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Clinical application of psychiatric assessment and treatment in psychosomatic diseases

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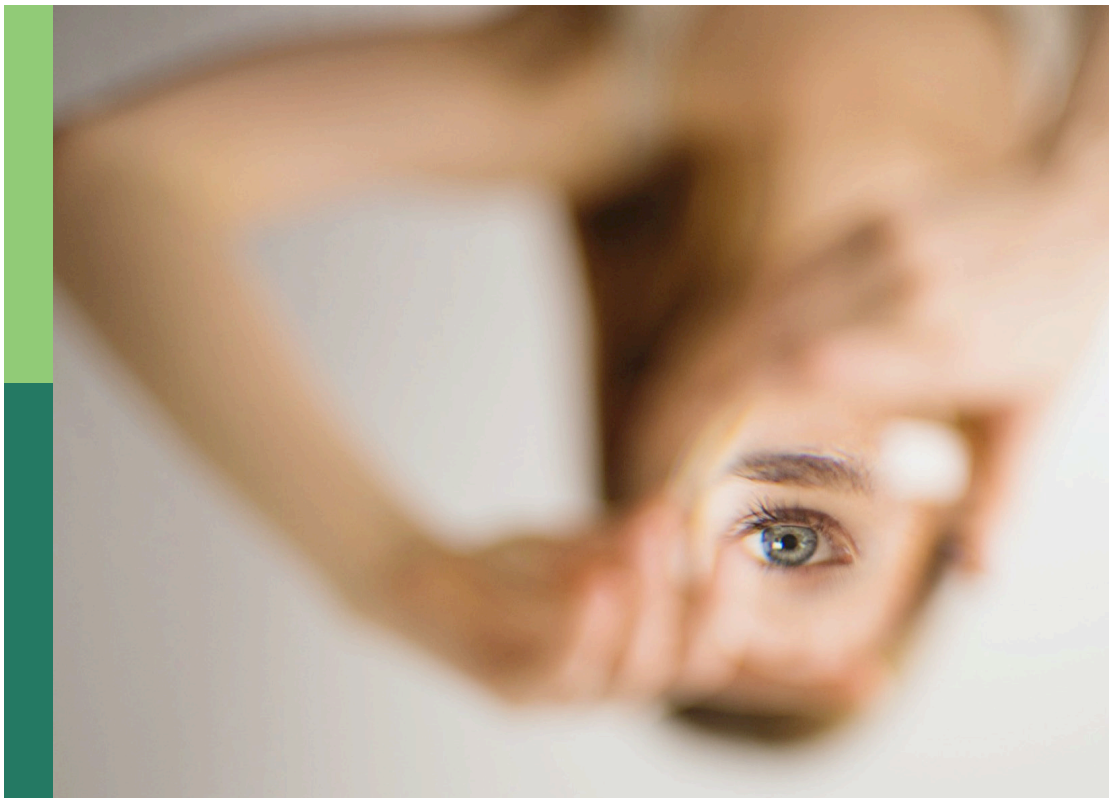

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Clinical application of psychiatric assessment and treatment in psychosomatic diseases

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Editorial: Clinical application of psychiatric assessment and treatment in Psychosomatic diseases

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Psychosomatic diseases, medication, psychotherapy, physical therapy, psychological assessment, fMRI

Editorial on the Research Topic
Clinical application of psychiatric assessment and treatment in Psychosomatic diseases

Introduction

Psychosomatic diseases are widely regarded as a result of the complex interplay between both psychological factors and physiological conditions. As such, in the field of healthcare the diagnosis and treatment of such disorders have become a significant challenge, which would necessitate collaborations among multiple disciplines and professions (Zhong et al., 2023b), as well as close cooperation among physicians, psychologists, and other healthcare professionals (Settineri et al., 2019).

This Research Topic presents a collection of 10 original articles, comprising seven studies utilizing psychological scales and psychotherapy in patients with Psychosomatic diseases and three studies investigating the neuroimaging mechanisms underlying mood/cognitive function using resting-state functional magnetic resonance imaging and psychological scales. Among the seven studies on psychological scales and therapy, four primarily focused on assessing the disease status of Psychosomatic diseases encompassing substance use disorder (SUD), breast cancer, orofacial pain, and infertility; two studies evaluated treatment efficacy for bipolar disorder (BD) and Psychosomatic diseases; and one study explored psychotherapy for chronic pelvic pain. Among the three studies on the neuroimaging mechanism, two studies examined major depressive disorder (MDD); and one study investigated generalized anxiety disorder (GAD).

Psychological scales and psychotherapy

Psychological assessment involves the collection of psychological information from individuals using various measurement tools and techniques to understand their cognitive

abilities, emotional states, and behavioral manifestations (Grassi et al., 2014; Figueiredo-Ferraz et al., 2021). It is commonly used in clinical practice for diagnosing psychosomatic disorders, assessing their severity, and developing personalized intervention plans and treatment strategies. Two studies utilized psychological scales to evaluate disease severity and assist diagnosis. Huang G. et al. employed neuroimaging techniques along with Natural History Interview (NHI) and Barratt Impulsiveness Scale (BIS-11) to study the cognitive performance and neurofunctional impairments related to psychiatric conditions in methamphetamine (MA) abusers. Their research revealed a correlation between attentional bias in MA addicts and the N200 component, which can be used to detect psychiatric factors in abstinent MA abusers. Li et al. utilized the Somatic Symptom Disorder B Criteria Scale (SSD-12), Whiteley Index-8 (WI-8), and other measures to quantitatively assess patients' perceptions and coping strategies related to bodily discomfort, as well as the distress level of somatic symptoms. They also employed the Fear of Cancer Recurrence-4 (FCR-4) and Functional Assessment of Cancer Therapy-Breast (FACT-B) scales to evaluate the magnitude of fear of cancer recurrence and the quality of life in breast cancer patients. These assessments can help breast cancer patients understand their psychological factors and improve their quality of life.

Two studies used psychological scales to assess treatment efficacy. Schmidt et al. evaluated the effectiveness of biofeedback therapy using anonymous quantitative self-report questionnaires and qualitative semi-structured interviews. Jing et al. utilized efficacy scales to assess the treatment outcomes of bipolar disorder.

Additionally, international standardized psychological assessment scales need to be culturally adapted to be more scientifically applicable to the local population (Phillips et al., 1991; Shi et al., 2017). Ou-Yang et al. developed the Chinese version of the Biopsychosocial Impact Measurement-Short Form (BPIm-S), which demonstrated good psychometric quality and can be used to assess functional limitations and psychosocial distress in patients with orofacial pain in China. Mubashir et al. developed the Social Comparison Scale (SCS) and Submissive Behavior Scale (SBS), which exhibited acceptable psychometric properties in Pakistani women with primary infertility, as confirmed by confirmatory factor analysis with good model fit indices.

Psychological therapy, by modulating the bio-psycho-social factors, offers a new perspective on appropriate treatment for mind-body disorders (Hilbert et al., 2019). Huang J. et al. reported a case of chronic pelvic pain syndrome in which the patient achieved effective relief through a combination of medication and psychological therapy.

Psychological scales and brain imaging

Neuroimaging techniques combined with psychological scales, have been extensively employed in investigating structural and functional brain disorders (Gao et al., 2022, 2023; Wang et al., 2022; Zhong et al., 2023a). Meng et al. found that abnormal connectivity patterns were observed in the left middle temporal gyrus in GAD, underscoring the significance of GAD pathophysiology. Zhou et al. found that adolescent MDD with a history of suicidal attempts exhibited reductions in the amplitude of low-frequency fluctuations in the bilateral medial superior frontal gyrus and bilateral precuneus, potentially serving as indicators of MDD and suicidal attempts. Additionally, Wang et al. discovered that decreased regional homogeneity in the salience network may contribute to cognitive impairments in patients with MDD.

Summary

Psychological scale assessment involves expertise from various fields, including medicine, psychology, and sociology. These assessment scales can be combined with multiple research techniques to study psychosomatic disorders. The treatment of psychosomatic disorders requires the integration of knowledge from medicine, psychology, and sociology, among other disciplines. We advocate for enhanced interdisciplinary collaboration among experts in the medical, psychological, and sociological fields to collectively address the challenges posed by psychosomatic disorders and provide patients with improved assessment, treatment, and management approaches. Interdisciplinary collaboration can also facilitate prevention and early intervention of psychosomatic disorders, thereby reducing incidence rates and minimizing long-term negative impacts.

Author contributions

YG and HY reviewed all articles, summarized individual studies' findings, and drafted the manuscript. All other editors participated in editing articles and reviewed and had access to the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Abnormal hubs in global network as potential neuroimaging marker in generalized anxiety disorder at rest

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Background: Mounting studies have reported altered neuroimaging features in generalized anxiety disorder (GAD). However, little is known about changes in degree centrality (DC) as an effective diagnostic method for GAD. Therefore, we aimed to explore the abnormality of DCs and whether these features can be used in the diagnosis of GAD.

Methods: Forty-one GAD patients and 45 healthy controls participated in the study. Imaging data were analyzed using DC and receiver operating characteristic (ROC) methods.

Results: Compared with the control group, increased DC values in bilateral cerebellum and left middle temporal gyrus (MTG), and decreased DC values in the left medial frontal orbital gyrus (MFOG), fusiform gyrus (FG), and bilateral posterior cingulate cortex (PCC). The ROC results showed that the DC value of the left MTG could serve as a potential neuroimaging marker with high sensitivity and specificity for distinguishing patients from healthy controls.

Conclusion: Our findings demonstrate that abnormal DCs in the left MTG can be observed in GAD, highlighting the importance of GAD pathophysiology.

