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Cognitive-behavioral therapy to normalize social learning for patients with major depressive disorders: study protocol for a single-arm clinical trial

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Abstract

Background The current study aims to explore the efficacy of cognitive behavioral therapy (CBT) in normalizing social learning capabilities and its underlying neural processes among patients with MDD, in terms of enhancing learning towards positive social feedback, and reducing excessive learning towards negative social feedback. This study also explores the potential for learning impairments in social contexts as a biomarker to predict the effectiveness of CBT.

Methods In a single-centre, single-arm, open-label trial, 60 outpatients with MDD will undergo 12 sessions of CBT in three months. Data collection of patients will be administered at baseline and at the endpoint of the treatment. Additionally, 60 heathy controls will be recruited as a comparative group to assess deviations from the normal functions in the patients with MDD before and after CBT. Data collection of the HC group will be administered at baseline. Data collection of the two groups comprises of demographic information, clinical assessments, psychological assessments, and behavioral experiments (i.e. the Door Game and the Trust Game) in conjuction with task-based function magnetic resonance imaging (fMRI) scanning. Data analysis comprises of an estimation of social learning capabilities by computational modeling, and identification of baseline abnormalities, treatment effects and endpoint abnormalities on social learning capabilities and its neural activities.

Discussion This trial aims to assess the efficacy of CBT in normalizing social learning capabilities among patients with MDD by leveraging high ecological validity paradigms and computational modeling. This trial also contributes to understanding psychosocial biomarkers of CBT treatment effectiveness in reducing depressive symptoms.

Trial registration ChiCTR2400094841 (www.chictr.org.cn; registration date: 12/29/2024) (retrospectively registered).

Keywords Cognitive behavioral therapy, Social learning, Major depressive disorders, Trust game, Computational modeling

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Background

Patients with major depressive disorders (MDD) experience psychosocial dysfunctions, which tend to persist even after symptom recovery [1]. It is estimated that 30% patients suffer from severe long-term social impairments and 10% patients suffer from permanent social impairments for more than 20 years [2], which constitute an important source of indirect costs to the society [3]. Social dysfunctions would exacerbate clinical symptoms progressively with time [4]. Given its relevance with clinical symptom exacerbation, there is a need to understand its emergence mechanisms, which facilitates development of intervention strategies to reduce its emergence.

Emerging reinforcement learning theories in recent years have identified the abnormal learning capability in social contexts as one critical driver of social dysfunctions among MDD patients [5, 6]. Learning impairments could provide additional explanations above and beyond previously identified shaping factors of social dysfunctions (e.g., emotion dysregulations, attentional biases to negative stimuli, and theory of mind deficits) [3] to explain why patients' abnormal social behavior continuously emerge in dynamic social interactions. Interventions on learning capabilities in social contexts is thus pivotal for social rehabilitation.

Abnormal learning capabilities in social contexts

Successful social interactions rely on learning capabilities. This involves a reinforcement learning (RL) process, in that individuals adjust their inference on others' traits, motivations, attitudes, and form beliefs about others based on feedback (observation histories). Based on these beliefs, they select the optimal behavior that could maximize gain in a social context [7, 8]. In the following paragraphs, we first review abnormal learning patterns in social contexts in depressive individuals in previous empirical studies, and then explain how they give rise to negative inferences towards self and others [6], and in turn lead to social dysfunctions.

Amounting evidence pointed to learning deficits among MDD patients in probabilistic learning tasks, primarily characterized by inadequate learning to positive feedback in the non-social [9, 10] and social domain [11, 12], and excessive learning to negative feedback in the non-social [13] and social domain [14]. More recently, Jin et al. [8] employed RL models and found that MDD patients exhibited inadequate learning to reciprocal outcomes and excessive learning to betrayal outcomes in the investor-role Trust Game (TG), a high ecological validity paradigm to study social interactions. Studies further revealed abnormal neural activities underlying the encoding of positive and negative prediction error (PE). Depressive individuals had abnormal encoding of positive PEs in the midbrain, striatum, orbitofrontal cortex, dorsal anterior cingulate cortex and hippocampus [10, 15–18], and abnormal encoding of negative PEs in the habenula [19].

The two patterns of learning abnormalities, inadequate learning to positive outcomes and excessive learning to negative outcomes, would generate solid negative expectations towards self and others among depressive individuals [6]. Kube et al. [6] postulated that depressive individuals on the one hand, are difficult to adjust negative expectations based on opposing positive evidence due to diminished learning capabilities to rewards, and tend to strengthen negative expectations due to excessive assimilation of negative evidence, eliciting a self-reinforcing negative feedback loop. In line with the viewpoint, Barrett et al. [5] proposed a similar lock-in phenomenon among depressive individuals, in that negative predictions would exacerbate excessive assimilation of negative evidence and prevent exploration of positive counter-evidence. In support of this notion, empirical studies have found an incapability to adjust negative expectations upon receipt of positive evidence among depressive individuals [20–22]. On the other hand, Kube et al. [6] postulated that the positive expectations of depressive individuals are fragile and difficult to maintain because excessive learning of negative evidence could easily reverse positive expectations. Thus, they would lack the immunity to negative disconfirming evidence. Although Kube et al. [21] found no difference in the change of positive expectation facing disconfirming negative evidence between healthy controls and depressive individuals in the domain of personal performance evaluation, no studies to date have directly compared how the two groups differ in assimilation of other-relevant social feedback.

Existing computational modeling studies on both healthy individuals revealed that negative expectations about others would transfer into higher probability of abnormal social behavior (e.g. diminished trust and diminished cooperation), in both model-based learning processes (e.g. others have diminished trustworthiness or diminished reciprocal tendency) [23–25] or model-free learning processes (i.e. the cooperation option has diminished or is valued lower than the non-cooperation option) [26]. Therefore, a critical step to ameliorate social dysfunctions is to break patients' negative expectation towards others by normalizing social learning capabilities.

