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The THINC-it tool: temporal sensitivity to change over time

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Abstract

Introduction Cognitive dysfunction is believed to be among the core features of Bipolar Depression(BD-D). However, its evaluation and available treatments are limited. Here, we conducted a longitudinal follow-up clinical trial using the THINC-it tool to evaluate temporal sensitivity to change over time in cognitive function among patients with bipolar depression from a Chinese cohort. It is helpful to verify whether the scale can continuously and reliably measure cognitive function in different time points and reduce the measurement error caused by time factors. Hope our findings could provide insights into the significance of the THINC-it tool as an iterative clinical cognitive evaluation tool.

Methods A total of 120 patients with bipolar depression(40 males and 80 females, respectively) alongside 100 healthy controls(23 males and 77 females, respectively) were recruited in the study. All participants were interviewed for 8 weeks, using the 17-item Hamilton Depression Rating Scale (HAMD-17) and the Young Mania Rating Scale(YMRS). The primary dependent measure was the previously validated THINC-it tool, followed by psychometric analysis.

Results Repeated measures of the THINC-it tool at baseline, one-week, and eight-week periods were conducted after controlling for age, gender, and education effects. Results from the general linear model revealed no significant time differences in variances($P > 0.05$). Similarly, adjusting for confounding factors (age, gender, education, and HAMD-17 scores), results from the longitudinal analysis showed that there were no significant differences in cognitive impairment over time($P > 0.05$). However, we found significant differences between BD-D and Healthy Control(HC) groups with regards to Spotter, Codebreaker, Trails, Perceived Deficits Questionnaire for Depression-5-items(PDQ-5-D), and THINC-it Total composite($P < 0.05$), but not in Symbol Check ($p = 0.191$).

Conclusion These findings indicate that the THINC-it tool effectively detects sensitivity to change in groups and maintains stability at times, indicating that it is a feasible and reliable instrument for evaluating cognitive dysfunction in Chinese patients with bipolar depression.

Keywords Bipolar depression, Cognitive impairment, THINC-it

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Introduction

Bipolar Depression(BD-D) refers to a state of depression during disease occurrence, while depressive episodes represent the most challenging phase to treat [1]. Previous studies have shown that the risk of suicide is 20–30 times higher in bipolar depressive episodes than in the general population [2]. Cognitive impairment is a common characteristic of bipolar depression, both at the acute episode and the remission stage, which is also characterized by other symptoms, such as sad mood, anhedonia, hopelessness, and low self-esteem [3, 4]. Furthermore, cognitive deficits, particularly reduced attention/alertness, executive and memory function, are prevalent in patients with bipolar depression. It is well known that the euthymic state and the severity of mood symptoms significantly affect cognition, causing it to improve and worsen throughout the course of the disease. Cognitive impairment negatively affects a patient's quality of life and psychosocial functioning [5], a phenomenon that has made it a major public health concern [6]. Therefore, clinicians are advised to assess cognitive symptoms in BD-D patients routinely.

Some researchers have adopted the Cambridge Neuropsychological Test Automatic

Battery(CANTAB) to detect impairments in executive control, visual-spatial memory, speech learning and memory, spatial cognition, and language working memory of BD-D patients [7]. Some researchers have applied the Wisconsin Card Sorting Test (WCST) to reveal that BD-D patients have a poor understanding memory and executive function [8]. On the other hand, the MATRICS Consensus Cognitive Battery(MCCB) test has been applied to evaluate depressive episodes and identify specific cognitive domains that show greater dysfunction, such as information processing speed, visual learning, and problem-solving [9]. Additional evidence has revealed inconsistent findings regarding the inability to determine the specific domains of cognitive impairment. This contradiction in findings has been attributed to the different cognitive function assessment tools used. Neurocognitive assessment has some limitations in clinical practice, and 37% of cognitive assessment tools in BD-D are utilized. In addition, only a few cognitive assessment tools are really applicable to the diseases of interest (0% for BD-D) [10]. Therefore, identification of a simple and effective screening tool for cognitive function in BD-D patients is imperative to effective management of this condition by mental health workers.