KEYWORDS

generalized anxiety disorder, degree centrality, magnetic resonance imaging, receiver operating characteristic, middle temporal gyrus

Introduction

Generalized anxiety disorder (GAD) is characterized by chronic, diffuse, unrealistic state anxiety about some life situations and often manifested as persistent mental stress accompanied by dizziness, chest tightness, palpitations and other physical symptoms, which is the most common anxiety disorder, with high incidence rate, prolonged course,

recurrent attacks, high comorbidity rate with physical diseases and other mental diseases, and heavy disease burden (Richards et al., 2015; Stein and Sareen, 2015). GAD is currently lack of effective objective biological markers, which are mainly diagnosed through symptomatology, because it overlaps with other anxiety and depression disorders in symptomatology (Blazer et al., 1991; Grados et al., 2005). In clinical work, based on symptomatic diagnosis and prognosis evaluation, misdiagnosis often occurs. Therefore, it is very important to explore potential neuroimaging markers for the diagnosis and prognosis of GAD.

Functional neuroimaging technology has been widely used in the study of neuropsychiatric diseases (Gao et al., 2021, 2022a,b,c; Lin et al., 2022) including GAD because of its excellent temporal and spatial resolution, as well as its medium advantages of safety, non-invasive and no exposure to radioactive substances (Logothetis et al., 2001). A large number of functional magnetic resonance studies have found that GAD patients have abnormal changes in multiple related neural networks in multiple functional abnormal brain regions, which indicates that the pathogenesis of GAD may be related to the abnormal synthesis of functional networks in multiple brain regions, rather than the function of a single brain region caused by an abnormality in the network (Bashford-Largo et al., 2022; Monteiro et al., 2022). Previous studies have found that the functional connectivity of the amygdala and prefrontal cortex in GAD patients is decreased, and some studies have found that local signals in these brain regions are decreased, such as local consistency and low-frequency amplitude (De Bellis et al., 2000). However, there are also some studies with opposite results. It is worth noting that the abnormal brain regions in GAD patients are often not bilaterally symmetrical, and the activation of frontal lobes in different hemispheres is associated with different symptoms of GAD (Yassa et al., 2012). At least the following two factors can explain this difference: First, patients with anxiety disorders subtypes are not screened, and it is difficult to guarantee the homogeneity of patients; second, the research methods and the analysis software used are inconsistent (Gray et al., 2019; Costache et al., 2020). Therefore, it is necessary to choose GAD with high homogeneity as the research object to explore the characteristics of brain functional network in GAD patients, clarify the brain imaging mechanism of GAD, and find the methods of early diagnosis and treatment of GAD.

Degree centrality (DC), recently been applied to reveal the core of brain networks. An increase in voxel-wise DCs in brain regions indicates an increased degree of their global connectivity, whereas a decrease in voxel-wise DCs in brain regions indicates a decreased degree of their global connectivity. Previous researchers have used DC to study different neuropsychiatric diseases such as major depressive disorder (Guo et al., 2022), attention deficit and hyperactivity disorder (Zhou et al., 2019), bipolar disorder (Deng et al., 2019), and schizophrenia (Yu X. M. et al., 2021). However, the changes of brain DC values in GAD patients remain unclear.

In the present study, we hypothesized that abnormal DCs were associated with clinical variables in GAD patients and could serve as potential neuroimaging markers to differentiate GAD from healthy controls.

Materials and methods

Participants

Thank you very much for your suggestions. We have sorted out the inclusion criteria and exclusion criteria of subjects in the manuscript submitted this time.

41 GAD patients were recruited from Taihe Hospital affiliated to Hubei Medical University. Inclusion criteria are as follows: (1) Conform to GAD diagnostic criteria in Diagnostic and Statistical Manual of Mental Diseases (DSM-5); (2) Age 18–55, normal intelligence; (3) Han nationality, right hand; (4) Hamilton Anxiety Scale (HAMA) score $\geq$ 24.

The exclusion criteria were as follows: (1) Current or past medical history of mental disorders other than GAD diagnosed by DSM-5; (2) History of mental or neurological diseases of first-degree relatives; (3) Previous history of brain trauma, alcohol or drug dependence; (4) Have used any psychotropic drugs within 24 h (5) Breastfeeding and pregnant women; (6) Patients with contraindications to MRI examination.

Forty-five healthy people with gender, age and education level matching GAD group were recruited as healthy control (HC) through advertisement.

Inclusion criteria: (1) HAMA score <8; (2) Han nationality, right hand; (3) No history of neuropsychiatric disease;

Exclusion criteria are the same as those of GAD patients.

Our research was recognized by the Ethics Committee of Taihe Hospital affiliated to Hubei Medical University, and all participants signed a written informed consent form.

MRI acquisition and processing

Resting-state fMRI data were obtained using a 3.0 T Philips MRI at Taihe hospital. All subjects were asked to stay awake with their eyes closed. Resting-state functional images were acquired using echo-planar imaging sequences with the following parameters: repetition time/echo time (TR/TE) 2000/30 ms, 31 slices, 220 × 220 matrix, 90° flip angle, 24 cm field of view, 5 mm thick layers without gaps. Functional MRI data processing was performed using the data processing assistant for rs-fMRI (Chao-Gan and Yu-Feng, 2010), which works with SPM12 implemented in MATLAB. converts the DICOM format images obtained by scanning into NIFTI format, and removes the images at the first 10 time points. Taking into account the time when the machine magnetic field reaches stability and the adaptation time of the subject to the environment. Image preprocessing is performed on the converted data. The processing process includes: slice timing due to the different time obtained at each layer; Estimating head motion parameters during scanning and performing head motion

correction; The head movement corrected image space was normalized to the Montreal Neurological Institute (MNI) standard space, and the voxel size was resampled to 3 mm × 3 mm × 3 m (Normalization). The image is subjected to de linear drift and filter (0.01–0.08 Hz) to reduce low-frequency drift and filter high-frequency physiological noise (such as breathing and heartbeat). The next step is to analyze the subjects whose translational motion in each direction (x, y, z) is <2 mm and whose rotational angle is <2°.

DC calculation

DC values were calculated using "Rest-DC" toolkit in rest package.[1] The Pearson correlation coefficient is used to calculate the DC measure, and the Pearson correlation coefficient between all voxel pairs of time series is used to construct the graph of each participant. In this figure, each brain voxel is regarded as a node, and the significant correlation between nodes is regarded as an edge, and then the n * n matrix of Pearson correlation coefficient between each pair of voxels is obtained to establish each subjective whole brain functional connection. Next, in order to improve the normality, Fisher's r-to-z transform is applied to transform each correlation matrix into a Z-score matrix. The sum of the Z values between the voxels and the selected voxels and all other voxels is then calculated to generate a weighted DC for the voxels. In addition, in order to eliminate the potential false connectivity, the threshold of Pearson correlation coefficient was set at $r > 0.25$ (Zhou et al., 2021) by thresholding each correlation at $p < 0.01$.

Statistical analysis

All statistical analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, IL, United States). Independent two-sample t-tests and chi-square tests were used to determine demographic differences between GAD patients and HCs.

Correlation analysis

DC values were extracted from abnormal brain regions between the two groups. To explore the difference of DC between MDD patients and HCs, a voxel-by-voxel two-sample t-test was performed. The significance threshold was set at $p < 0.01$. The abovementioned t-tests were performed with gender, age, and years of education as covariates as these factors may confound the results. Pearson correlation coefficients were calculated to detect correlations between abnormal DC values and clinical variables.

1 http://www.restfmri.net/

Results

Demographic and clinical variables

Demographic and clinical variables are shown in Table 1. There was no significant difference between GAD patients and HCs in terms of gender-, age- and educational level ($p > 0.01$).

Significant DC difference across groups

Figure 1 shows the significant difference in DC values between the two groups (GAD and HCs). Compared with the control group, increased DC values in bilateral cerebellum and left middle temporal gyrus (MTG), and decreased DC values in the left medial frontal orbital gyrus (MFOG), fusiform gyrus (FG), and bilateral posterior cingulate cortex (PCC; Figure 1; Table 2).

ROC of DC value analysis

Five DC abnormal regions (bilateral cerebellum, left MTG, left MFOG, FG, and bilateral PCC) were observed in the patient group. Further analysis of this result revealed that the abnormal DC value in the left PCC showed the highest AUC (0.7317; Figures 2, 3).

Correlations between DC values and clinical variables

There was no significant correlation between DC values and clinical data.

Discussion

As a core index to measure network performance, degree centrality has been applied to the research of brain disease network in recent years, which has helped to explore the mechanism of brain network in brain disease imaging and the diagnosis and prognosis of brain functional diseases (Guo et al., 2022). Forty-one

TABLE 1 Demographic information.

Characteristics	Patients ($n = 41$)	Controls ($n = 45$)	χ^2 or T	Value of p
Gender (male/female)	41 (16/25)	45 (18/27)	3.77	0.05[a]
Age (years)	35.09 ± 2.54	35.20 ± 3.50	3.14	0.08[b]
Education (years)	9.12 ± 2.68	10.56 ± 2.03	1.41	0.24[b]
HAMA (scores)	27.90 ± 2.14			

HAMA, Hamilton Anxiety Scale.
[a]The p-value for gender distribution was obtained by chi-square test.
[b]The p-value were obtained by two sample t-tests.