Learning abnormalities in social contexts and negative schema

Despite robust abnormal learning pattern in social contexts found in depressive individuals, its forming mechanisms are seldomly investigated. Existing theories have posited that negative schema would elicit an attention misallocation process, which in turn elicit abnormal

learning patterns. Specifically, Kube et al. [6] posits that the disregard for positive evidence might be due to lack of expected precision in positive evidence and too much precision placed on negative prior beliefs. This precision misplacement originates from the abnormal top-level misallocation of attentional weight towards lower-level signals [27, 28]. Excessive attention directed towards negative stimuli is further associated with the situational activation of negative schema [29]. Specifically, Beck posited that depressive individuals hold implicit negative schema relevant to self-evaluations, expectancies about the future and the surrounding world [30]. Negative schema would be activated by stressors in the environment congruent with negative schematic belief, which further shapes information processing in the direction of guiding excessive cognitive focus towards negative stimuli in the environment [31]. Thus, reversing the negative schema by interventions is pivotal for normalizing the social learning patterns among depressive individuals.

Cognitive-behavioral therapy (CBT)

Cognitive-behavioral therapy (CBT) is one of the most evidence-based psychological intervention for patients with MDD. Amounting evidence points to its effectiveness in treating depression. According to the most recent review by Cuijpers et al. [32], CBT has a response rate of 42% and a remission rate of 36% in randomized controlled studies, a moderate-to-large effect sizes in differences in depressive symptoms between CBT and control conditions after treatment. In addition, CBT has a comparable effect in the short term and a larger effect in the long term compared to pharmacotherapies [32].

As CBT is built upon Beck's negative triad of depression, the primary target of CBT is to correct the core negative schema that would elicit other abnormal psychological processes (e.g. negative beliefs, depressive symptoms, and bias information processing, etc.). The intervention target of CBT is identical with the hypothesized main cause of social learning abnormalities: negative schema. Despite evaluation on the effectiveness of CBT in normalizing social learning capabilities is lacking, considerable evidence points to its effectiveness in correcting negative schema [33, 34], revealing the potential of CBT to intervene social learning abnormalities among depressive individuals. Taking a step further, it is expected that the treatment response group, compared with the treatment non-response group, will receive greater improvements in social learning capabilities given their greater magnitude in the correction of negative schema and greater reduction in depressive symptoms.

The current study utilizes a CBT intervention program with an ultimate purpose of correcting negative schema among MDD patients. To prompt the progressive discovery and correction of negative schema, the topic schedule would be sequenced in accordance with Beck's cognition model [35]. This model distinguished four key layers of cognitive dysfunctions among depressive individuals, which are negative automatic thoughts, cognitive distortions, dysfunctional assumptions, and beliefs and schemas, from external to internal, respectively. Following this rationale, the program first helps patients establish the connection between thoughts, emotions and behavior. Building upon this, the program then helps patients identify negative automatic thoughts residing at the surface of cognition, cognitive distortions that produce these automatic thoughts, dysfunctional assumptions residing at inner layer which produce cognition distortions, and beliefs and schema residing at the core layer of cognition. The program encourages patients to revise distorted cognition and develop more rational ways of thinking, strengthen positive behavior styles, and develop positive coping strategies to problems.

Due to the relevance of social learning capabilities and the intervention target of CBT (i.e. negative schema), we would like to further investigate whether pre-tretament social learning abnormalities on the behavioral and neural level could serve as a biomarker for CBT treatment effectiveness. Identified biomarkers of CBT treatment effectiveness include inflammatory markers [36], genetic biomarkers associated with low mood [37], blood transcriptomic markers [38], resting-state neuroimaging biomarkers [39] and so on. Reward PEs has high reliability thus could be used as biomarkers in psychopathology [40]. However, only one study found that the neural encoding of reward PE in the right striatum and right amygdala in probabilistic learning tasks could predict treatment responses to CBT among depressed patients [41]. No studies to date has examined the social PE signals in high ecological validity social interaction paradigms, our study aims to fill this vacuum in the current literature. Establishing biomarkers relevant to social learning and its neural activities could complement known biomarkers of CBT.

Objectives

This study has several objectives:

1. Providing evidence for the efficacy of CBT in normalizing learning patterns in social contexts among all patients with MDD and among the treatment-response MDD group.
2. Providing evidence for the efficacy of CBT in normalizing the neural activities associated with learning process among all patients with MDD and among the treatment-response MDD group.
3. Investigating the potential for learning impairments in social contexts as a biomarker for predicting the effectiveness of CBT.

Note that normalizing learning patterns refers to enhancing learning towards positive social feedback, and reducing excessive learning towards negative social feedback. Normalizing the neural activities associated with learning process concerns about the encoding of positive PE and negative PE.

Methods and analysis

Study design

This is a single-centre, single-arm, open-label trial designed to assess the efficacy of CBT in normalizing social learning capabilities among patients with MDD. MDD patients will be enrolled from the Outpatient Department of Beijing Anding Hospital, Capital Medical University via psychiatrists' recommendation about this research project. To explore the extent of deviations from the normal functions in various assessments (e.g. social learning capabilities, symptoms, and negative beliefs, etc.) among patients pre and post treatment, we also included a healthy control group assessed only at baseline. Sixty healthy controls will be recruited in Beijing via online advertisements and neighborhood postings. The two groups would not exhibit significant differences in the above demographic variables. All participants are required to provide written informed consent before enrolment. Patients will be assessed at screening, baseline, and post-treatment. Healthy control will be assessed at baseline. The study has been retrospectively registered at www.chictr.org.cn (Registration number: ChiCTR2400094841; registration date: 12/29/2024). The first participant was recruited on May 24th 2023. Recruitment of new patients is expected to complete between 2023-05-24 and 2025-06-30. Data collection of all endpoint assessments is expected to be finalized by the end of 2025. There were no difficulties in recruitment and inclusion of eligible patients, or implementation of CBT treatments within the first months of recruiting and subsequent recruiting. Figure 1 shows an overview of the study design.

Study population and eligibility criteria

MDD patients will be screened for eligibility by trained psychiatrists according to the followed inclusion and exclusion criteria. Patients who meet the termination criteria in the midst of experiment or treatment will be excluded. We expect to recruit a total of 60 eligible patients.

