-parameter model) and signals from the cerebrospinal fluid and white matter from the data, were regressed. To reduce the effect of low-frequency drift and high-frequency physiological noise, temporal bandpass filtering (0.01–0.08 Hz) and linear detrending were used. The correlation of the average time series in the resting state was calculated as a functional connectivity (FC) matrix. To increase the normality of the matrixes, Fisher's Z transformation was performed.

2.4. Graph analysis of network topology

Graph-theoretic analysis was performed using the GRETNA toolbox (Wang et al., 2015) and illustrated using BrainNet Viewer (Xia et al., 2013). We used global properties to describe changes in brain networks, with the following parameters: clustering coefficient (Cp), shortest path length (L), small-worldness (SW), global efficiency (Eg) and local

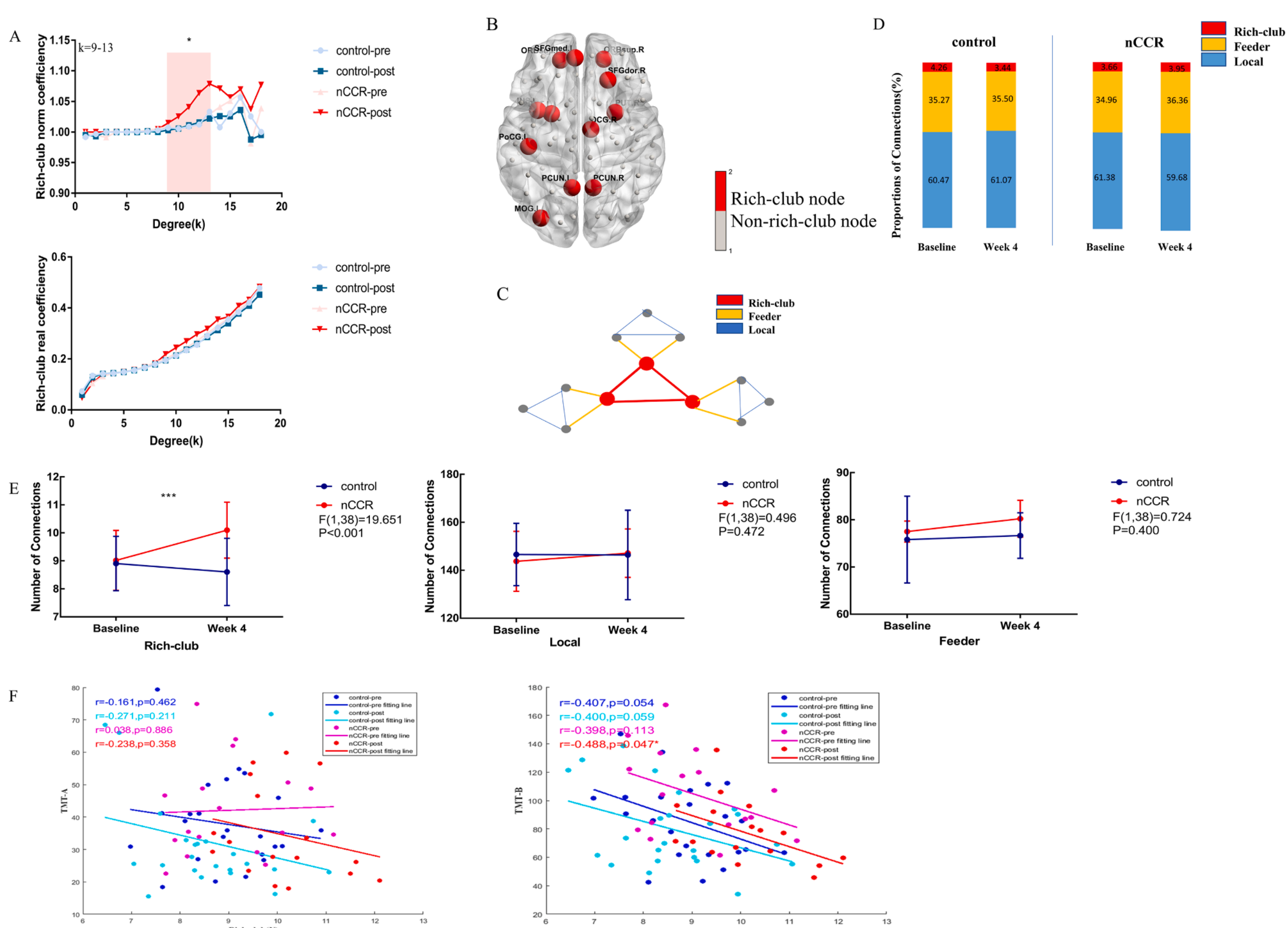

Fig. 2. Rich-club organization. (A) The rich-club normalized (top) and real curves (bottom). (B) Distribution of rich-club (red) and non-rich-club (grey) nodes. (C) Different classifications of structural brain network connections. (D) The proportion of rich-club connections (red), feeder connections (yellow) and local connections (blue) of the structure brain network for each group. (E) Line graphs display the changes in the numbers of rich-club, feeder and local connections for each group at baseline and 4 weeks. (F) Scatter plots of the number of rich-club connections against TMT-A and TMT-B scores. **Abbreviations:** HAMD, Hamilton Depression Scale; MMSE, Mini-Mental State Examination; DS, Digit Span Test; VFT, Verbal Fluency Test; TMT-A, Trail-Making Test A; TMT-B, Trail-Making Test B; nCCR, neuroplasticity-based computerized cognitive remediation; SFGdor.R, right dorsolateral superior frontal gyrus; ORBsup.L, left orbital superior frontal gyrus; ORBsup.R, right orbital superior frontal gyrus; SFGmed.L, left medial superior frontal gyrus; SFGmed.R, right medial superior frontal gyrus; INS.L, left insula; MOG.L, left middle occipital gyrus; PoCG.L, left posterior central gyrus; PCUN.L, left precuneus; PCUN.R, right precuneus; PUT.L, left putamen; PUT.R, right putamen. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

efficiency (Eloc). A more detailed description of these indicators is provided in the supplementary materials.

2.5. Rich-club organization