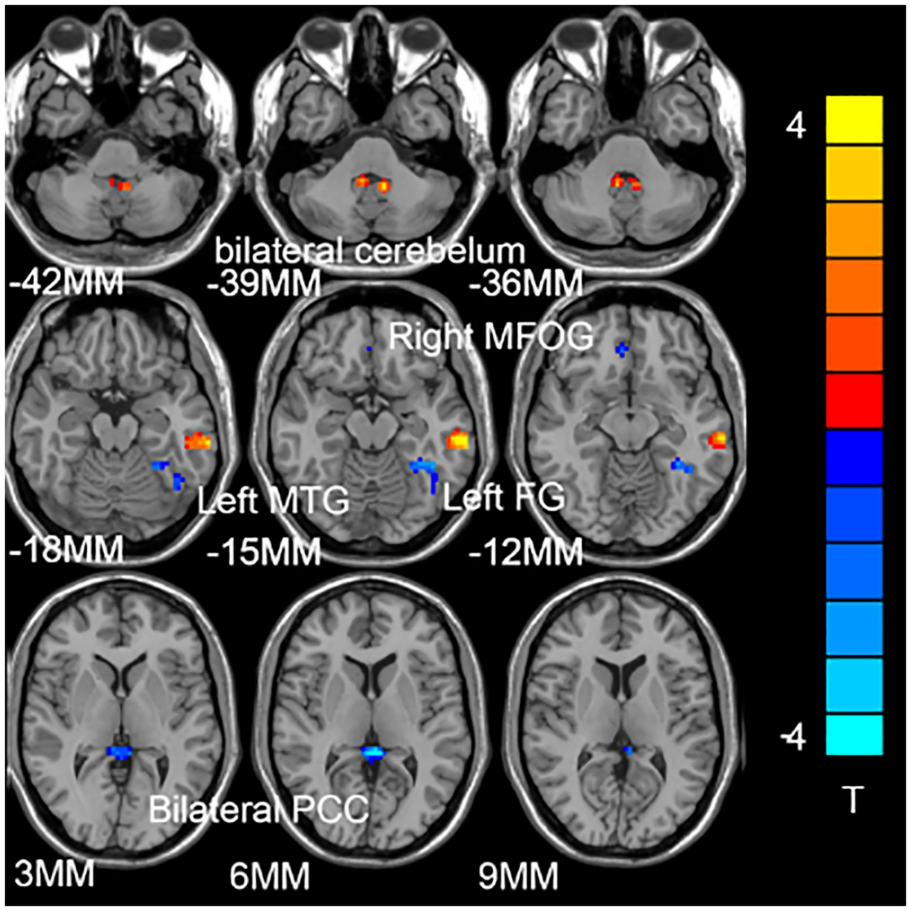

FIGURE 1
Compared with the healthy control subjects (HCs), the brain regions of patients with generalized anxiety disorder (GAD) have abnormal degree centrality (DC) values. The blue represents the decrease in DC value, and the red represents the increase in DC value.

TABLE 2 Alterations of DC between patients and controls. (at baseline, after treatment) and controls.

Cluster location	Peak (MNI)			Number of voxels	*T*-value
	X	*Y*	*Z*		
Bilateral cerebellum	±9	−48	−39	46	3.71
Left middle temporal gyrus	6	−48	18	111	4.03
Left fusiform gyrus	51	42	6	30	−3.38
Right medial orbital frontal gyrus	9	63	24	67	−3.51
Bilateral posterior cingulate cortex	±39	−45	45	30	−3.86

DC, degree centrality; MNI, Montreal Neurological Institute.

GAD patients and 45 health controls participated in the study. We found that there were increased DC values in bilateral cerebellum and left middle temporal gyrus (MTG), and decreased DC values in the left medial frontal orbital gyrus (MFOG), fusiform gyrus (FG), and bilateral posterior cingulate cortex (PCC) comparing to health controls. Furthermore, ROC has been used for biomedical applications in the diagnosis of GAD, and found that the DC value of the left MTG successfully discriminate the two groups with highest degree of accuracy and AUC (0.7317).

The temporal lobe, including the parahippocampal gyrus, FG, amygdala, and entorhinal cortex (Kaur et al., 2022), is often the target of functional and structural studies of GAD (De Bellis et al., 2000). MTG plays a key role in language, emotion and long-time memory (Preston and Wagner, 2007). Neuroimaging has also repeatedly revealed activation of abnormal regions of the MTG, which act as third visual associative brain regions and are associated with cognitive functions such as memory, language, and visual perception (Binney et al., 2010). Consistent findings

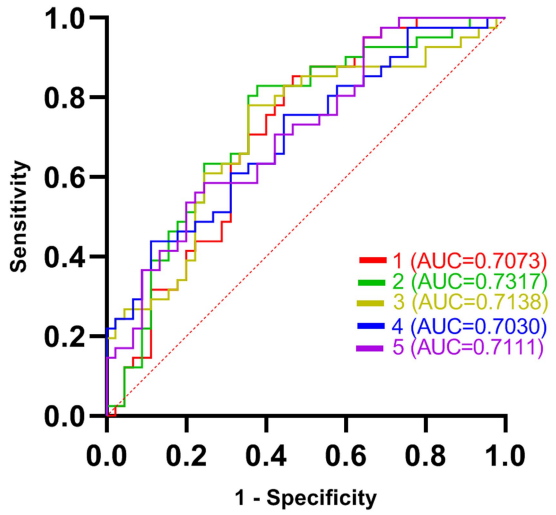

FIGURE 2
The receiver operating characteristic (ROC) curves of brain regions with abnormal degree centrality (DC) values in discriminating generalized anxiety disorder (GAD) patients from healthy controls (HCs). AUC represents the area enclosed by the coordinate axis under the ROC curve. Curve 1 represents the bilateral cerebellum; Curve 2 represents the left middle temporal gyrus; Curve 3 represents the left fusiform gyrus; Curve 4 represents the right medial orbital frontal gyrus; Curve 5 represents the bilateral posterior cingulate cortex.

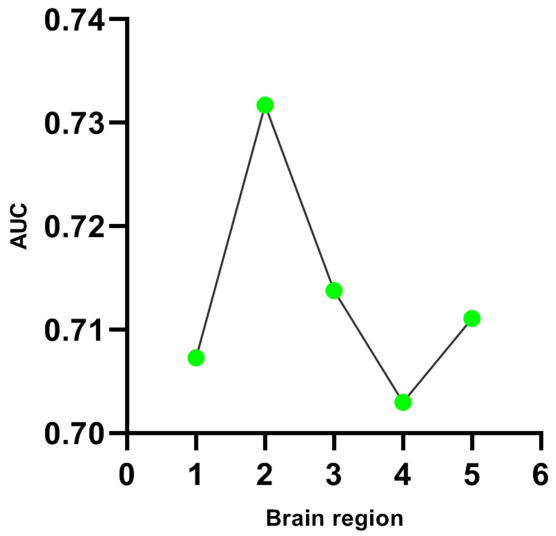

FIGURE 3
Line diagram of AUC in brain regions with abnormal DC values. The first green dot represents the bilateral cerebellum; The second green dot represents the left middle temporal gyrus; The third green dot represents the left fusiform gyrus; The fourth green dot represents the right medial orbital frontal gyrus; The fifth green dot represents the bilateral posterior cingulate cortex.

from neuroimaging studies suggest that the temporal lobe is involved in emotional processing and social cognition (Uno et al., 2010). Furthermore, the MTG is a key node in a broad network of frontal, parietal, occipital, and subcortical structures. Therefore, this abnormally activated region of MTG may also affect the function of the temporal lobe. In this study, our results suggest that increased DCs in MTG may be associated with emotional and cognitive deficits in GAD patients, although cognitive tests were not assessed in this study. In addition, the DC value in the right MTG of the patient group was decreased, which may explain the clinical manifestations of cognitive decline such as learning, memory, and attention in GAD patients. However, no correlation was found between symptom severity and disease duration in patients with GAD and the reduction in DC values, suggesting that the reduction in DC values is a characteristic change in GAD independent of the severity of symptoms in patients. Furthermore, abnormal DC values of MTG can strongly differentiate patients from controls. The ROC results also support the notion that reduced DC values in the MTG may be a characteristic change in GAD.

In this study, reduced DC in the FG was revealed in GAD relative to healthy controls, which implies dysfunction in these regions might be associated with the pathogenesis for GAD. FG locates in the visual recognition network, a part of the temporal lobe, is the facial recognition area of human brain, which is involved in negative cognitive model. T Furmark et al. revealed that decreased reactivity in the bilateral fusiform gyrus in response to fearful faces, as well as increased connectivity between the fusiform gyrus and amygdala, and decreased connectivity between the fusiform gyrus and ventromedial prefrontal cortex in GAD (Mansson et al., 2013). Decreased fusiform connectivity during processing of fearful faces in social anxiety disorder (Cui et al., 2020a). From the perspective of dynamic local brain activity, recent two studies found that GAD exhibited increased dynamic ALFF variability in widespread regions, including the bilateral FG, dorsomedial prefrontal cortex, orbital frontal gyrus, inferior parietal lobule, and temporal gyrus (Chen et al., 2020b; Cui et al., 2020b). In addition, A Meta-Analysis based on fMRI studies showed patients with GAD had significantly lower activation of the left cerebellar and FG (Yu X. et al., 2021). These findings might be associated with the facial mood perception and negative cognition, and it may be the part of the neuropathological mechanism of social withdrawal symptoms in GAD.

The frontal lobe is involved in cognitive control. The main function of the prefrontal lobe is to participate in high-level cognitive functions, including attention, thinking and task execution (Mcallister-Williams et al., 2010). Previous MRI studies on anxiety neural circuits found that the activation of the prefrontal lobe was enhanced in the process of emotional activation (Etkin et al., 2009). It also plays a compensatory role and regulate fear related circuits such as amygdala and insula. Abnormal structural and functional alterations in the frontal lobe have been also reported in many previous reports in patients with GAD (Chen et al., 2020a; Porta-Casteras et al., 2020). For example, Schienle et al. found that the volume of the

dorsal prefrontal cortex of GAD patients increased by structural phase scanning, which may be the compensatory increase caused by the pathological high activation of anxiety stimulation in this brain region of GAD patients (Schienle et al., 2011). Etkin et al. found that the functional connection between bilateral amygdala and dorsal prefrontal lobe was enhanced in GAD patients at rest, suggesting that the functional connection between prefrontal lobe and other brain regions also participated in the compensatory effect (Etkin et al., 2009). In this study, we found that the DC value of the MFOG in GAD patients was lower than that in the control group suggesting that the MFOG of GAD patients also had abnormal functions.

PCC, the master node of default mode network (DMN), is functionally involved in visual spatial information, mental image, metaphor understanding and episodic memory (Greicius et al., 2003). Previous studies have shown that PCC is involved in the pathogenesis of GAD (Porta-Casteras et al., 2020). Regarding its structure, researchers have demonstrated that there is a positive correlation between the gray matter volume of PCC and conceptual creativity. In addition, a large number of studies have shown that the enhancement of the cortical surface area of PCC mainly contributes to the morphological changes of the sagittal brain in adults. In addition, recent studies have shown that PCC may also play an important role in mental imagery and the correlation between vivid memory and egocentric perspective, and its enhanced capacity is related to the tendency to recall autobiographical memories of egocentric plots (Yang et al., 2022). High language innovation ability, including high fluency, originality and flexibility, indicates that the regional functional homogeneity of PCC is reduced. These symptoms are also the most common symptoms in GAD patients. The meta-analysis showed that PCC is a driving recognition activated by familiarity (Busler et al., 2019). PCC also promotes consciousness networks in the nervous system, and GAD patients have selective hypometabolism. In addition, Uretone et al. have found that adolescents with anxiety disorder are abnormally activated in the task state. This study also found that the DC value of bilateral PCC in GAD patients was lower than that of normal controls, suggesting that the patients may be in abnormal emotional integration at rest, leading to anxiety and other symptoms that cannot be controlled by clinical manifestations.