Inclusion criteria

(1) Diagnosis of Major Depressive Episode in accordance with the DSM-IV criteria, confirmed by the MINI-International Neuropsychiatric Interview (MINI);
(2) No use of antidepressant medications for at least 14 days prior to enrollment;
(3) Both biological parents must be of Han ethnicity;
(4) Age between 18 and 45 years, with both males and females eligible;

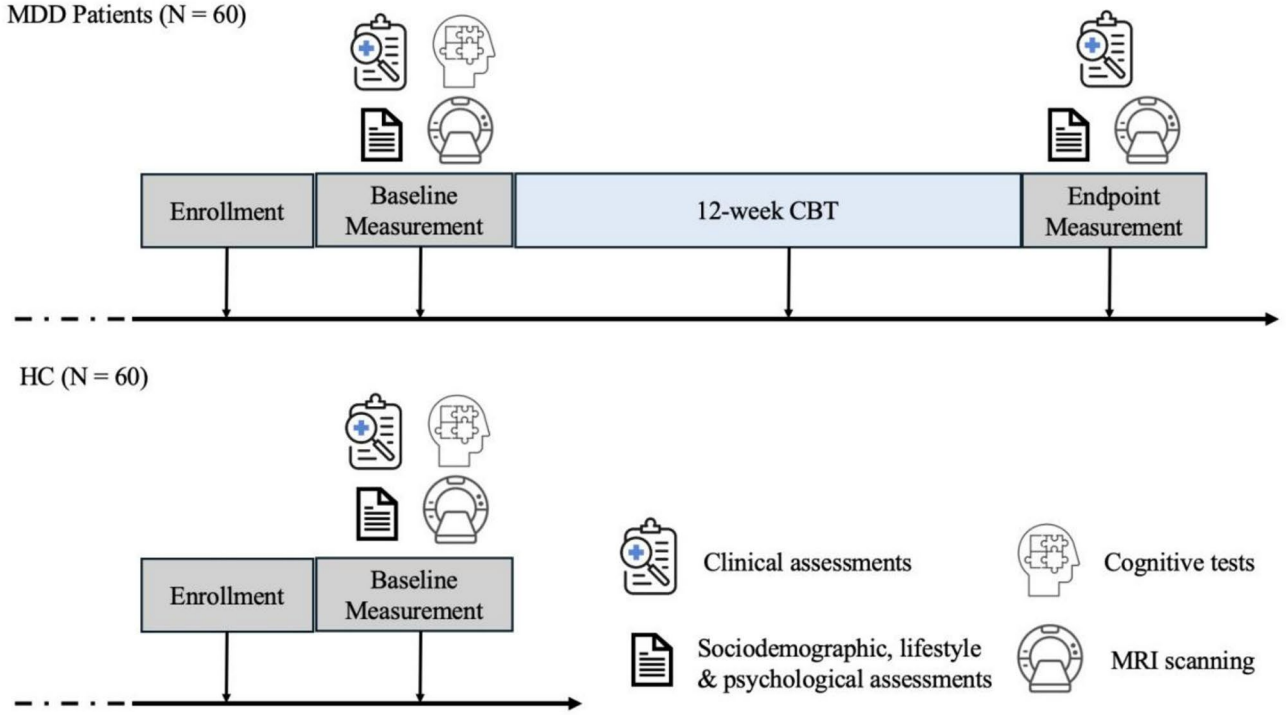

Fig. 1 Trial design and flow of MDD patients and HC

(5) Education level of junior high school or higher;
(6) The patient must sign a written informed consent form.

Exclusion criteria

(1) Individuals with psychotic disorders, bipolar disorders or other disease-accompanied psychiatric disorders that meet the DSM-IV diagnostic criteria;
(2) Individuals with a history of diagnosed organic brain diseases or chronic serious physical illnesses requiring treatment, such as diabetes, thyroid diseases, hypertension, heart diseases, etc. that needs medication;
(3) Patients with a history of manic or hypomanic episodes;
(4) Patients with a history of alcohol or substance dependence and acute intoxication;
(5) Women who were pregnant, breastfeeding, and intend or may become pregnant during the trial;
(6) Individuals who have received electroconvulsive therapy (ECT) in the 6 months prior to enrollment;
(7) Individuals with color blindness, color weakness, deafness, stuttering, or other conditions that may affect neurocognitive testing;
(8) Individuals with implanted cardiac pacemakers, cochlear implants, or any other metallic foreign bodies, or those with other contraindications for magnetic resonance imaging (MRI);

Termination criteria

(1) Individuals who withdraw their informed consent;
(2) Individuals deemed by the researcher to require withdrawal due to safety concerns or other factors;
(3) Individuals who score ≥ 6 on the Young Mania Rating Scale (YMRS), ≥ 3 on the suicide item of the Hamilton Depression Rating Scale-17 (HAMD-17), or meet any other exclusion criteria during the course of the study.

The eligibility of healthy patients will be screened by trained psychiatrists according to the following inclusion and exclusion criteria. Healthy controls who meet the termination criteria in the midst of experiment will be excluded. Trial design and flow of patients and healthy controls is shown in Fig. 1.

Inclusion criteria

(1) Age between 18 and 45 years, with both males and females eligible;
(2) Education level of junior high school or higher;
(3) Both biological parents must be of Han ethnicity;
(4) The individual must sign a written informed consent form.

Exclusion criteria

(1) Individuals diagnosed with mental disorders that meet DSM-IV Axis I criteria as confirmed by the MINI-International Neuropsychiatric Interview (MINI);
(2) Individuals who have previously taken psychiatric medications or received psychological counseling;
(3) Individuals with a history of consciousness disorders, schizophrenia, or other mental illnesses that involve personality changes;
(4) Individuals with a family history of mental disorders that meet DSM-IV Axis I criteria within three generations;
(5) Individuals with a history of diagnosed organic brain diseases or chronic serious physical illnesses requiring treatment, such as diabetes, thyroid diseases, hypertension, heart diseases, etc.;
(6) Individuals with a history of alcohol or substance dependence and acute intoxication;
(7) Women who were pregnant, breastfeeding, and intend or may become pregnant during the trial;
(8) Individuals with color blindness, color weakness, deafness, stuttering, or other conditions that may affect neurocognitive testing;
(9) Individuals with implanted cardiac pacemakers, cochlear implants, or any other metallic foreign bodies, or those with other contraindications for magnetic resonance imaging (MRI).