An ideal cognitive screening tool should be easy to operate, effectively identify cognitive and non-cognitive dysfunction, and efficiently quantify the extent of an identified deficit. However, most of the currently used tools are associated with many limitations. For example, although both the Mini-Mental State Examination(MMSE) and Montreal Cognitive Assessment(MoCA) have short scales, are easy to administer, and feasible to implement, their design for evaluating dementia does not confer enough sensitivity to the specific domains of cognitive impairment that commonly affect patients with BD-D. Moreover, Cogstate, WebNeuro, and MCCB involved commercial instruments and were rather complicated, time-consuming, costly, and inappropriate for routine on-site applications. The THINC-integrated tool [11], which was designed and developed by the Brain and Cognition Discovery Foundation, is a simple and easy-to-use cognitive tool for clinical screening of depression. Notably, it is the first cognitive tool used to verify the reliability and validity of unipolar and bipolar depression in Chinese populations [12, 13]. Functionally, the THINC-it tool takes about 10–15 min to perform, and its objective composites comprise an operation tutorial, which helps subjects to independently complete the operation. Through self-management, the tool be used while patients wait for a doctor in the waiting room. For the aforementioned reasons, this tool significantly saves time and medical resources; thus, it is a cost-effective and reproducible strategy for clinical practice. Results from a previous study showed that the THINC-it has excellent reliability and validity [12], although this study adopted a longitudinal design. To date, only a handful of studies have explored the time reliability of the THINC-it tool. It is helpful to verify whether the tool can continuously and reliably measure cognitive function in different time points and reduce the measurement error caused by time factors. In addition, it also is helpful to observe the change trend of cognitive function in individuals with bipolar depression over time, and verify the applicability of the tool in different situations. Therefore, in the present study, we conducted a repeated longitudinal assessment to evaluate this tool's sensitivity to change in adult BD-D patients.

Methods

Participants and selection criteria

This 8-week sensitivity to change study, in which we assessed cognitive function using the THINC-it(ClinicalTrials.gov Identifier: NCT04471454), was conducted in two specialist mental hospitals in Shanghai, China, between February 1 and December 31, 2020. Participants were recruited from patients suffering from bipolar depression through convenience sampling. Subjects were included in the BD-D group if they were between 18 and 65 years old. They were diagnosed with bipolar disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition(DSM-5) by a consensus between two independent senior psychiatrists who had the title of associate chief physician or above. All participants were Chinese and remained in euthymia

throughout the follow-up period, with a disease duration of 5 years or less and fewer than 5 depressive episodes. Patients with taking drugs or undergoing treatments that seriously influenced their cognitive function, and comorbid diseases affecting cognitive impairment, such as severe diabetes, obesity, and long-term alcohol abuse, were excluded.

Healthy controls (HC), including students, nurses, doctors, company employees, and homemakers, were voluntarily recruited from the same districts as the hospitals in Shanghai. Both male and female individuals aged 18–65 years were enrolled. These subjects were included in the study if they did not meet the diagnostic criteria of psychiatric disorders based on DSM-5 criteria. However, they were required not to have any history of neurological diseases, severe or complex physical diseases, alcohol dependence habits, or a family history of psychiatric disorders among their first-degree relatives.

Measurements

Four psychiatrists evaluated cognitive function. Before the evaluation, the consistency of scale scores was tested. No significant differences between raters were found as far as possible, and training-related procedures were adopted to eliminate any errors caused by subjective factors. The assessment was carried out continuously in a quiet environment.

Assessments were performed using the iPad version of the THINC-integrated tool (https://progress.im/en/content/download-thinc-it%C2%AE-tool). This instrument consists of four objective tests: Spotter, Symbol Check, Codebreaker, and Trails, and one subjective test, PDQ-5-D. The tool identifies the leading cognitive domains, such as executive function, processing speed, attention/vigilance, and working memory. To calculate THINC-it composite scores, we assigned the THINC-it tasks a weight of 0.20. Higher total scores denoted more severe cognitive impairment(Table 1).