This study has several limitations. First, the sample size of this study is small. Second, all study subjects focused on middle-aged people and could not cover the characteristics of GAD patients in other age groups. Third, we did not recruit patients with various types of anxiety disorders. Therefore, it is difficult to further explore the neurobiological differences of different subtypes of GAD.

Taken together, our findings in this study suggest that GAD patients have a unique DC pattern. Decreased DC values of the left MTG may be a stable and unique neurobiological feature of GAD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the medical ethics committee of Taihe Hospital affiliated to Hubei University of Medicine. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JM, HeL, RW, SJ, and ZiM conceived the project idea. LM, YZ, and HaL implemented the method and performed the experiments. ZhM supervised the project. WJ provided critical suggestions for the design of the experiment. XW directed the revision of the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Case report: New insights into persistent chronic pelvic pain syndrome with comorbid somatic symptom disorder

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Chronic pelvic pain syndrome (CPPS) is generally defined as pain in the pelvic area that persisted for 3–6 months or longer. The pain can be constant or episodic and functionally disabling. Any dysfunction of the central nervous system can lead to central sensitization, which enhances and maintains pain as well as other symptoms that are mediated by the central nervous system. It occurs in subgroups of nearly every chronic pain condition and is characterized by multifocal pain and co-occurring somatic symptoms. Somatic symptom disorder (SSD) is defined as a condition in which having one or more somatic symptoms, such as excessive worries, pressure, and catastrophic events. These symptoms can be very disruptive to a patient's life and can cause significant distress. SSD cases with severe symptoms frequently undergo repeated medical investigations and the symptoms often lead patients to seek emergency medical treatment and consult with specialists repeatedly, which is a source of frustration for patients and clinicians. Here we report a case that Asian female with persistent CPPS with comorbid SSD, who got in trouble for up to 8 years. This case reminds clinicians to pay excessive attention to the diagnosis of CPPS with comorbid SSD after recovery from acute COVID-19, with hope of raising awareness in the identification of SSD and present new insight into appropriate treatment for each woman who suffers from it.

KEYWORDS

chronic pelvic pain syndrome, comorbidities, somatic symptom disorder, COVID-19, case report

Introduction

Chronic pelvic pain syndrome (CPPS) is generally defined as pain in the pelvic area that persisted for 3–6 months or longer. The pain can be constant or episodic and functionally disabling (1). Approximately one-third of women with CPPS seek medical treatment, although the prevalence of the disease ranges from 4 to 16% (2). The prevalence of female CPPS varies globally according to the inclusion criteria, but is estimated to affect 6–25 percent of women of

reproductive age (3–5). It was estimated that CPPS treatment costs 880 million dollars annually (6). Women reported losing working days about 15% of the time, and work efficiency decreased about 45% of the time (7, 8).

In addition to central sensitization of pain, CPPS is a symptom of pathology in other somatic structures or viscera (9). However, the cause of pain may not be identified in some women, and some women will experience persistent pain despite being treated for presumed causes (10). A variety of factors can contribute to the development of CPPS, including pathology or dysfunction of any of the multiple organ systems at play in the pelvis (9). In recent years, Somatic symptom disorder (SSD) has become increasingly prevalent among adolescents (11, 12). SSD are defined by the DSM-5 as a condition in which having one or more somatic symptoms, as well as excessive worries, and as spending too much time and energy dealing with them, resulting in a loss of social and personal opportunities (13, 14). People with this disorder may have symptoms such as chronic pain, fatigue, dizziness, or shortness of breath. These symptoms can be very disruptive to a person's life and can cause significant distress.

The misdiagnosis of complex, unusual, and multisystem diseases is common. The pursuit of curing a symptom without a physical cause could drain hospital and patient resources (15). Herein, we discuss an Asian female with persistent CPPS with SSD, who got in trouble for up to 8 years and present new insight about CPPS with SSD.

Case report

An Asian female, Miss A, 23 years old, presented with persistent chronic pelvic pain disorder pain. As of 2014, she was initially experiencing irregular lumborum pain, feeling cold, and gradually developing lumbo-abdominal dull pain without any previous psychiatric history. The sudden onset of dysmenorrhea is more than 10 days before menstrual period and relieved by taking Yasmin. However, after taking Yasmin for half a year, she became depressed, irritable, and cried easily. The pain in the pelvis intensified in 2021, accompanied by swelling in the vulvar area as well as pain in the pubic region (**Table 1**). Her depression history warranted a referral to the psychiatry team after interventions failed. It took her 4 months to be admitted to the psychiatry department outside a hospital in April 2022. The clinician adjusts Sodium Valproate and Lorazepam due to rapid mood changes into anger or depression with persistently elevated moods and increased talking activity. The physical examinations at several hospitals revealed no abnormalities.

It was diagnosed that SSD was present on 14 August 2022, and treatment to target SSD was begun the following day. In the wake of her somatic symptoms becoming more severe and her hospital course becoming more refractory, we transferred her to our inpatient psychiatry ward. She is being treated on this ward for the remainder of her stay. According to the psychiatric examination conducted on admission, she had persistent pelvic pain, which became worse when she walked or became tired. In a curious turn of events, the pain disappeared once she fell asleep. The clinician adjusted the doses of several medications, including Vortioxetine (10 mg qd), Tandospirone (30 mg qd), Pregabalin (75 mg qd), Trazodone (25 mg qd), Fluphenazine (2 mg qd), and Methycobal (1.5 mg). The patient's basic metabolic panel, white blood cell count, blood cultures, thyroid function, autoimmune tests, cerebrospinal fluid studies, CT scan of the head, and MRI of the brain were all normal.

In the following weeks, Vortioxetine and Pregabalin doses were increased to 15 mg each and 150 mg, respectively (**Table 2**). Her insomnia and somatic symptoms were hoped to be diminished by trials of transcranial magnetic stimulation (TMS), transcranial direct-current stimulation (tDCS) and psychotherapy. Following the adoption of the adjusted therapy, Miss A reported that her pain had eased and showed evidence of improvement. The SSD strategies worked well for her, and her pain diminished. A follow-up appointment is scheduled for her to consider further therapy after she had been discharged home. During our phone contact, she followed up for 2 months, but was unwilling to follow up afterward.

Discussion

Chronic pelvic pain syndrome is a painful condition that may be a result of disease in a somatic or visceral structure, or a manifestation of central sensitization to pain (16). Chronic pain may be the only diagnosis available for some women who suffer from CPPS, and the condition can be frustrating for both patients and clinicians (4). It is likely that central sensitization contributes to chronic pelvic pain syndrome in these women. Any dysfunction of the central nervous system can lead to central sensitization, which enhances and maintains pain as well as other symptoms that are mediated by the central nervous system (17). It occurs in subgroups of nearly every chronic pain condition and is characterized by multifocal pain and co-occurring somatic symptoms (18).

The use of devices unjustified by a clinical diagnosis may result in a real disability for the patient suffering from somatic symptom disorder (SSD) (19). Multiple factors can contribute to SSD, including excessive pressure, catastrophic events including abuse or bullying, chronic diseases, mental illness, and a family history of chronic pain (20). SSD cases with severe symptoms frequently undergo repeated medical investigations, a characteristic that stands out as particularly relevant and common (13). The aforementioned symptoms often lead patients to seek emergency medical treatment and consult with specialists repeatedly (21). Hospital admissions are also common and extensive investigations are conducted repeatedly.

The cost of medical care for people with SSD is high, accounting for about $250 billion in incremental costs in the USA alone each year (22, 23). SSD is associated with a number of psychosocial factors, including genetics, sexual abuse, cognitive distortions, and family conflict. Global public health has been greatly impacted by the COVID-19 pandemic. It is crucial to recognize that mental health issues can be influenced by various stressors, such as fears of infection, social distancing measures, and economic and social burdens. Studies have shown that individuals may be at risk of developing SSD after being infected with COVID-19 (24–27). Primary care clinicians are generally effective in managing these patients. Diagnoses may vary, with a lack of response to various treatment attempts. Multiple treatments may not be effective, depending on the diagnosis. The vicious circle of persistent SSD symptoms, seeking medical care, and ineffective treatment can negatively influence the patient and his or her family, with time spent searching for possible causes and, in extreme cases, disrupting the family dynamics.

TABLE 1 Characteristics of pain from 2014 to 2021.

Year	2014	2016	2021	April–August 2022
Characteristics of pain	Lumborum pain irregularly		Lumbo-abdominal pain intensified	Lumbo-abdominal pain intensified
	Lumbo-abdominal dull pain	Lumbo-abdominal dull pain irregularly	Accompanied with the vulvar and pubes swelling pain	With the vulvar and pubes swelling pain
	Dysmenorrhea	Dysmenorrhea	Dysmenorrhea	Dysmenorrhea

TABLE 2 Prescribed medication over 8 years.