Termination criteria

(1) Individuals who withdraw their informed consent;
(2) Individuals deemed by the researcher to require withdrawal due to safety concerns or other factors.

Sample size

The sample size is calculated using G*Power based on paired sample t-test. Referring the minimal effect size of Cohen's d = 0.37 in the effect of CBT treatment on learning capabilities estimated by reinforcement learning models reported by Brown et al. [42], we assume a comparable small effect size (Cohen's d = 0.37) of CBT treatment on the direction of improving social learning capabilities. Setting the significance level at 0.05 (single-tail), and the statistical power at 0.80, the estimated total sample size is 47 patients. Considering a potential drop rate of approximately 15% and the occurrence of potential head motions of 5% which influence the quality of neuroimaging data in both baseline and endpoint data

collection, we aim at 60 MDD patients. Correspondingly, we aim at 60 healthy controls.

CBT intervention

Following the commonly used framework, settings, and structure of standard CBT sessions, and taking into account the practical circumstances of this study, the protocol consists of 12 1-hour treatment sessions, held twice a week for Session 1–4, once a week for Session 5–10, and once for two weeks for Session 11–12, for a total duration of 12 weeks. The treatment is divided into three phases: Phase 1 (Sessions 1–2): This initial phase focuses on building the therapeutic relationship and assessment. Phase 2 (Sessions 3–10): This treatment phase aims to improve the patient's symptoms and address core issues. Key contents include emotional recognition, behavioral activation, learning the cognitive triangle, identifying automatic thoughts and schemas, cognitive restructuring, and problem-solving. Phase 3 (Sessions 11–12): This concluding phase focuses on relapse prevention and closure. Each treatment session is structured as follows: (1) reviewing and discussing the previous session's homework; (2) setting the agenda for the current session; (3) completing targeted tasks; (4) assigning homework for the next session; (5) providing feedback.

Data collection

An overview of data collection plans for all visits is listed in Table 1. MDD are measured at baseline and end post (i.e. pre and post treatment), whereas HC are only measured at baseline.

Sociodemographic information and lifestyle habits

At baseline, sociodemographic data will be collected using a structured self-report questionnaire. This information will include the participant's birth date, gender, height, weight, marital status, education level, employment status, household income, and living area. Also, all participants will self-report lifestyle habit, such as smoking, drinking and drug abuse.

Table 1 An overview of data collection plans for all visits for MDD and HC

Category	Measurement name	Group	Field visits for MDD	
		(MDD/HC)	Baseline	Endpoint
Sociodemographic information Lifestyle habits	birth date, sex, height, weight, marital status, education level, employment status, household income, and living area	Both	x	
	smoking, drinking and drug abuse	Both	x	
Clinical assessments	HAMD (psychiatrist measure)	MDD	x	x
	HAMA (psychiatrist measure)	MDD	x	x
	YMRS (psychiatrist measure)	MDD	x	x
	PHQ-9	Both	x	x
	GAD-7	Both	x	x
	BDI-II	Both	x	x
	Psychopathology histories	Both	x	
	Family histories of psychiatric diagnoses	Both	x	
Cognitive assessments	MCCB– processing speed	Both	x	
	MCCB– executive control	Both	x	
	MCCB– working memory	Both	x	
	CPT	Both	x	
Psychological assessments	CFI	Both	x	x
	CBQ	Both	x	x
	DAS	Both	x	x
	LOT-R	Both	x	x
	TIP	Both	x	x
	SHAPS	Both	x	x
	ATQ-N	Both	x	x
	CERQ	Both	x	x
Experiment	Door Game + rTG	Both	x	x
Neuroimaging	T1- and T2-weighted structural imaging, rs-fMRI, Fieldmap scanning, task-based fMRI	Both	x	x

Note: abbreviations: HAMD: Hamilton Depression Rating Scale-17; HAMA: Hamilton Anxiety Rating Scale; YMRS: Young Mania Rating Scale; PHQ-9: Patient Health Questionnaire-9; GAD-7: General Anxiety Disorder-7; BDI-II: Beck's Depression Inventory-II; MCCB: MATRICS Consensus Cognitive Battery; CPT: continuous performance test; CBQ: Cognitive Biases Questionnaire; DAS: Dysfunctional Attitude Scale; LOT-R: Revised Life Orientation Test; TIP: Trust in People; SHAPS: Snaith-Hamilton Pleasure Scale; ATQ-N: Automatic Thoughts Questionnaire-Negative; CERQ: Cognitive Emotion Regulation Questionnaire; rTG: repeated Trust Game

Clinical assessments

Two independent trained psychiatrists undergoing consistency training to eliminate evaluation biases will administer the HAMD-17 [43], the Hamilton Anxiety Rating Scale (HAMA) [44] and the YMRS [45] at baseline to assess clinical symptoms for all MDD patients. All participants will finish self-report measures of depressive and anxiety symptoms, including the Patient Health Questionnaire-9 (PHQ-9) [46], General Anxiety Disorder-7 (GAD-7) [47], and the Beck's Depression Inventory-II (BDI-II) [48]. All MDD patients will self-report when current and first onset occurs, and the number of MDD onsets. All MDD patients will self-report family histories of psychiatric diagnoses.

At the endpoint, two independent trained psychiatrists (YJ and FS) will administer the HAMD-17, HAMA and YMRS. All participants will finish self-report measures of depressive anxiety symptoms (i.e. PHQ-9, GAD-7, BDI-II) at the endpoint.

The psychometric properties of the Chinese version of HAMD-17 [49], HAMA [50], YMRS [51], PHQ-9 [52], GAD-7 [53], and BDI-II [54] have been validated in previous studies.