Rich-club organization refers to the tighter network connections formed between high-degree nodes of the brain than between lower-degree nodes (Colizza et al., 2006; van den Heuvel and Sporns, 2011). The rich-club phenomenon could be well explained based on the normalized rich-club coefficients (RCs). The determination of the rich-club regions was based on the group average network, which was calculated based on at least 75% of all connections in the group. Then, the hub nodes were determined based on the first 13% (top 12) of the highest degree value of subjects in all groups (van den Heuvel et al., 2012; van den Heuvel and Sporns, 2011; van den Heuvel et al., 2013). Three types of connections described edges in the structural network: rich-club connections link rich-club hubs; feeder connections link rich-club hubs and non-rich-club hubs; local connections link non-rich-club hubs (Fig. 2C). The normalized RC value was greater than 1 in the range of degree values, which indicated the existence of a rich-club property in the brain network. The normalized RC is usually the normalization of RC, which is calculated based on 1000 random networks for each subject. The RC could be computed by the following formula (Colizza et al., 2006):

$$\phi(k) = \frac{2E_{>k}}{N_{>k}(N_{>k} - 1)}$$

where $E_{>k}$ refers to the actual number of connections between a sub-network of nodes and $N_{>k}(N_{>k} - 1)$ means the maximum number of possible connections between them.

2.6. SC-FC coupling

SC-FC coupling refers to the strength of the correlation between structural and functional network connections. The non-zero edges of the structural network connections were re-transformed to a Gaussian distribution. Then, rich club, feeder, local, and overall connections in the structural network were analyzed with the method of Pearson correlation with the corresponding connections in the functional network, which generated different types of SC-FC coupling for each brain network (Cao et al., 2020; van den Heuvel et al., 2013).

2.7. Statistical analysis

SPSS 22.0 software (SPSS Inc., Chicago, USA) was used to compare demographic (age, education and gender), clinical neuropsychological scales and network graph-theoretic indicators. In terms of demographic information, age and education between the control and nCCR groups were compared by the two-sample t-test, but gender was compared by the $\chi 2$ test. We used analysis of variance (ANOVA) to compare the significant differences in network graph-theoretic indicators between the control and nCCR groups. Correlation analysis was used to compare the relationship between network metrics and clinical information.