Year	2014	2016	2021	April 2022	June 2022	3 August 2022	22 August 2022	30 August 2022
Antidepressants								
Duloxetine	–	–	–	1# qd	–	–	–	–
Trazodone	–	–	–	1# qn	1# qn	25 mg qd	25 mg qd	25 mg qd
Brintellix	–	–	–	–	–	10 mg qd	15 mg qd	20 mg qd
Anxiolytics								
Tandospirone	–	–	–	3# qd	–	30 mg qd	30 mg qd	60 mg qd
Pregabalin	–	–	–	–	–	75 mg qd	150 mg qd	150 mg qd
Antipsychotics								
Sodium valproate	–	–	–	1# qd	–	–	–	–
Fluphenazine	–	–	–	–	4# qn	2 mg qd	–	–
Paliperidone	–	–	–	–	–		3 mg qd	3 mg qd
Sedatives								
Lorazepam	–	–	–	0.5# qd	–	–	–	–
Zolpidem	–	–	–	1# qn	–	–	–	–
Others								
Methycobal	–	–	–	–	–	1.5 mg qd	1.5 mg qd	1.5 mg qd
Vitamin B6	–	–	1# tid	1# tid	1# tid	1# tid	1# tid	1# tid
Yasmin	*	*	–		–	–	–	–

*Take the medicine but no record the accurate dosage.

Children and adolescents with SSD may suffer adverse effects if a diagnosis of SSD is missed in childhood or adolescence, or invasive therapies are prolonged. When SSD is not recognized, school attendance can be lost, functional disability might be permanent, and psychiatric diseases, such as depression or anxiety disorder, might go unnoticed. Additionally, patients with SSD frequently had comorbid psychiatric conditions, including anxiety, depression, and post-traumatic stress disorder. There is a strong correlation between psychiatric disorders and persistent pain, which can reduce adherence to treatment and lead to self-medication or self-treatment with drugs (28). The majority of adolescents with SSD had neurologic symptoms, while 39% had pain-related symptoms (29). In studies of patients with SSD with depression and anxiety disorders, high comorbidity rates were observed (30–32). Approximately 30–60 percent of primary care SSD patients suffer from comorbid anxiety disorder and/or depression disorder. A serious concern is that patients suffering from SSD have a higher risk of suicide.

According to the biopsychosocial framework, biologic, psychological, and social factors are dynamically intertwined in pain. In terms of chronic pain treatment, cognitive behavioral therapy (CBT) is a first-line option, and more research has been done on CBT than other kinds of psychotherapy, which is why we recommend it (33, 34). Psychological approaches such as motivational interviewing, mindfulness, meditation, and other relaxation techniques can be used to treat SSD. Furthermore, neuromodulation, which modulates relevant brain networks, may be a promising treatment option. In a systematic review, TMS was found to be the most frequently used treatment, followed by electroconvulsive therapy and tDCS (35). It may reduce opioid use when combined with exercise and other components of interdisciplinary rehabilitation. No matter whether patients with SSD are diagnosed with known overlapping pelvic pain conditions, multimodal treatment may provide benefit to patients without SSD that fails to respond to syndrome-specific treatment.

Conclusion

Women find it difficult to accept the diagnosis of CPPS with comorbid SSD, despite the availability of adequate multidisciplinary hospital services. In addition to being common, it is associated with high levels of suffering. Parent and physician often seem to

do nothing when they are asked to do nothing as part of their treatment. This case reminds clinicians to pay excessive attention to the diagnosis of CPPS with comorbid SSD after recovery from acute COVID-19, with hope of raising awareness in the identification of SSD and present new insight into appropriate treatment for each woman who suffers from it.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Peking University Sixth Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZ and JH drafted the manuscript. JS and YD critically revised the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

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

Publisher's note

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Multiple examinations indicated associations between abnormal regional homogeneity and cognitive dysfunction in major depressive disorder

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Background: This study aimed to investigate the relationships between regional neural activity and multiple related indicators in patients with major depressive disorder (MDD).

Methods: Forty-two patients and 42 healthy controls (HCs) were enrolled. Pearson/Spearman correlation analyses were applied to examine the associations between abnormal regional homogeneity (ReHo) and different indicators in the patients.

Results: Compared with HCs, patients with MDD had increased ReHo in the left inferior temporal gyrus (ITG) and decreased ReHo values in the left putamen, anterior cingulate cortex (ACC), and precentral gyrus. The ReHo of the left putamen was positively correlated with the PR interval, Repeatable Battery for the Assessment of Neuropsychological Status 4A, and Discriminant analysis (D), and negatively correlated with Ae (block) and Ae (total) in the patients. The ReHo value of the left ACC was positively correlated with the severity of depression, Stroop Color Word Test of C – 2B +100 in reaction time, and negatively correlated with Ce (Missay) and Perseverative Responses in the patients. The ReHo of the left ITG was positively correlated with the Neuroticism scores and negatively correlated with the Lie scores in the patients.

Conclusion: These results suggested that the decreased ReHo of the salience network might be the underpinning of cognitive impairments in patients with MDD.

KEYWORDS

major depressive disorder, regional homogeneity, support vector machine, salience network, cognition

Introduction

Major depressive disorder (MDD) is a highly prevailing and disabling mental disorder associated with high morbidity and mortality (Fagiolini et al., 2013). About 20 to 30% of individuals with MDD evolve into chronic disease (Angst et al., 2009; Murphy and Byrne, 2012). It affects about 350 million people around the world. By 2030, MDD will be the leading cause of the burden of disease worldwide

(Collins et al., 2011). Plenty of studies have shown that patients with MDD have aberrant brain imaging (Zhang et al., 2018; Liang et al., 2020; Yang et al., 2021), clinical (Caldwell and Steffen, 2018; Kircanski et al., 2019), event-related potentials (ERPs; Landes et al., 2018; Kim et al., 2020; Fan et al., 2021; Xin et al., 2021), and cognitive indicators (Pan et al., 2019). MDD is a heterogeneous disease (Harald and Gordon, 2012), and its etiology remains vague. Combining clinical factors, ERPs, cognitive indicators and other factors to explore the changes of brain functional activity in patients with MDD may provide valuable evidence for understanding the etiology of depression.

MDD is a psychological abnormality concerning mood dysregulation, including neuroendocrine changes, autonomic nervous system (ANS) disorder, immune system activation rhythm disturbances, and oxidative stress (Halaris, 2017). The Hamilton Depression Rating Scale (HAMD; Gibbons et al., 1993; Stefanis and Stefanis, 2001) and Hamilton Anxiety Rating Scale (HAMA; Clark and Donovan, 1994) have been frequently used to assess the severity of depression and anxiety separately to help clarify clinical diagnosis and degree division of mood disorders. The social disability screening schedule (SDSS; Yang et al., 2013), social support rating scale (SSRS; Qin et al., 2021), simplified coping style questionnaire (SCSQ; Lin et al., 2020), and Eysenck personality questionnaire (EPQ) are widely used to assess the psychological status of patients with MDD. Studies have shown that patients with MDD have abnormal EPQ scores (Małyszczak et al., 2019; Wu et al., 2019; Otsubo et al., 2021). Many investigations have reported that patients with MDD exhibit a variety of abnormal biological indexes during outpatient and hospitalization. Heart rate in patients with MDD is significantly increased at rest (Williams et al., 2011). The co-morbidity between MDD and cardiovascular disease (CVD) is a matter of public knowledge. A meta-analytic study found that MDD was recognized as a major risk element for mortality in coronary heart disease (CHD; Barth et al., 2004). And heart rate variability(HRV)pertains to the variation in heart rate and measures the interplay between the sympathetic and parasympathetic nervous systems (Kidwell and Ellenbroek, 2018). Previous researches have established the key element in the link between MDD and CVD with a declining HRV (Musselman et al., 1998; Stapelberg et al., 2012). Several meta-analysis studies have reported that MDD is associated with increased total triglyceride (TG) and cholesterol (CHOL), and low high density lipoprotein (HDL), low density lipoprotein (LDL), and omega-3 polyunsaturated fatty acids (PUFA; Lin et al., 2010; Pan et al., 2012; Persons and Fiedorowicz, 2016). Besides, the thyroid hormones in patients with MDD were lower than those in HCs (Zhou Y. et al., 2021), and thyroid hormones were applied as a supplementary treatment for MDD (Mcintyre, 2016). Moreover, decreased antioxidant uric acid was observed in patients with MDD (Bartoli et al., 2018). A large number of studies have described the relationship between Hypercortisolemia and MDD (Parker et al., 2003; Stetler and Miller, 2011; Nobis et al., 2020). Hypercortisolemia has been linked to depression with ruminations (Stewart et al., 2013), psychogenic depression (Schatzberg et al., 1984), and melancholic and psychotic depressive subtypes (Krishnan and Nestler, 2008; Kunugi et al., 2015). Hypercortisolemia was also depicted as a possible biomarker for treatment-resistant depression (TRD) and persisted after remission (Markopoulou et al., 2009).

A systematic review and meta-analysis by Rock and Roiser et al. suggested that cognitive impairment was a central feature of MDD (Rock et al., 2014). About two-thirds of patients with MDD have cognitive impairment (Afridi et al., 2011). Studies have shown that cognitive impairment persists beyond the acute episode of MDD, with a third to half of the remissive patients with MDD still having a cognitive impairment (Reppermund et al., 2009).

Notably, There is a good deal of tools widely used in measuring cognitive function in MDD, including the Wisconsin Card sorting test (WCST; Nakano et al., 2008; Liao et al., 2021), Stroop Color Word Test (SCWT; Shi et al., 2020; Duan et al., 2021; Zhou Q. et al., 2021), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Guan et al., 2021; Teng et al., 2021), eye-tracking test (Takahashi et al., 2021), and ERP (Bruder et al., 2011; Jaworska and Protzner, 2013; Klawohn et al., 2021; Tseng et al., 2021; White et al., 2021), which have proved that the cognitive domains including executive functioning, learning and memory, processing speed, decision-making, concentration, and attention are notably impaired in patients with MDD (Pan et al., 2019; Wang et al., 2020).