Cognitive assessments

At baseline for all participants, we will administer three cognitive tests from the Chinese version of the MATRICS Consensus Cognitive Battery (MCCB) [55] and the Continuous Performance Test (CPT) [56] to assess four cognitive domains: speed of processing, executive control, working memory, and attention. The psychometrics properties of MCCB are well-established, with evidence for its test-retest reliabilities and cross-cultural consistencies [55]. The psychometric properties of the Chinese version of MCCB have also been validated in previous studies [57].

Psychological assessments

All participants will complete self-reported measures of Cognitive Flexibility Inventory (CFI) [58], Cognitive Biases Questionnaire (CBQ) [59], Dysfunctional Attitude Scale (DAS) [60], Revised Life Orientation Test (LOT-R) [61], Trust in People (TIP) [62], Snaith-Hamilton Pleasure Scale (SHAPS) [63], Automatic Thoughts Questionnaire-Negative (ATQ-N) [64], and Cognitive Emotion Regulation Questionnaire (CERQ) [65] at baseline. MDD patients will complete the above psychological measures again at the endpoint after the 12-week treatment. The psychometric properties of the Chinese version of CFI [66], CBQ [67], DAS [68], LOT-R [69], TIP [70], SHAPS [71], ATQ-N [72] and CERQ [73] have been validated in previous studies.

Experiment

Overview All participants will finish the experiment at baseline. MDD patients will conduct the experiment again after the 12-week treatment. The experiment contains the Door Game and the rTG programmed in Eprime2.0. Each participant will be matched with six partners, including two with good/neutral/bad initial expectations each. After being matched with a partner, participants will first complete four rounds of the Door Game with the partner and then proceed to engage in ten rounds of the rTG with the same partner. We first manipulate participants' initial expectations of their partners (good/neutral/bad) via the Door Game. We aim to investigate how participants' initial expectations will be altered by social learning towards the reciprocal behaviors of the partners in the subsequent rTG. A reinforcement learning model will be used to characterize the learning process. The experiment procedure is shown in Fig. 2.

Door Game The Door Game is adapted from Van der Biest et al. [74]. In each round of the game, participants choose between a yellow door and a blue door to open. While opening one of them leads to a reward of 50 yuan, opening the other leads to a loss of 50 yuan. Before opening the door in each round, participants will receive advice from their partner regarding which door to open, and they can choose to follow or disregard this suggestion. After making their choice, participants will receive feedback on their earnings or losses, allowing them to determine whether the partner's advice was correct or not after each round. The experiment manipulates the number of correct cues provided by the partner across four rounds of the open-door game to manipulate participants' initial expectation of the partner. Partners with a good/neutral/bad initial expectation will offer four/two/zero correct cues, respectively.

rTG In the rTG, participants engage in 10 rounds of play with the same partner. At the beginning of each round, participants start with 20 yuan and then choose between investing 4 yuan and 16 yuan to their partner. The invested amount is multiplied by 4 when transferred to the partner, who may choose to return half of the money received or not return any at all. The investment-return payoff matrix is illustrated in Table 2. Note that in the case of high investment (i.e. investing 16 yuan), there are simultaneously high rewards (return from the partner) and high risks (non-return by the partner). Participants need to assess the trustworthiness of the partner by learning about the return behavior observed in the previous round in order to inform their investment strategy for the next round, which essentially entails a social learning process.

External validity control Participants will be informed at the beginning that they are about to engage in a