3. Results

3.1. Demographic and clinical characteristics

Five MDD patients were excluded due to excessive head motion parameters during MRI scans (the data of patients with a maximum displacement of head movement in any direction of more than 3 mm or a rotation angle of more than 3° were removed). Therefore, this study included 17 MDD patients in the nCCR group and 23 in the control group. Demographic and clinical neuropsychological scale information of the two groups are listed in Table 1. There were no significant differences in age, gender, or education between the nCCR and control groups over 4 weeks (all $p > 0.05$). The HAMD, TMT-A, and TMT-B scores decreased, while the DS, VFT, and MMSE scores increased in the nCCR group after treatment. There was a treatment × time interaction in HAMD ($p = 0.002$), TMT-B ($p = 0.004$), and VFT ($p = 0.036$) parameters between the nCCR and control groups (Table 1).

3.2. Network analysis

3.2.1. Rich-club analysis and behavioural significance

The rich-club normalized (top) and real curves (bottom) at the group-level structural brain networks in all subjects are presented in Fig. 2A. MDD patients in the nCCR group demonstrated an increase in the rich-club normalized coefficient over 4 weeks. There was a significant interaction between the nCCR and control groups (k = 9-13, $p <$ 0.05). The rich-club nodes were mainly located in the right dorsolateral superior frontal gyrus, bilateral orbital superior frontal gyrus, bilateral medial superior frontal gyrus, left insula, left middle occipital gyrus, left posterior central gyrus, bilateral precuneus and bilateral putamen (Fig. 2B). The rich-club organization of structural brain networks could be divided into three types of connections: rich-club, feeder and local connections (Fig. 2C). Then, we calculated the density of these connections in all MDD patients in the structural network. At baseline, rich-club connections accounted for 4.26% and 3.66% of the total network connections, feeder connections accounted for 35.27% and 34.96%, and local connections accounted for 60.47 and 61.38% in the control and treatment groups, respectively. Rich-club connections reached 3.44 and 3.95%, feeder connections reached 35.50 and 36.36%, and local connections reached 61.07% and 59.68% of the total connections, respectively, in the control and treatment groups after 4 weeks (Fig. 2D). The number of rich-club connections was significantly increased over 4 weeks in participants receiving nCCR compared to the baseline. There was a significant interaction ($p < 0.001$) between the nCCR and control groups (Fig. 2E). Furthermore, a pairwise association between the connections of rich-club organization and clinical indicators was obtained in the nCCR group after 4 weeks of treatment. The number of rich-club connections was significantly negatively correlated with the TMT-B score (r = -0.488, $p = 0.047$) (Fig. 2F).

3.2.2. Global topological properties and correlation analysis for structural network

Global topological properties between the nCCR and control groups after 4 weeks are illustrated in Fig. 3. The metrics of Eg ($p < 0.001$) and SW ($p < 0.001$) in MDD patients both showed significant interaction effects between group (nCCR or control) and time (baseline or 4 weeks) in MDD patients (Fig. 3A). After 4 weeks of cognitive training, MDD patients in the treatment group showed increased Eg and SW compared to baseline. Eg was statistically associated with TMT-B score (r = -0.551, $p = 0.022$) in the treatment group at week 4 (Fig. 3B). Furthermore, the number of rich-club connections was significantly positively correlated with Eg ($r = 0.792$, $p < 0.001$) in MDD patients in the treatment group at week 4 (Fig. 3C). Additionally, the correlations between other topological properties and the number of rich-club organization are shown in Fig. S1.

3.2.3. Global topological properties and correlation analysis of rich-club connections corresponding to structural networks in functional networks

The changes in the global topological properties of rich-club connections in resting-state fMRI networks in MDD patients after treatment were presented in Fig. 4. Eg had a significant interaction ($p = 0.043$) between the nCCR and control groups over 4 weeks (Fig. 4A). The Eg showed an increase in MDD patients after 4 weeks of treatment compared to baseline. Furthermore, Eg was negatively related to TMT-B score (r = -0.528, $p = 0.029$) in the treatment group at week 4 (Fig. 4B).