Table 1 THINC-it tasks and details of primary metrics for each test

THINC-it	Cognitive domains	Measure
Spotter	attention/alertness and executive function	Mean of the log-transformed reaction time (seconds)
Symbol Check	working memory, executive function, and attention/concentration	accuracy of trails
Codebreaker	executive functions, processing speed and attention/concentration	Total number correct
Trails	executive function	Time to complete (seconds)
PDQ-5-D	attention/alertness, memory, and concentration	Sum of items

Abbreviations THINC-it-THINC-integrated tool, PDQ-5-D-Perceived Deficits Questionnaire for Depression–5-items

A 17-item Hamilton Depression Rating Scale (HAMD-17) was used to assess the severity of depression based on the following delimitation scores: total score<7, >17, and >24 for no, mild or moderate, and severe depression symptoms, respectively.

The severity of mania was assessed using a Young Mania Rating Scale (YMRS) based on the following delimitation scores: total scores<5, <12,<19, <29, and ≥30 for no, mild, moderate, severe, and extremely severe mania symptoms, respectively.

Procedure

According to the DSM-5 criteria for each BD-D, patients were diagnosed based on a consensus by specialist psychiatrists. This was accomplished using three steps: Firstly, all sociodemographic information was collected from all patients. Cognitive assessment, which took approximately 30 min, was administered in the following order: PDQ-5-D→Spotter→Symbol Check→Codebreaker→Trails. At the same time, Bipolar depression and HC subjects were requested to complete a full set of cognitive assessments, namely the THINC-it, and clinical scale evaluation(HAMD-17, YMRS) once during the first visit. During the second visit, which happened one week later, we randomly selected 48 patients to undergo the second THINC-it retest. This process took 15 min. The second visit was also used to evaluate estimates of test-retest reliability. Finally, 69 patients completed the THINC-it retest and clinical scale evaluation(HAMD-17, YMRS) at the end of 8 weeks, which took only 30 min. The third visit was used to evaluate estimates of temporal reliability (see flowchart 1).