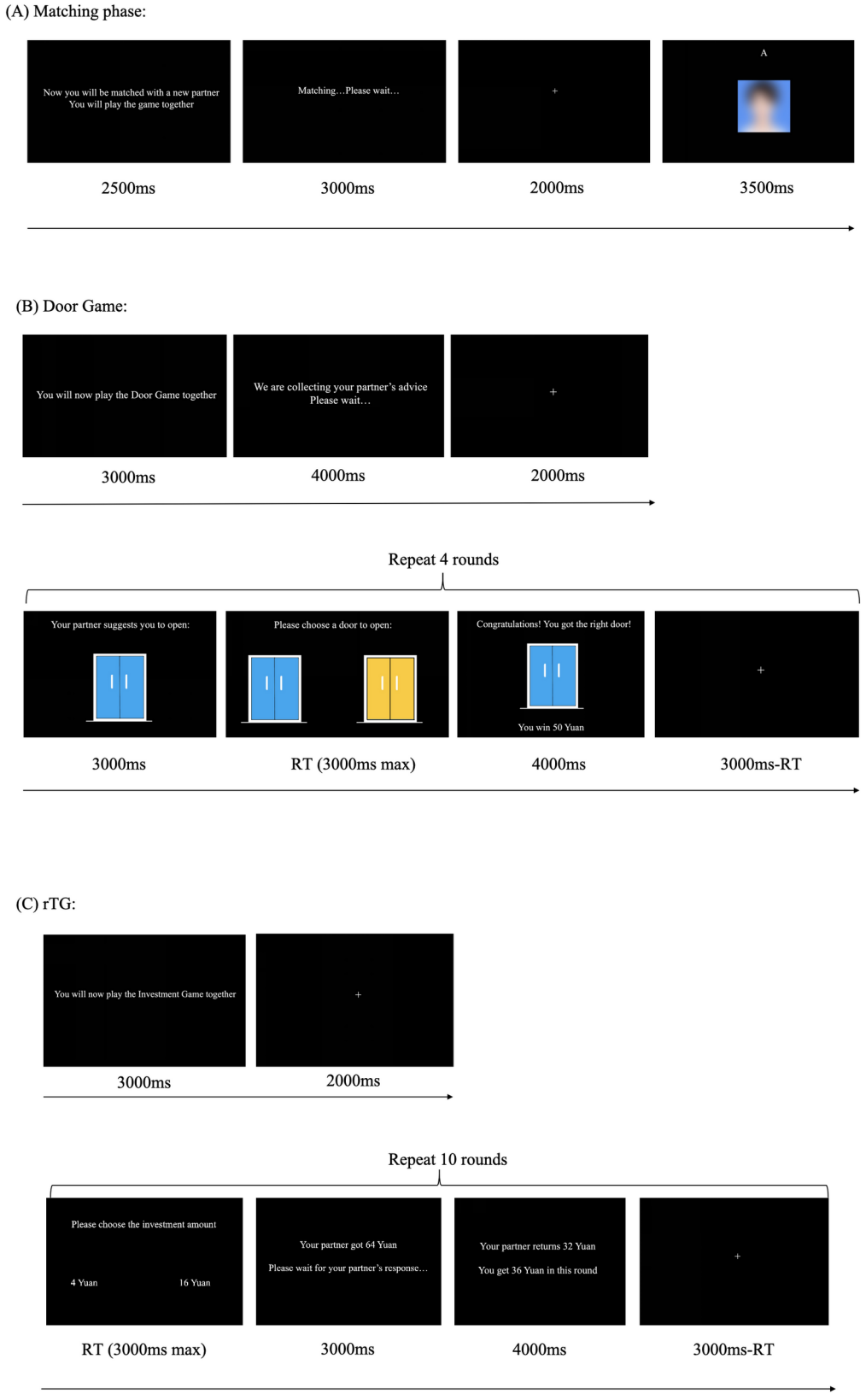

Fig. 2 Experiment procedure. (**A**) Matching phase. (**B**) The Door Game. (**C**) rTG

Table 2 The investment-return payoff matrix for the participant

	Trustee (Partner)	
Trustor (Participant)	**Return (Half)**	**Non-return**
High-invest (16 yuan)	36 yuan	4 yuan
Low-invest (4 yuan)	24 yuan	16 yuan

real-time interactive game, although the responses of the partners are actually computer-programmed. Multiple steps will be taken to enhance participants' belief in engagement in real-time interaction with other people. First, we provide the technical details in the instruction that real-time interaction is enabled by embedding a specific Visual Basic module in E-prime. Second, the experimenter will request a photo from the participants one day before the experiment, informing them that the photo will be processed with Gaussian blur and will be presented to their partners the next day. Participants will also be informed that they will see a blurred version of the partners' photo during the experiment. Third, the actual money earned during the experiment will be converted into a monetary reward (ranging from 0 to 10 yuan), and so will be their partners, so that participants have a motive for social learning about partners to maximize their earnings and influence partners' earnings.

Neuroimaging data

This study utilizes a Siemens Magnetom Prisma 3.0T magnetic resonance scanner at Beijing Anding Hospital, Capital Medical University, to acquire the high-resolution 3D structural MRI, fieldmap images, resting state fMRI data and task fMRI data from all participants. Neuroimaging data will be acquired for all participants at baseline and for MDD patients at the endpoint after the 12-week treatment.

The 3D high-resolution structural MRI will be obtained using a 3D-FSPGR sequence in the sagittal orientation with the following parameters: repetition time (TR) = 10 ms, echo time (TE) = 4 ms, matrix = 256 × 192, field of view (FOV) = 240 mm × 240 mm, 144 slices, slice thickness = 1 mm, and flip angle = 12°. This sequence lasts for 6 min.

Fieldmap images will be acquired using a dual-echo gradient-echo sequence, with parameters set to: TR = 0.52 s, TE = 4.92/7.38 ms, slice thickness = 3.5 mm, slice spacing = 0.7 mm, voxel size = 3.13 × 3.13 × 4.2 mm^3, and flip angle = 60°. This sequence generates one magnitude image and two phase images for correcting magnetic field inhomogeneities. This sequence lasts for 1 min.

The resting-state and task fMRI data will be acquired using a gradient echo-planar imaging (EPI) sequence in the axial orientation, with the following parameters: TR = 2000 ms, TE = 30 ms, FOV = 240 mm × 240 mm, acquisition matrix = 64 × 64, flip angle = 90°, number of slices = 33, slice thickness = 3.5 mm, and slice spacing = 0.7 mm. The resting-state sequence lasts for 8 min. The task-state sequence comprises two equal-length 10-minute sessions, with a 30-second break between the sessions. During the task fMRI scanning, participants will finish the Door Game and the rTG task.

Outcomes

Primary outcome

Primary outcomes are changes in social learning capabilities of patients with MDD between the baseline and the endpoint. Specifically, referring to Jin et al. [8], variations of Rescorla-Wagner (RW) RL models will be built to depict the social learning process. Key processes in the baseline RW-RL model include calculation of the prediction error (formula (1)), valuation updates (formula(2)), and action selection (formula (3)). The RW model speculates that the agent adjusts the expected utility associated with sharing the money with the partners V_s based on how much reward r_s she/he obtains from the environment, and that the agent maximizes her/his reward by reducing the discrepancy (the prediction error δ) between the actual reward and the expected utility (formula (1)). The learning rate α, a free parameter in the model, weights the amount of prediction error used to update the expected utility (formula(2)). The investment behaviors at the next time point t + 1, denoted by the probability of investment $P_s(t+1)$, is then given a softmax function of (1) the expected utility of trust behaviors $V_s(t+1)$, (2) the expected utility of not making an investment and keeping the money to oneself $V_k(t+1)$, and (3) a free parameter τ, which denotes the preference for exploration versus exploitation of the advantaged option (formula (3)).

$$\delta_t = r_s - V_s(t) \quad (1)$$

$$V_s(t+1) = V_s(t) + \alpha\,\delta \quad (2)$$

$$P_s(t+1) = \frac{exp\left(\frac{V_s(t+1)}{\tau}\right)}{exp\left(\frac{V_s(t+1)}{\tau}\right) + exp\left(\frac{V_k(t+1)}{\tau}\right)} \quad (3)$$

In model variations, different learning rates will be specified for the learning rate for gains (i.e. α_G) and losses (i.e. α_L). Social learning capabilities include both the learning rate for gains (i.e. α_G) and losses (i.e. α_L). The goodness of fit will be evaluated by fitting models to behavioral data. Free parameters will be derived within the optimal model.