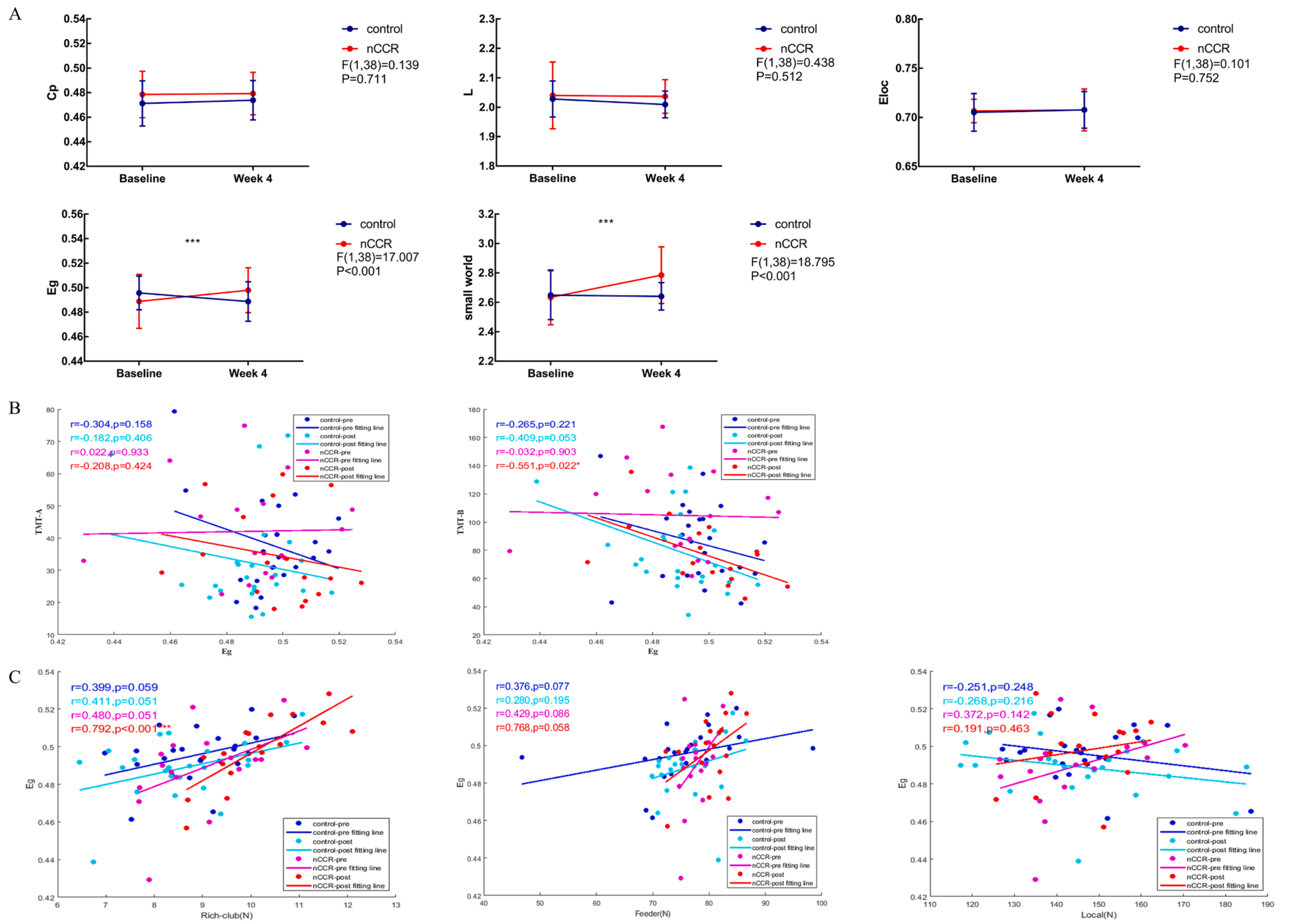

Fig. 3. The global topological properties and correlation analysis of the structured brain network. (A) Line graphs display the change in the global topological properties for each group at baseline and 4 weeks. (B) Scatter plots of Eg against TMT-A and TMT-B scores. (C) Scatter plots of Eg against the number of rich-club, feeder and local nodes. **Abbreviations:** Eg, global efficiency; Eloc, local efficiency; Cp, the average clustering coefficient; L, shortest path length; TMT-A, Trail-Making Test A; TMT-B, Trail-Making Test B; nCCR, neuroplasticity-based computerized cognitive remediation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