Most of the research theories on the causes of MDD comprise of psychological, biological, and social factors (Beck and Bredemeier, 2016; Brouwer et al., 2019), but few studies have combined these factors in a single study (Kennis et al., 2019). Many of them mainly discuss the relationship between a certain index of patients with MDD and the whole brain activity, whereas there are few studies on exploring local brain activity in patients with MDD by combining multiple indicators. Brain activity in the bilateral orbital frontal cortex (OFC) of patients with MDD was reduced, resulting in decreased ability of patients with MDD to inhibit negative stimuli (Zhang et al., 2016). A structural neuroimaging study has shown decreased volume of the caudate nucleus and lateral orbitofrontal cortex (LOC) and a thinning of the bilateral insula cortex, which are associated with decreased working memory performance and processing speed in MDD (Saleh et al., 2017). The dynamic functional network connectivity in MDD showed that stronger links existed among sensory-related regions than those in HCs (HCs), which were connected with extroversion and neuroticism of the EPQ in the patients (Wu et al., 2019). A study combining ERP and functional magnetic resonance imaging(fMRI) showed that ventral striatum activation and feedback negativity amplitude decreased in patients with MDD, and there was a significant correlation between feedback negativity amplitude and ventral striatum activation (Foti et al., 2014). Hence, it has a pivotal role in discussing the correlation between brain function changes and functional impairment in patients with MDD.

Regional Homogeneity (ReHo) is a voxel-based analysis, which is according to the synchronicity between the time sequences of a given voxel and its neighboring voxels. ReHo is computed by the Kendall consistency coefficient (KCC) of blood oxygen level-dependent (BOLD) time series. ReHo has a good test–retest reliability (Zuo and Xing, 2014), and it can show the local features of cerebral activity. Higher ReHo values indicate higher coherence and centrality of local brain activity (Lv et al., 2018). ReHo is usually calculated in the low-frequency range, with low frequencies (0.01–0.08 Hz) being sensitive to cortical activity (Song et al., 2014). Many studies have found abnormal ReHo in patients with MDD, such as MDD with gastrointestinal symptoms (Yan et al., 2021a), melancholic MDD patients (Yan et al., 2021b), treatment-resistant depression (Guo et al., 2011b), and first-episode and treatment-naive depression (Guo et al., 2011a). Up to now, it is still unclear whether ReHo is related to various clinical indicators in MDD.

Previous studies separately report that patients with MDD have a diversity of brain structural and functional connectivity abnormalities, which are associated with manifold abnormal indicators. Nonetheless, there is an inconsistency with the results on abnormal functional synchronization of brain regions at rest in patients with MDD, and the interconnection with multifarious indicators remains unclear. Therefore,

we collected fasting blood samples, HAMA, HAMD, SDSS, SSRS, SCSQ, EPQ, WCST, SCWT, RBANS, eye-tracking test, ERP and resting state MRI data of MDD patients and healthy subjects for comparison, and conducted correlation analysis with abnormal ReHo value of depression. This study aims to examine the alterations of brain functional synchronization in patients with MDD and their correlations with various indicators including biological, clinical, psychological, and cognitive indicators. We hypothesized that patients with MDD would exhibit abnormal ReHo in multiple brain regions, which were associated with clinical and cognitive parameters.

Materials and methods

Participants

Because of head movement and data deficiency, we excluded 4 patients with MDD and 3 HCs. Finally, 42 patients with MDD and 42 HCs were enrolled in the analysis. We recruited patients with MDD from the outpatient and inpatient departments of Foshan Third People's Hospital, which are aged between 18 and 60 years old. According to the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (*DSM*-5; American Psychiatric Association, 2013), the diagnosis was determined independently by two psychiatrists. All patients met the following inclusion criteria: (1) patients with first-episode or recurrent MDD; (2) right-handed; and (3) patients with first-episode MDD were drug-naïve and patients with recurrent MDD were drug-free for at least 2 weeks. Exclusion criteria were: (1) serious physical diseases especially organic cardiopathy or substance abuse; (2) other serious mental diseases, including schizophrenia, bipolar disorders, intellectual disability, and dementia; and (3) patients currently undergoing or preparing to undergo other clinical studies.

HCs were recruited from the local community through posters. They were excluded if they suffered from any medical and neurological disorders, psychotic symptoms, and substance abuse. All subjects obtained relevant information through a written informed consent and this study was approved by the Ethics Committee of Foshan Third People's Hospital.

Collection of related indicators

Twelve milliliters of peripheral venous blood was collected from all subjects at a fasting state. Blood lipid, thyroid hormone, cortisol, and uric acid were detected by the enzymatic method with the automatic biochemical analyzer. Electrocardiography (ECG) data were collected by a 12-lead ECG machine. HAMA and HAMD were used to evaluate emotional states. EPQ, SDSS, SSRS, and SCSQ were applied to evaluate the psychological status of the subjects. The RBANS, SCWT, and WCST were utilized to assess cognitive function. Eye movement analysis was performed using an eye movement analyzer, and event-related brain potentials were analyzed using an evoked potentiometer.

Image capture and processing

Resting-state functional magnetic resonance imaging was performed using a 3.0 T GE scanner (GE 3.0 T Signa Pioneer). During image collection, subjects were required to keep quiet and still and stay awake with closing their eyes. Foam pads were used to reduce the head movement of the subjects, and soft earplugs were used to reduce the noise of the scanner. The parameter setting of repetition time (TR)/echo time (TE) in this study is 2000/30 ms, the number of layers is 36, the number of rows and columns in the MR image layer is 64*64 matrix, the flip Angle is 90°, the field of view (FOV) is 24 cm, the thickness of the exciting layer is 4 mm, no gap, and a total of 250 volumes (500 s).

Data Processing Assistant for Resting-State fMRI (DPARSF) software package (Chao-Gan and Yu-Feng, 2010) was used to preprocess the collected image data. Since the signal was unstable at the beginning of the collection and subjects needed to adapt to the environment, the first 10 time points of each subject were removed. Subjects with a maximum translation of no more than 2 mm in the X, Y, and Z axes and a maximum rotation of no more than 2° in each axis were included in the subsequent analysis. The 240 left volumes underwent slice timing and head motion correction. Then, the data of different subjects were registered to the standard MNI space using the echo plane imaging (EPI) template to solve the problem of brain morphology differences between different subjects and spatial location inconsistency during scanning. The data were resampled to 3*3*3 mm^3 resolution. The acquired images were bandpass filtered (0.01~0.08 Hz) and linearly detrended.

ReHo analysis

We performed ReHo analysis using the DPARSF toolbox to investigate the functional synchronization of spontaneous neural activity. ReHo describes the synchronization between a voxel and its neighboring voxel time series. The calculation formula of KCC has been stated in a previous study (Zang et al., 2004). In the voxel-based analysis method, the ReHo maps of subjects are obtained according to the KCC value of the time series of a given voxel and its nearest voxel (26 voxels). To reduce the influence of individual differences on KCC values, it is necessary to divide the KCC of each voxel by the average KCC of the whole brain to obtain a standardized ReHo profile. The generated imaging data were spatially smoothed and a Gaussian kernel with a full width of 4 mm was used to achieve a half-maximum value.

Statistical analysis

A Chi-square test was used to analyze the difference in gender of patients with MDD and HCs. Two-sample *t*-tests were used to analyze the blood biochemical, ECG, psychological status, and cognitive indicators of the two groups. The significance level was set at $p < 0.05$.

For the voxel-based ReHo map, the differences between patients with MDD and HCs were compared by two-sample *t*-tests with education level, gender, age and mean framewise displacement (FD) as covariates. The significance level was corrected for multiple comparisons based on Gaussian Random Field (GRF) theory (voxel significance: $p < 0.001$, cluster significance: $p < 0.05$).

Correlation analysis

Pearson/Spearman correlation analyses were performed to clarify the correlation between ReHo values and various indicators in the

TABLE 1 Demography and clinical characteristics.

Variables	Patients	Controls	*p*-value
Age (years)	26.43 ± 10.79	35.14 ± 12.54	0.001[a]
Sex (male/female)	15/27	18/24	0.503[b]
Years of education (years)	13.48 ± 2.48	12.62 ± 3.72	0.218[a]
Height(cm)	163.64 ± 7.92	163.83 ± 7.85	0.912[a]
Weight(kg)	55.07 ± 11.06	59.88 ± 10.50	0.044[a]
HAMD	24.80 ± 7.22[c]	2.55 ± 3.54[c]	<0.001[a]
HAMA	16.60 ± 5.70[c]	2.03 ± 2.69[c]	<0.001[a]
TSH3UL(mIU/L)	1.65 ± 0.83[c]	2.17 ± 0.90[c]	0.226[a]
FT3(pmol/L)	4.38 ± 0.80[c]	4.80 ± 0.57[c]	0.006[a]
FT4(pmol/L)	14.64 ± 2.72[c]	14.55 ± 2.98[c]	0.893[a]
HR(times/min)	74.18 ± 11.67[d]	67.29 ± 10.22[c]	0.006[a]
QRS width(ms)	96.10 ± 11.60[d]	96.52 ± 11.36[c]	0.868[a]
PR interval(ms)	139.10 ± 16.73[d]	152.24 ± 19.20[c]	0.001[a]
QTc(ms)	371.40 ± 20.89[d]	394.95 ± 26.23[c]	<0.001[a]

HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; TSH3UL, Thyroid Stimulating Hormone; FT3, Free Triiodothyronine; FT4, Free Thyroxine; HR, Heart Rate.
[a]The *p*-values were obtained by two sample *t*-tests.
[b]The *p*-value for sex distribution was obtained by a Chi-square test.
[c]$n = 42$.
[d]$n = 40$.

TABLE 2 Comparison of patients and healthy controls in psychological status.

Variables	Patients (n=42)	Controls (n=42)	*p*-value
EPQ			
P	51.20 ± 8.19	47.23 ± 12.68	0.092[a]
E	40.16 ± 11.42	48.72 ± 13.93	0.003[a]
N	68.37 ± 9.19	45.08 ± 10.01	<0.001[a]
L	44.92 ± 11.30	56.93 ± 11.62	<0.001[a]
SDSS score	7.07 ± 2.42	0.02 ± 0.15	<0.001[a]
SSS			
Total score	28.60 ± 8.71	43.14 ± 9.33	<0.001[a]
Objective support score	7.45 ± 3.41	10.93 ± 2.85	<0.001[a]
Subjective support score	14.50 ± 5.23	23.36 ± 5.91	<0.001[a]
Utilization of support	6.64 ± 2.12	8.86 ± 2.05	<0.001[a]
SCSQ			
Total score	26.83 ± 8.42	29.90 ± 9.43	0.119[a]
Active coping	16.50 ± 6.19	22.90 ± 7.35	<0.001[a]
Negative coping	10.33 ± 4.24	7.00 ± 4.35	0.001[a]

EPQ, Eysenck Personality Questionnaire; P, Psychoticism; N, Neuroticism; E, Extraversion; L, Lie; SDSS, Social Disability Screening Schedule; SSS, Social Support Revalued Scale; SCSQ, Simplified Coping Style Questionnaire.
[a]The *p*-values were obtained by two sample *t*-tests.

patients. $p < 0.05$ was considered as the significant threshold. The Bonferroni correction was performed for several dependent or independent statistical tests that were performed simultaneously.