Statistical analysis

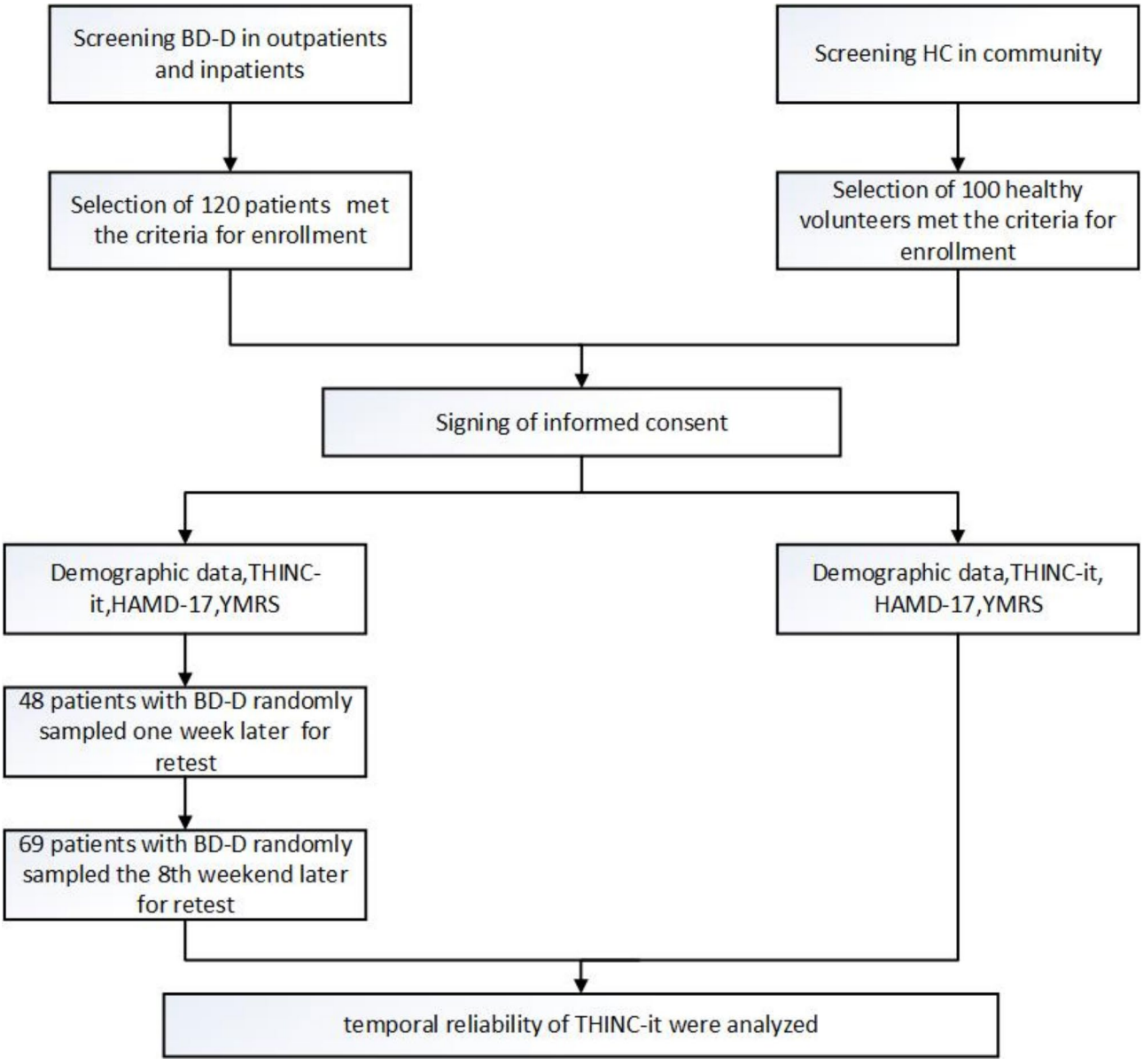
The sample size should be calculated according to Mclntyre [14]. Considering a 20% loss rate, we finally recruited 120 BD-D patients and 100 healthy controls into the study.

Statistical analyses were performed using SPSS 22.0. Primary cognitive impairment was analyzed using a composite z score of the THINC-it, according to Mclntyre [15]. Differences in baseline demographic characteristics between groups were assessed using 2-sided chi-square, Mann-Whitney, and *t*-tests, while longitudinal analysis was performed using a generalized linear model. Data followed by $P<0.05$ were considered statistically significant.

Results

Demographic information of subjects in the present study

A total of 120 patients with Bipolar Depression were recruited across two psychiatric hospitals in Shanghai,



Flowchart 1 Showed the flowchart of recruitment and the follow-up process

with two excluded from the analysis because of failing the screening test and anxiety. Moreover, 100 healthy controls were also recruited. The BD-D group comprised 40 males (33.3%), and 80 females (66.7%), with a mean age of 31.0±10.8 years and average education years of 14.2±2.6 years. On the other hand, the healthy controls comprised 23 males (23%) and 77 females (77%), with a mean age of 31.6±6 years, and average education years of 15.9±3.6 years. At the end of one week, we randomly followed up 48 patients in the baseline period to conduct the THINC-it retest to verify the test-retest reliability of the scale. Finally, we completed follow-up in 69 patients in the 8th week. Conversely, 51 patients did not complete follow-up, of which 11 could not be systematically followed up because of time constraints, and 40 field-normalized patients could not be revisited due to the ongoing COVID-19 pandemic. We found a significant change in years of education between BD-D and HC groups ($p<0.001$)(Table 2).