3.2.4. SC-FC coupling and correlation analysis

The strength of SC-FC coupling of MDD patients showed an increasing trend after 4 weeks of treatment, while there was no significance in all SC-FC coupling. Interestingly, there was a significant interaction in the strength of SC-FC coupling in rich-club connections (p = 0.018) between the nCCR and control groups over 4 weeks (Fig. 5A). Further analysis of SC-FC coupling strength and clinical indicators showed that the strength of SC-FC coupling in rich-club connections had a significant negative correlation with TMT-A (r = -0.626, p = 0.007) and TMT-B scores (r = -0.591, p = 0.012), respectively, in the treatment group at week 4 (Fig. 5B). All the connections of SC-FC coupling strength were significantly positively associated with the number of rich-club connections (r = 0.753, $p < 0.001$) in the MDD patients after 4 weeks of treatment (Fig. 5C).

4. Discussion

We explored the changes in the patterns of rich-club organization in structural networks and functional brain dynamics between the treatment group and the control group of patients with MDD. The principal findings in this clinical trial were as follows: (1) There was a significant interaction in TMT-B score and rich-club connections between nCCR and control groups over 4 weeks. (2) Additionally, SC-FC coupling between structural network connections and functional network connections in MDD patients was confirmed, especially in rich-club connectivity, which may be a neuropsychiatric marker with strong predictive power, helping us to discover the efficacy of nCCR in MDD patients. As a result, accumulating evidence confirms the improvement in cognitive control ability with nCCR.

In the present study, there was a trend towards decreasing TMT-B scores in both the nCCR and control groups, but there was a significant interaction between the two groups over 4 weeks. The TMT-B task involves cognitive function, especially executive function, including working memory, processing speed, and task-switching ability, and the TMT-A is a measure of visuomotor tracking ability (Arnett and Labovitz, 1995). The TMT-B, which requires quick task switching and decision making, is more sensitive to alterations in executive function (Sanchez-Cubillo et al., 2009). The reduced time spent on TMT tasks reflects better cognitive control ability (Arnett and Labovitz, 1995). The interaction of TMT-B scores between the two groups over 4 weeks after treatment indicated that computerized cognitive training could better improve the executive function of MDD patients.

It is noteworthy to observe a significant interaction in rich-club connectivity between the control and nCCR groups over 4 weeks. Rich-club connections play an important role in the connection among specific structural modules representing different brain functions (Sporns, 2013) as a core structure in neural networks, which mainly participate in the communication of information between different modules (Kim and Min, 2020). Previous studies have found that significant reductions in rich-club connections were observed in MDD patients compared to healthy controls (Liu et al., 2021b). Reduced rich-club connections reflect a decreased ability to integrate information among brain regions, disruption of information transmission, and reduced global efficiency in the whole brain network (Liu et al., 2021b; van den