Results

Participants and clinical baselines

There was no significant difference in years of education and gender between patients with MDD and HCs (Table 1). But there was a statistical difference in age ($p = 0.001$). There were significant differences in HAMD and HAMA ($p < 0.001$).

Biological indexes differences between patients with MDD and HCs

In terms of thyroxine, we collected data from 42 individuals for each group of patients with MDD and HCs. There was a statistical difference in FT3 ($p = 0.006$), and no statistical difference was detected in the rest parameters (Table 1). Forty patients with MDD and 42 HCs had the ECG data. There were significant differences in HR ($p = 0.006$), PR interval ($p = 0.001$), and QTc ($p < 0.001$), except for QRS width (Table 1).

There were no statistically significant differences in TG, CHOL, HDL, and LDL between the two groups. In terms of cortisol, 41 data were collected from patients with MDD, and 42 data were collected from HCs. There was no statistically significant difference between the two groups. In terms of uric acid, 41 data were collected from patients with MDD or healthy subjects. There was no statistical difference between them (Supplementary Table S1).

Psychological status differences between patients with MDD and HCs

As shown in Table 2, both 42 Patients with MDD and 42 HCs completed the psychological status assessment. There were significant differences in the scores of Extraversion (E; $p < 0.001$), Neuroticism (N; $p < 0.001$), and Lie (L; $p = 0.038$), except for Psychoticism (P) in the EPQ. There were significant statistical differences in the total scores of SDSS between patients with MDD and HCs ($p < 0.001$). In terms of SSS, there were significant differences in total scores ($p < 0.001$), objective support scores ($p < 0.001$), subjective support scores ($p < 0.001$), and utilization of support ($p < 0.001$) between the two groups. In terms of SCSQ, except for the total scores, there was a statistical difference between active coping ($p < 0.001$) and negative coping ($p = 0.001$).

Cognitive status differences between patients with MDD and HCs

As shown in Table 3 and Supplementary Table S2, only Responses Answer (RA) showed significant differences between patients with MDD and HCs ($p = 0.008$) in the WCST examination, whereas Categories Completed (CC), Correct Responses (RC), Errors Responses (RE), Perseverative Responses (RP), and Perseverative Responses Errors (RPE) showed no significant differences. In the RBANS test, there was no significant difference between the two groups. In eye movement examination, there were statistical differences in the Number of Eye Fixation (NEF; $p < 0.001$), Responsive Search Score (RSS; $p = 0.025$), and Discriminant analysis (D; $p = 0.004$)

TABLE 3 Comparison of patients and healthy controls in cognitive status.

Variables	Patients (n=42)	Controls (n=42)	p-value
WCST			
CC	5.00 ± 1.21	5.26 ± 1.23	0.328[a]
RA	46.05 ± 2.71	44.00 ± 4.02	0.008[a]
RC	34.55 ± 5.58	34.93 ± 3.58	0.711[a]
RE	11.50 ± 6.88	9.02 ± 6.21	0.087[a]
RP	3.57 ± 4.94	2.14 ± 3.33	0.124[a]
RPE	1.79 ± 2.85	0.81 ± 1.45	0.052[a]
RBANS			
Immediate memory	42.15 ± 10.40	42.83 ± 11.69	0.781[a]
Visuospatial/ constructional	18.73 ± 2.16	17.90 ± 2.29	0.100[a]
Language	17.60 ± 4.43	18.57 ± 4.20	0.311[a]
Attention	60.60 ± 14.11	64.81 ± 16.09	0.212[a]
Delayed memory	48.33 ± 9.65	49.60 ± 10.66	0.574[a]
EEM			
NEF	21.11 ± 5.95	27.52 ± 4.32	<0.001[a]
RSS	3.71 ± 1.51	4.60 ± 1.62	0.025[a]
D	5.53 ± 1.40	4.47 ± 1.50	0.004[a]
ERP			
N100	103.73 ± 15.35	107.86 ± 34.86	0.508[a]
P200	174.53 ± 21.59	177.62 ± 23.66	0.545[a]
N200	230.21 ± 31.52	211.79 ± 44.69	0.038[a]
P300 (ms)	309.74 ± 24.20	287.10 ± 50.80	0.012[a]

WCST, Wisconsin card sorting test; CC, Categories Completed; RA, Responses Answer; RC, Correct Responses; RE, Errors Responses; RP, Perseverative Responses; RPE, Perseverative Responses Errors; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; EEM, Exploratory eye movement; NEF, number of eye fixation; RSS, responsive search score; D, Discriminant analysis; ERP, Event related potential. [a]The p-values were obtained by two sample t-tests.

TABLE 4 Comparison of 41 patients and 42 healthy controls in SCWT.

Variables	Z-value	p-value
Reaction time		
At	−3.290	0.001[b]
Bt	−3.631	0.000[b]
Ct	−2.924	0.003[b]
(C − B)/A	−1.066	0.287[b]
C − 2B + 100	−2.519	0.012[b]

SCWT, Stroop color word test. [b]The p-values were obtained by the Mann–Whitney U-test.

between the two groups. In the ERP examination, there was no statistical difference between the two groups in N100 and P200, but there was a statistical difference in N200 (p = 0.038) and P300 (p = 0.012). To the reaction time of SCWT, there were significant differences in At, Bt, Ct, and C − 2B + 100 between patients with MDD and HCs (Table 4), but no significant differences in (C − B)/A, and in the error reaction.

ReHo: Group comparisons

ReHo in the left ITG of patients with MDD significantly increased compared with that of HCs. By contrast, decreased ReHo values were found in the left putamen, anterior cingulate cortex (ACC), and precentral gyrus (Table 5; Figure 1).

The correlations between ReHo values and symptoms and related factors

As shown in Figure 2, the ReHo value of the left putamen was positively correlated with the PR interval of ECG (r = 0.365, p = 0.021), RBANS 4A (r = 0.334, p = 0.035), and D of eye movement examination (r = 0.428, p = 0.023), and negatively correlated with Ae (block; r = −0.397, p = 0.010) and Ae (total) of Stroop word color test (r = −0.327, p = 0.037) in the patients. The ReHo value of left ACC was positively correlated with HAMD score (r = 0.316, p = 0.047), C − 2B + 100 of Stroop word color test (r = 0.326, p = 0.037); and negatively correlated with Ce (Missay) of Stroop word color test (r = −0.315, p = 0.045) and RP of WCST (r = −0.346, p = 0.025) in the patients. The ReHo value of the left precentral gyrus was positively correlated with the N of EPQ (r = 0.318, p = 0.040) and negatively correlated with the L of EPQ (r = −0.446, p = 0.003) in the patients. However, no correlation could survive the Bonferroni correction. In addition, ReHo values of the left putamen, ACC, ITG, and precentral gyrus were not correlated with scores of HAMA, blood biochemistry, SSS, SDSS, and SCSQ in the patients.

Discussion

This study was designed to detect the alterations of ReHo of patients with MDD and its relationship with a lot of clinical indicators. We observed notable differences between patients with MDD and HCs, with ReHo values increased in the left ITG; and decreased in the left putamen, ACC, and precentral gyrus. In the meanwhile, the ReHo values of left PG, putamen, and ACC are interconnected with multitudinous indicators in patients with MDD.

The results showed that abnormal ReHo values in patients with MDD were concentrated to the left side of the brain. Previous studies on the dominant cerebral hemisphere had shown that the left hemisphere had a dominant role in coordinating the hands to carry out complex movements and processing tools, as well as using language to communicate (Goodglass and Kaplan, 1963). Therefore, we speculated that the left cerebral hemisphere had a key role in MDD.

Brain network dysfunction is thought to underlie the cognitive and emotional abnormalities in MDD (Kaiser et al., 2015). Current researches have shown that MDD is caused by the interaction of three key networks (the central executive network, default mode network, and salience network) and the deficits in the functional connections between them and other brain regions (Culpepper, 2015). In this study, brain regions with abnormal ReHo values in patients with MDD were mainly involved in the salience network. The regional brain components of the salience network contain the dorsal ACC, putamen, anterior insula, and mid-cingulate, which mediate emotional regulation, monitoring for salient events, interoceptive awareness, and motivational behaviors (Yun and Kim, 2021).

Consistent with previous studies (Yang et al., 2015; Fu et al., 2018; Liu et al., 2021), the ReHo values of the left putamen were reduced in patients with MDD. Previous studies have revealed that the left putamen volume was smaller in patients with MDD than that in HCs, and the left putamen was smaller in melancholic MDD compared with non-melancholic MDD (Sachs-Ericsson et al., 2018), suggesting that abnormal spontaneous neural activity in the left putamen of patients with MDD has an anatomical basis. The results of correlation analysis showed that the ReHo values of the left putamen were positively correlated with D of the eye tracking test and RBANS 4A, and negatively correlated with Ae (block) and Ae (total) of SCWT. All of them are cognitive indicators, which are mainly related to attention and semantic retrieval. A study showed that the left anterior putamen operated in conjunction with classical language regionals in the dominant (left) hemisphere, directly related to semantic retrieval and comprehension by using the meta-analytic connectivity modeling (MACM) technique (Vinas-Guasch and Wu, 2017). In addition, other studies have shown that the left putamen is associated with the dorsal prefrontal cortex (DLPFC) by using probabilistic tractography, indicating that DLPFC may aid individuals to maintain mental health at both cognitive and emotional levels (Brosch et al., 2021). The putamen is an important node of the salience network, and DLPFC is an important component of the executive control network (Gunning et al., 2021). Therefore, reduced ReHo values in the left putamen may lead to dysfunctions of the salience network and cognitive impairments in MDD. The DLPFC played a role in goal-driven attention, working memory, task switching, problem-solving, planning, and novelty seeking

TABLE 5 Regions with abnormal ReHo values in the patients.