Interaction effect of time and groups on each THINC-it subtest at baseline, one and eight-week follow-ups

Results from the generalized linear model revealed no significant differences in time after adjusting for age, gender, and education at baseline, one- and eight-week periods. However, we found significant differences between groups in the Spotter, Codebreaker, Trails, PDQ-5-D,

Table 2 Demographic information of subjects in the present study cohort

Characteristic	BD-D (n = 120)	HC (n = 100)	t/χ2	P Value
Age, (years, mean ± SD)	31.0 ± 10.8	31.6 ± 6.0	-0.537	0.592
Gender (n, %)				
Male	40 (33.3)	23 (23.0)		
Female	80 (66.7)	77 (77.0)		
Marital status (n, %)			36.546	< 0.001
Never married	84 (70.0)	40 (40.0)		
Married	27 (22.5)	60 (60.0)		
Divorced	9 (7.5)	0 (0.0)		
Occupation(n, %)			46.756	< 0.001
Unemployed	32 (26.7)	6 (6.0)		
Employment	51 (42.5)	78 (78.0)		
Retired	1 (0.8)	0 (0.0)		
Student	36 (30.0)	16 (16.0)		
level of education, (years, mean ± SD)	14.2 ± 2.6	15.9 ± 3.6	-3.831	< 0.001
Educational level (n, %)			21.771	< 0.001
Junior high school	7 (5.8)	2(2.0)		
Senior high/Technical secondary school	21(17.5)	1(1.0)		
College and above	92 (76.9)	97 (97.0)		
Scales scores				
HAMD-17 (mean ± SD)	4.2 ± 7.2			
YMRS (mean ± SD)	0.3 ± 1.6			

Abbreviations BD-D-Bipolar depression, HC-Healthy Controls, HAMD-17-17-item Hamilton Depression Rating Scale, YMRS-Young Mania Rating Scale, SD-standard deviation

Table 3 P-values for time, group interaction from the longitudinal analysis, adjusted for age, gender and education

Item	Group	Time
Spotter	**< 0.001**	0.119
Symbol Check	0.191	0.833
Codebreaker	**0.004**	0.407
Trails	**< 0.001**	0.262
PDQ-5-D	**< 0.001**	0.093
THINC-it Total composite	**< 0.001**	0.115

Abbreviations THINC-it-THINC-integrated tool, PDQ-5-D-Perceived Deficits Questionnaire for Depression–5-items

Note: Generalized linear model; Bold values indicated that P-values < 0.05 were considered statistically significant

Table 4 P-values for time interaction from longitudinal analysis, adjusted for age, gender, education, and HAMD-17 score, in patients only

Item	Time	p-value
Spotter	0.146	0.138
Symbol Check	0.844	0.745
Codebreaker	0.457	0.381
Trails	0.375	0.492
PDQ-5-D	0.136	0.241
THINC-it Total composite	0.147	0.258

Note P-values < 0.05 were considered statistically significant

and THINC-it Total composite, but not in Symbol Check ($p = 0.191$) (Table 3).

Time interaction on each THINC-it subtest at baseline, 1-week, and 8-week follow-ups, adjusted for age, gender, education, and HAMD-17, in BD-D patients only

Results from an eight-week longitudinal follow-up design, conducted solely on BD-D participants, revealed no significant improvements in the subtests and the total composite of THINC-it times after adjusting for age, gender, education, and HAMD-17 scores($P > 0.05$) (Table 4).

Discussion

Although the THINC-it tool is not currently widely employed, it is increasingly favored by scholars because of multiple advantages, including free, simple, fast mode of operation and time stability. In the present study, we analyzed the patient's sensitivity to change, verified time stability, and directly evaluated the efficacy of this tool in clinical application.

Results from the longitudinal analysis revealed changes in cognitive impairment from baseline to the end of the 8th week across three visits. Notably, we found significant differences between the BD-D and HC groups regarding the Spotter, Codebreaker, Trails, PDQ-5-D, and total composite of THINC-it, but not in Symbol Check. These results were consistent with findings from a previous study [13], which reported that similar cognitive domains were impaired in clinical depression. This phenomenon might be attributed to the difficulty in understanding the operating rules for most subjects (including healthy controls) during the actual test. Firstly, the difficulty coefficient of operation was large, which allowed the distinguishing of low scores. Secondly, we only considered accuracy in our statistical analysis and excluded reaction time, which might have introduced bias. Previous studies have shown that impairment represents the main cognitive domains, including attention/vigilance, executive function, and processing speed, consistent with findings from a cross-sectional study [16], but contrasted those from other cross-sectional explorations [17, 18]. These discrepancies might be due to the use of different tools.