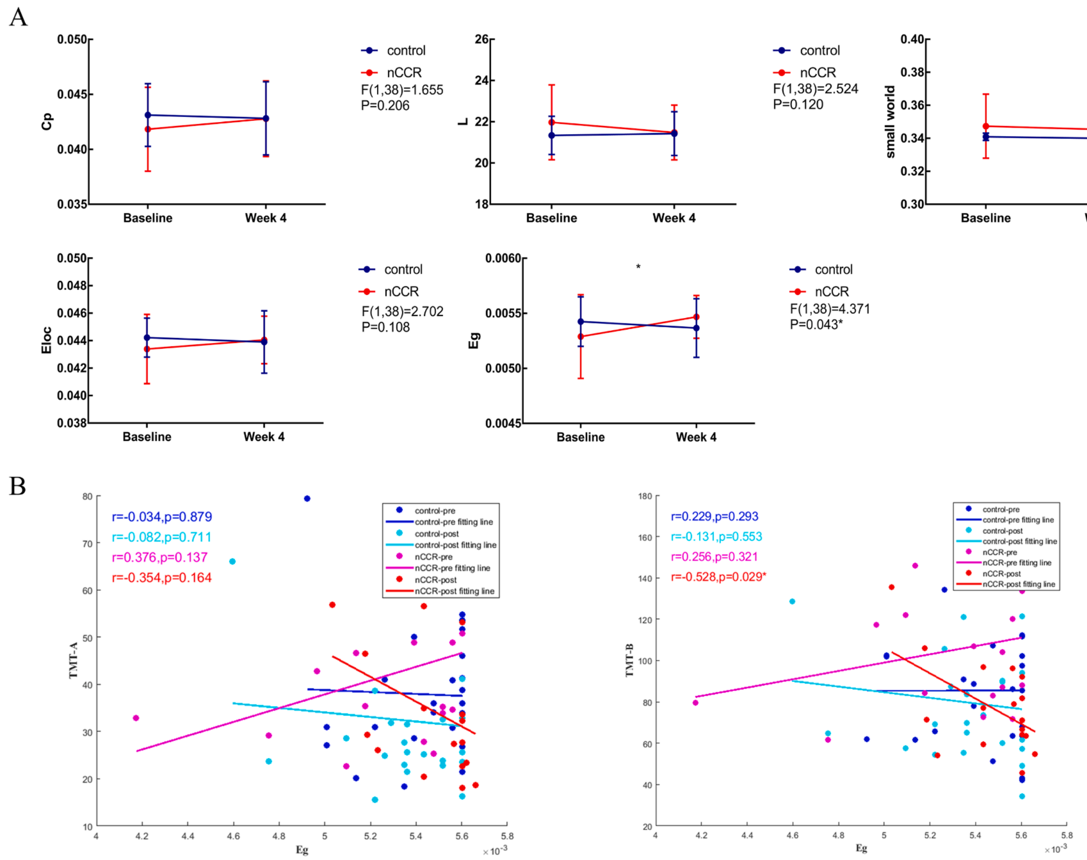

Fig. 4. The global topological properties of rich-club connections in functional brain networks. (A) Line graphs display the change in the global topological properties for each group at baseline and 4 weeks. (B) Scatter plots of Eg against TMT-A and TMT-B scores. **Abbreviations:** Cp, clustering coefficient; Eg, global efficiency; Eloc, local efficiency; L, shortest path length; TMT-A, Trail-Making Test A; TMT-B, Trail-Making Test B; nCCR, neuroplasticity-based computerized cognitive remediation. * $p < 0.05$.

Heuvel et al., 2013). Reductions in in rich-club connections and global efficiency have been reported in articles on MDD (Liu et al., 2021b; Misic et al., 2014; Schirmer et al., 2019; van den Heuvel et al., 2012; van den Heuvel et al., 2013). The rich-club network, which is closely related to higher-order cognitive functions, is easily disrupted in most brain diseases (Griffa and Van den Heuvel, 2018). In this study, the rich-club connections in the control group tended to decrease compared to the local and feeder connections. A recent meta-analysis of psychiatric disorders also showed that rich-club connections in MDD patients are more likely to be disrupted than other types of network connections in the brain (Crossley et al., 2014). In addition, we recruited volunteers with treatment-resistant MDD who joined our experiment because of poor drug response. Therefore, in the present study, the number of rich-club connections in the control group showed a decreasing trend.

The current study observes a potential relationship between TMT-B and rich-club connections. The relationship between cognitive dysfunction and network abnormalities has been demonstrated in neuropsychiatric disorders (Gao et al., 2020; Liu et al., 2020; Mallas et al., 2021; Martino et al., 2020; Wang et al., 2021; Zhang et al., 2021a). Improvement in cognitive function is also often accompanied by changes in brain network connectivity (Chan et al., 2020; Chu et al., 2021; Gunning et al., 2021; Martens et al., 2021; Ten Brinke et al., 2021; Zhang et al., 2021b). After computerized cognitive training, MDD patients showed an increase in the cognitive control network (CCN), and the corresponding attention and working memory were significantly improved (Gunning et al., 2021). Yoon et al. found a negative correlation between rich-club connections and depressive symptom severity measured using the HDRS in MDD patients and confirmed a statistically significant increase in rich-club connection levels following creatine augmentation treatment in women with MDD, while the research did not find a relationship between rich-club connections and associated improvements in cognitive function after treatment (Yoon et al., 2016). Our current findings support a beneficial effect of nCCR on cognitive impairment and related network abnormalities. The reduction in the TMT-B score after computerized cognitive training may be attributed to increased rich-club connections, and this change is due to the compensatory neuro-reparative effect of computerized cognitive training. Because cognitive training is designed primarily for executive function, an increased level of rich-club connectivity may reflect the potential curative mechanism underlying computerized cognitive training. Therefore, we hypothesize that nCCR therapy improves executive function by promoting rich-club connectivity.