Secondary outcomes

Secondary outcomes are changes in depressive symptoms measured by the HAMD-17, PHQ-9 total scores and the BDI-II total scores, changes in anxiety symptoms

measured by the HAMA total scores and the GAD-7 total scores, and the changes in the psychological functions (i.e. cognitive flexibility measured by CFI, biased cognitions measured by CBQ, dysfunctional attitudes measured by DAS, optimism-pessimism measured by LOT-R, general trust tendencies measured by TIP, anhedonia measured by SHAPS, negative automatic thoughts measured by ATQ-N, and emotional regulation capabilities measured by CERQ) in the baseline and the endpoint.

Note that clinical efficacy is defined as the reduction rate, i.e. a reduction of HAMD-17 total scores ≥ 50% from baseline by the endpoint. Patients could be divided into the response/non-response treatment group according to this criterion.

Adherence

Psychotherapists in this study will undergo advanced training and supervision. Psychotherapists will be screened with a background in psychology and extensive therapeutic experience. Psychotherapists have all completed the China-CBT training series, which covers CBT for depression, schizophrenia, anxiety disorders, panic disorder, social anxiety, and obsessive-compulsive disorder. Before the treatment begins, psychotherapists will undergo uniform training for this CBT intervention program, which includes manual training, emergency plans, discussions, and other activities. After treatment starts, weekly group supervision will be held, comprising all members of the therapist group, with the most senior therapist among the serving psychotherapists as the group leader (i.e. PW). Additionally, every two weeks, the therapists will receive supervision from a senior domestic CBT expert Prof. ZL. Should any emergencies arise during the treatment process, immediate assistance from senior CBT supervisors in China will be available. Each case receiving CBT will undergo at least one supervision session, which will include case reporting, open discussions, case analysis, role-playing between therapist and patient, and feedback on therapy recordings.

Data management and monitoring

The multidimensional data, covering clinical data, experimental data, and fMRI data, will be stored in the established data platform in the Beijing Anding Hospital. We have established a standardized disease-specific cohort study dataset frames and data elements according to the Clinical Data Interchange Standards Consortium (CDISC), Standard Data Tabulation Model (SDTM) and Chinese nation or industry terminology and specifications. Each participant is assigned with a unique identification number, which ensures data confidentiality. All experimenters will collect data according to standard operating procedures (SOP). Quality control will be implemented at every step in the data collection process. Data platform will have additional backups and recovery functions, which ensures data security.

All principal investigators, co-investigators, and approved research team members involved in the study will have access to the final trial dataset for the purposes of analysis and reporting. Access will be granted upon completion of the trial and following a thorough data quality review. All investigators and personnel with access to the dataset will be required to sign confidentiality agreements that specifically prohibit the unauthorized disclosure of any identifiable information or data related to the trial participants. If applicable, data use agreements may be established with external researchers or institutions who may seek access to the dataset for collaborative research purposes. These agreements will define the scope of access, required approvals for data usage, limitations on data sharing, and stipulations on the publication of results arising from the use of the data.

Data analysis

Clinical data and psychological measurements

To explore the effect of CBT treatment on the primary outcome (i.e. social learning capabilities) and secondary outcomes, paired sample t-tests will be performed to examine the changes in social learning capabilities and other clinical and psychological assessments pre and post treatment. To explore potential deviations of social learning capabilities and other clinical and psychological states from normal population before treatment, independent sample t-tests will be performed to compare the baseline between-group (MDD vs. HC) differences on clinical and psychological measurements. To explore whether patients have fully recovered social learning capabilities, independent sample t-tests will be performed to compare the differences between post-treatment MDD patients and baseline HC on clinical and psychological measurements.

The recovery rate with respect to HAMD-17 total scores reduction will be calculated for each MDD patient, dividing each of them into the response/non-response treatment group. Mixed ANOVAs will be performed to explore the effect of treatment effectiveness (response/non-response) and time (pre/post treatment) on the primary outcome (i.e. social learning capabilities) and other clinical and psychological measurements.

Experimental data

Computational modeling Candidate reinforcement learning models will be built to depict participants' (as trustors) social learning process in the rTG. These reinforcement learning models differ in whether differential learning rates will be specified for gains versus losses rounds [8], conditions in which partners have different

initial expectations, and whether the model denotes a model-based learning (i.e. trustworthiness is evaluated) or a model-free learning (i.e. a Rescorla-Wagner RL process) [8, 23]. Model estimation will be conducted with the hierarchical Bayesian estimator in Rstan, which enables a simultaneous estimation of group- and individual-level parameters. Model comparison will be conducted based on the Leave-one-out information criteria (LOOIC) and the parsimony principle. Posterior prediction check, model recovery and parameter recovery will be performed for the optimal model to prove its robustness. Within the optimal model, group- and individual-level parameters will be extracted from the model for further analyses.

Baseline abnormalities of social functions Generalized mixed effects model (GLMM) will be used to explore the effects of group type (MDD/HC) and initial expectations about partners on the trust behavior indexed by the binomial outcome of high versus low investment in the baseline, and on the social learning processes indexed by the learning rates for gains and losses estimated from the RL models [8].

Treatment effects on social functions Among MDD patients, we will then use GLMM to explore the effects of treatment effectiveness (response/non-response), time (pre/post treatment), and initial expectations about partners on the trust behavior and the learning rate.

Endpoint abnormalities of social functions For MDD patients' endpoint data and HC baseline data, we will use GLMM to explore the effects of group type (MDD/HC) and initial expectations about partners on the trust behavior and the learning rate.

Neuroimaging data

1st level GLM First-level general linear model (GLM) analyses will be conducted to search for brain regions that encode PE for each individual. Specifically, a parametric analysis is used to identify brain regions modulated by PE, which essentially relates to social learning. As learning occurs at the time of feedback display, we specify this event as our interested event. We include the following main events: partners' suggestions display (Door Game), door selection (Door Game), feedback display (Door Game), decision (rTG), wait for partners' return (rTG), and the feedback display (rTG) in a one-factorial (partner expectation type) design matrix constructed by convolving each event onset with a canonical hemodynamic response function. The PE for each trial extracted from the computational model will be entered into the GLM as a parametric regressor at the feedback display event in the rTG. Residual effects of head motion will be accounted for by including the estimated six motion parameters for each participant as covariates.