In the present study, using the Symbol Check tool resulted in no significant differences regarding decreased working memory between the groups, possibly due to the dual-task paradigm. In addition, the subjects were easily distracted when performing multiple tasks, a phenomenon that could have resulted in no significant differences. This conclusion differs from that of Zhong [19] and Caadet al. [20], who attributed this phenomenon to the presence of confounding factors, such as disease status, assessment tools, and medication. In conclusion, the above results found that theTHINC-it can effectively distinguish bipolar depression and healthy people at

different time points, those could prove the effectiveness in varying time situations.

Our results showed that the BD-D patients recruited in the present study had the same overall cognitive performance at the time level, We could find that the THINC-it tool could stably evaluate bipolar depression at baseline, one-week, and eight-week periods. Pertinent to this study, we examined the sensitivity of THINC-it to change within the time across repeating measures and found that the THINC-it tool was less affected by changes in subjects' state and environment and could be used repeatedly in the clinic. McIntyre [13] found significant differences in the cognitive improvement of Symbol Check at the end of the 2nd and 8th weekends. Further, it showed that working memory was the only cognitive improvement domain with unipolar depression. The strength might be that the US FDA recognized vortioxetine for its independent and direct effect on cognitive function in MDD [21]. Results from a comprehensive reliability and validity analysis are expected to validate the THINC-it tool as a time-saving and economically-friendly method for assessing a conventional cognitive impairment.

Repeated assessments are a relatively common occurrence in clinical neuropsychology. Also, the results could be overestimated due to the learning effects of repeated measurements. However, the present study had several limitations that need to be taken into account. Firstly, we did not conduct structured diagnostic interviews to determine the diagnosis. Secondly, all patients were on psychotropic medication and psychotherapy at the time of the interviews, which might have impacted cognitive function. Third, our follow-up period was short. Therefore, it is not known whether the THINC-it tool would be sensitive to changes in individuals with cognitive dysfunction beyond eight weeks or longer. Finally, standardized measures (such as IQ tests) were not used, potentially affecting the accuracy of cognitive assessments. Additionally, the follow-up sample size was small due to COVID-19. Future efforts will focus on increasing the sample size and finding appropriate IQ tests to improve the standardization and scientific rigor of cognitive assessments.

In summary, the results of the present study revealed that the THINC-it tool, previously validated as a tool for screening cognition, is sensitive to changes and can maintain stability over time in adults with BD-D. These findings affirm this tool's effectiveness as a screening and repeating measures approach and indicate its potential application in clinical practice.

Abbreviations

BD-D	Bipolar Depression
HAMD-17	17-item Hamilton Depression Rating Scale
YMRS	Young Mania Rating Scale
HC	Healthy Control
PDQ-5-D	Perceived Deficits Questionnaire for Depression-5-items
CANTAB	Cambridge Neuropsychological Test Automatic Battery
WCST	Wisconsin Card Sorting Test
MCCB	MATRICS Consensus Cognitive Battery test
THINC-it	THINC-integrated tool
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
DSM-5	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

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Author contributions

Na.Z.: data analysis and writing-original draft preparation and revising. Jun.C. and Yiru.F.: designed the study, reviewing, and editing the final manuscript. Jia.H., YouSong. S., and Jun.C: sample collection. JingFang.L., XiaoHui.W., and Lu.Y.: complete psychopathology test. All authors approved the submitted version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Shanghai Mental Health Center(Ethics Approval No:2020-03) and the Shanghai Pudong Area Mental Health Centre(Ethics Approval No: PDJWLL2019010). All subjects voluntarily signed a written informed consent form prior to their inclusion in the study, which was conducted according to the guidelines of the Helsinki Declaration.

Consent for publication

The potentially identifiable images or data included in this manuscript can be published.

Competing interests

The authors declare no competing interests.

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