We found a significant interaction in Eg between the control and nCCR groups over 4 weeks in the structural network and functional network. Eg represents the integration of the brain network (Sporns, 2013) and measures the ability to transfer information between nodes in a network (Liu et al., 2021b). Liu et al. demonstrated that the disruption of network integration was related to cognitive impairment (Liu et al., 2020) and did not explore the relationship between global efficiency and specific cognitive impairment. In general, most of the studies merely assessed the correlation with depressive symptoms and did not pay attention to cognitive dysfunction, especially executive dysfunction. Further study showed that Eg was negatively associated with TMT-B scores in the nCCR group at 4 weeks, which suggests that the change in Eg reflects improvements in executive function. Moreover, Eg in the structural network was positively associated with the number of rich-club connections in the nCCR group at 4 weeks. van den Heuvel et al. investigated the change in global efficiency caused by selective

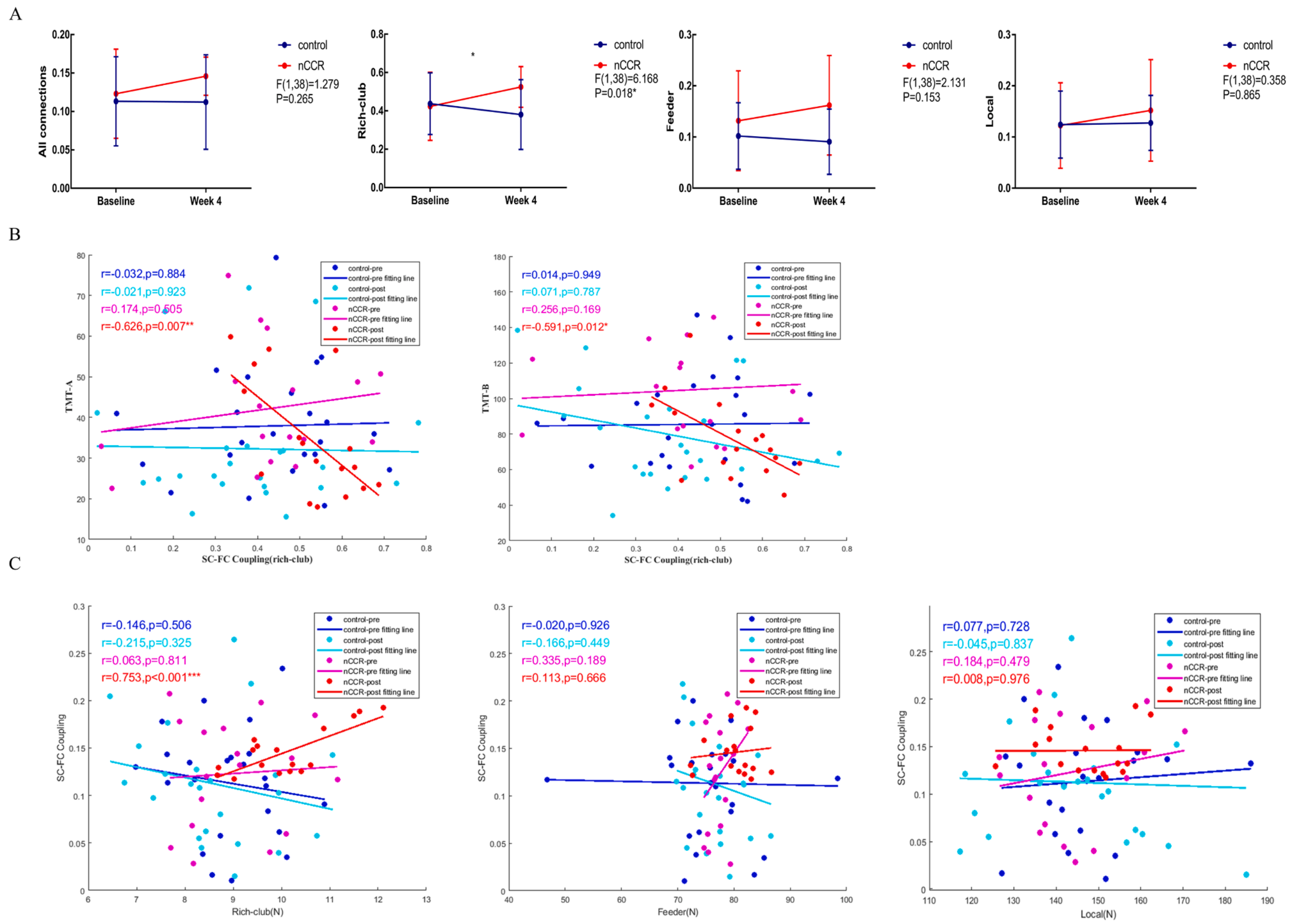

Fig. 5. SC-FC coupling of rich-club organization and behavioural significance in MDD patients. (A) The changes in SC-FC coupling of overall, rich-club, feeder, and local connections in MDD patients. (B) Scatter plots of the strength of SC-FC coupling in rich-club connections against TMT-A and TMT-B scores. (C) Scatter plots of all SC-FC coupling strengths and the numbers of rich-club, feeder and local connections. **Abbreviations:** Eg, global efficiency; Eloc, local efficiency; L, shortest path length; TMT-A, Trail-Making Test A; TMT-B, Trail-Making Test B; nCCR, neuroplasticity-based computerized cognitive remediation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

structural network damage and found that attacks on rich-club connections disrupted global efficiency approximately three times more than attacks on structural networks at random, indicating that rich-club connections play an indispensable role in the transmission of information between nodes (van den Heuvel and Sporns, 2011). Previous studies also proved that the network in MDD patients had lower global efficiency and disintegration of cortical hub architectures, which showed changes related to MDD (Korgaonkar et al., 2014; Singh et al., 2013). The increase in Eg indicates the improvement of the global information exchange efficiency in the brain network. MDD patients with such alterations show the repair of disruptions to global network integration capability and powerful information processing ability. The changes in global efficiency of structural and functional networks reflect the consistency of brain compensatory responses to cognitive training targeted at executive function.