2nd level GLM Aggregating 1st level GLMs, we will first conduct independent sample t-test to compare the between-group (MDD/HC) difference in the neural encoding of PE at baseline. We will then conduct mixed ANOVA to explore the effects of treatment effectiveness (response/non-response) and time (pre/post treatment) on the neural encoding of PE. We will lastly conduct independent sample t-test to compare the differences between post-treatment MDD patients and baseline HC on the neural encoding of PE.

Behavior-brain-psychological states association analyses For brain regions whose encoding of PE showing a significant between-group difference or treatment effect, we investigate the relationship between their mean regional activation and psychological state measures, and potentially the mediation effect of psychological state measures between group/treatment and neural activations.

Ethnics and dissemination

This study has obtained approval from the Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences in September 2021 (Protocol number #H21106), and the Institutional Review Board of the Beijing Anding Hospital (Protocol number #2022 (33)), in accordance with the Declaration of Helsinki. This study has been registered in the China Clinical Trial Registry (Protocol registration number: ChiCTR2400094841; registration date: 12/29/2024). All findings will be disseminated via peer-reviewed articles of scientific journals and contributed to both national and international conferences.

Consent to participate

During the initial contact, all prospective participants will be provided with comprehensive information about the study, along with standardized participant information sheets. At the screening stage, research associates from the respective study center will obtain voluntary written informed consent from each participant regarding their involvement in the study, as well as the storage, evaluation, and transfer of study-related data. Participants have the right to withdraw their written consent at any time without the need to provide a reason. Should a participant choose to withdraw their consent, they will have the option to decide whether their data should be deleted or destroyed, or if it may be used in anonymized form for this research project.

Patient and public involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Safety/harms

Previous studies have revealed little side effects for evidenced-based psychotherapies [75]. Adverse events (AEs) (e.g. private/occupational stress or patient-therapist relationship, etc.) and serious adverse events (SAEs) (e.g. severe events requiring medicate treatments or with potential permanent damage, etc.) will be screened for every treatment session. AEs will be reported to the principal investigator (YJ and YZ), and SAEs will be reported to the independent experts. Data monitoring will be conducted by a clinical monitor from the Beijing Anding Hospital to ensure clinical data in adherence to the study protocol, data quality control and to ensure patients' safety. Termination will be implemented in the following circumstances: (1) suicidal behaviors; (2) physical health is at-risk; (3) occurrence of SAE/AE with incompatible therapeutic implications; (4) informed consent withdrawal.

Discussion

Social function impairments among MDD patients, characterized by social withdrawal and powered by social learning abnormalities, tend to persist for years, yet the rehabilitation is unsatisfying. The current study aims to explore the effect of CBT in normalizing social learning process and its neural activities among MDD patients with a single-arm clinical trial. This study has two strengths. First, in contrast to previous studies which uses self-report measures of psychosocial functions (Matsunaga, Okamoto, Suzuki, 2010), this study adopts a high ecological validity social interaction paradigm (i.e. rTG) to evaluate potential improvements of social function and its relevant neural activities pre- and post-CBT treatment. Second, this study uses computational modeling to operationalize social learning capabilities and model-based fMRI analyses to identify the neural encoding of PE, which enables comparison on learning capabilities and neural activities between pre and post treatment among treatment response versus treatment non-response group. The current study also contributes to understanding psychosocial biomarkers of CBT treatment effectiveness in reducing depressive symptoms. By doing so, this study can diversify biomarkers of CBT treatment, as identified biomarkers primarily reside in the inflammatory, genetic, and blood transcriptomic category.

Abbreviations

MDD	Major depressive disorder
HC	Healthy control
CBT	Cognitive behavioral therapy
fMRI	Function magnetic resonance imaging
RL	Reinforcement learning
PE	Prediction error
MINI	MINI-international neuropsychiatric interview
ECT	Electroconvulsive therapy
HAMD	Hamilton depression rating scale-17
HAMA	Hamilton anxiety rating scale
YMRS	Young mania rating scale
PHQ-9	Patient health questionnaire-9
GAD-7	General anxiety disorder-7
BDI-II	Beck's depression inventory-II
MCCB	Matrics consensus cognitive battery
CPT	Continuous performance test
CBQ	Cognitive biases questionnaire
DAS	Dysfunctional attitude scale
LOT-R	Revised life orientation test
TIP	Trust in people
SHAPS	Snaith-hamilton pleasure scale
ATQ-N	Automatic thoughts questionnaire-negative
CERQ	Cognitive emotion regulation questionnaire
rTG	Repeated trust game
RW	Rescorla-wagner
CDISC	Clinical data interchange standards consortium
STDM	Standard data tabulation model
SOP	Standard operating procedures
LOOIC	Leave-one-out information criteria
GLMM	Generalized mixed effects model
AE	Adverse event
SAE	Serious adverse event

Supplementary Information

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Supplementary Material 1

Author contributions

YJ: conceptualization, methodology, software, investigation, formal analysis, validation, data curation, writing– original draft, visualizationSZ: conceptualization, methodology, validation, resources, writing– review & editing, supervision, project administrationPW: conceptualization, methodology, validation, resources, writing– review & editing, supervision, project administrationFS: conceptualization, methodology, investigation, data curation, writing– review & editingXW: conceptualization, investigation, resources, writing– review & editingYW: conceptualization, resources, writing– review & editingQC: conceptualization, investigation, resources, writing– review & editingJZ: conceptualization, investigation, resources, writing– review & editingFY: conceptualization, investigation, resources, writing– review & editingJZ: conceptualization, validation, visualization, writing– review & editingZL: conceptualization, resources, supervision, writing– review & editingYZ: conceptualization, methodology, software, validation, resources, writing– review & editing, supervision, project administration, funding acquisition.

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Data availability

Data and materials will be available upon reasonable requests to corresponding authors.

Declarations

Ethics approval and consent to participate

This study obtained approval from the Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences in September 2021 (Protocol number #H21106), and the Institutional Review Board of the Beijing Anding Hospital (Protocol number #2022 (33)), in accordance with the Declaration of Helsinki. All participants are required to provide written informed consent before enrolment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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