Prior evidence has shown that SC-FC coupling strength essentially reflects mental state (Batista-Garcia-Ramo and Fernandez-Verdecia, 2018; Huang and Ding, 2016). The structural network of the cerebral cortex provides the scaffold and foundation for shaping the functional network (Ghosh et al., 2008; Honey et al., 2007), which in turn can influence the structural network through neural plasticity (Honey et al., 2009). The present study investigating the relationship between SC-FC coupling and cognitive function confirmed that the strength of SC-FC coupling in rich-club connections is significantly negatively associated with TMT scores in the nCCR group at 4 weeks, which means that better executive function is related to higher SC-FC coupling in rich-club connections. Baum et al. confirmed that executive function is positively associated with SC–FC coupling (Baum et al., 2020). The rich-club network is significantly correlated with the consistency of structural and functional networks, suggesting that the rich-club network plays a leading role in global information exchange. The study carried out by Liu et al. demonstrated the disruption of SC-FC coupling in MDD patients compared to healthy controls (Liu et al., 2021b). The increased SC-FC coupling strength also proves the efficacy of nCCR from another perspective. According to our findings, rich-club connections had the greatest predictive power for distinguishing the efficacy of the nCCR intervention in MDD patients from the control group, indicating that rich-club connections, as a candidate neuroimaging biomarker, may serve as a more robust predictor in the early identification of MDD patients.

The current study has some limitations. First, this study had a small sample size. Second, the grouping of MDD patients was not completely random, and the patients were recruited according to the principle of monthly rotation. Third, due to ethical and patient safety concerns, patients were still taking antidepressants during nCCR treatment, and we could not determine if there was a therapeutic additive effect. Future studies should explore whether there is a synergistic effect between antidepressants and nCCR.

5. Conclusion

In summary, nCCR could repair disrupted rich-club organization and improve executive function in MDD patients, indicating an increase in network transmission efficiency and a greater ability to integrate information between systems in MDD patients. In addition, the rich-club connections offered greater predictive power to distinguish the efficacy of the nCCR intervention compared to the control treatment in MDD patients.

CRediT authorship contribution statement

Min Shu: Data curation, Writing – original draft, Investigation, Methodology. **Suyang Feng:** Data curation. **Jiacheng Liu:** Conceptualization, Writing – review & editing, Funding acquisition, Project administration.

Declaration of Competing Interest

All authors of this paper declare that they have no potential conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2022.114742.

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