Cluster location	Peak (MNI)			Number of voxels	*T*-value
	x	y	z		
Left putamen	−24	−6	3	52	−2.7740
Left anterior cingulate cortex	0	24	27	38	−2.7777
Left precentral gyrus	−45	6	48	32	−2.7984
Left inferior temporal gyrus	−45	−21	−24	23	3.9129

MNI, Montreal Neurological Institute; ReHo, regional homogeneity. The voxel size is 3*3*3 mm^3.

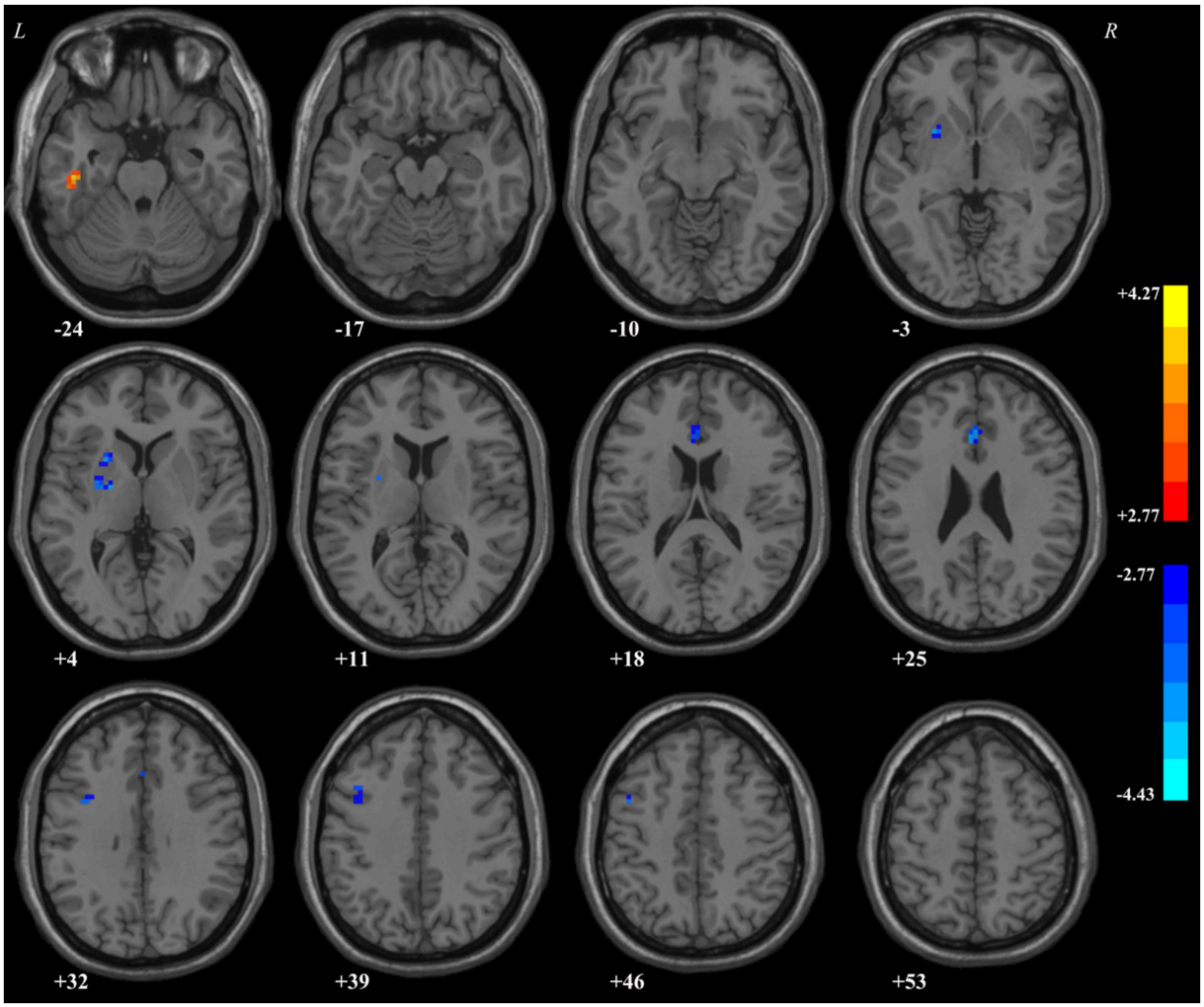

FIGURE 1
Regions with abnormal regional homogeneity values in the patients.

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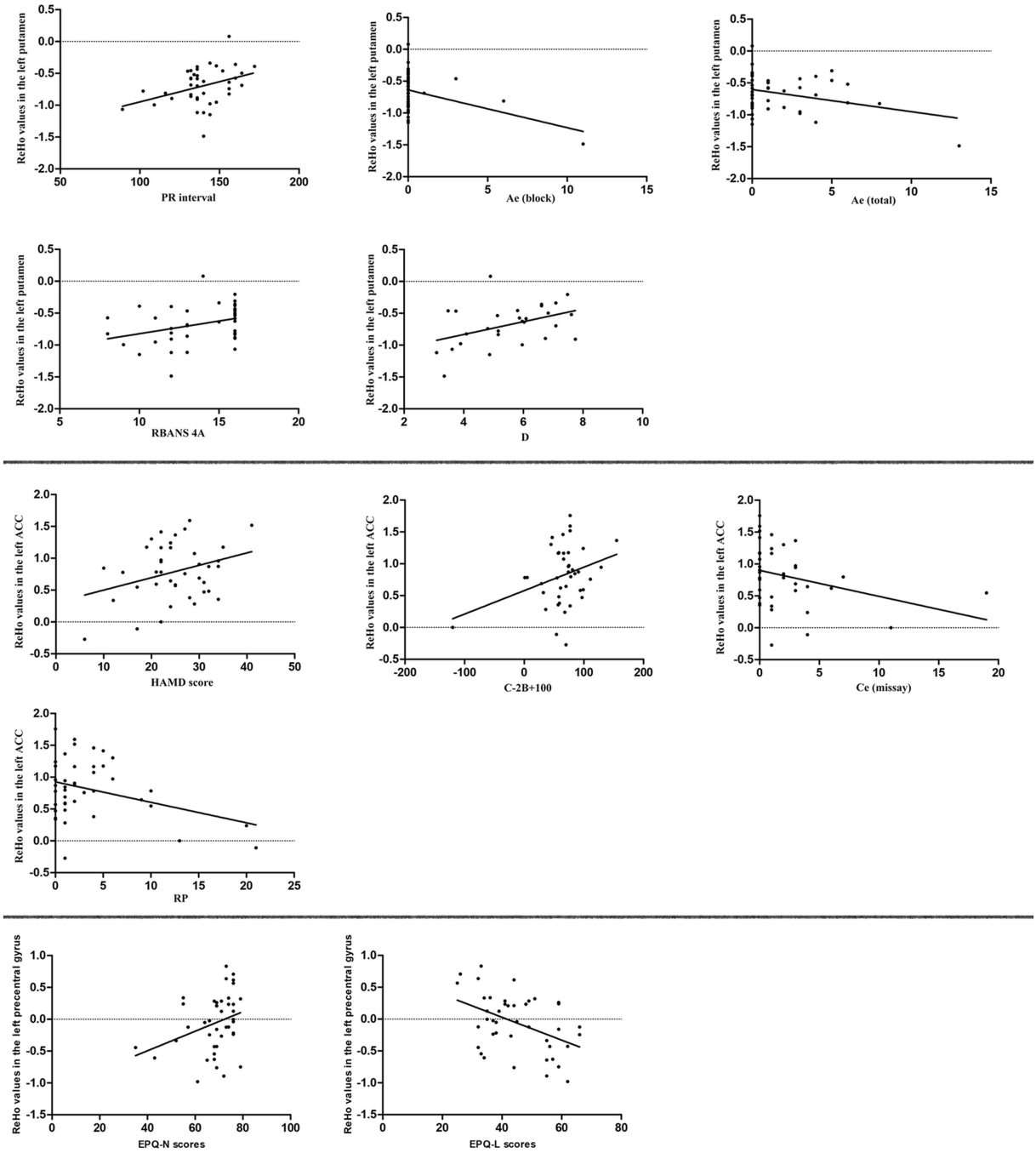

FIGURE 2
Pearson/Spearman correlation analyses showed that correlations between (1) the ReHo values in the left putamen and PR interval (r=0.365, p=0.021, df=39); (2) the ReHo values in the left putamen and Ae (block; r=−0.397, p=0.010, df=40); (3) the ReHo values in the left putamen and Ae (total; r=−0.327, p=0.037, df=40); (4) the ReHo values in the left putamen and RBANS 4A (r=0.334, p=0.035, df=39); (5) ReHo values in the left putamen and D (r=0.428, p=0.023, df=27); (6) the ReHo values in the left ACC and HAMD score (r=0.316, p=0.047, df=39); (7) the ReHo values in the left ACC and C – 2B+100 (r=0.326, p=0.037, df=40); (8) the ReHo values in the left ACC and Ce (missay; r=−0.315, p=0.045, df=40); (9) the ReHo values in the left ACC and RP (r=−0.346, p=0.025, df=41); (10) the ReHo values in the left precentral gyrus and EPQ-N score (r=0.318, p=0.040, df=41); and (11) the ReHo values in the left precentral gyrus and EPQ-L score (r=−0.446, p=0.003, df=41). ReHo, regional homogeneity; ACC, anterior cingulate cortex; HAMD, Hamilton Depression Rating Scale; EPQ, Eysenck Personality Questionnaire.

(Jones and Graff-Radford, 2021). Therefore, abnormal ReHo value in the left putamen leading to cognitive dysfunction in patients with MDD might be directly affecting semantic retrieval and understanding, and further leading to cognitive dysfunction by affecting DLPFC.

As for the correlation between ReHo values and clinical indicators in patients with MDD, abnormal ReHo values of the left putamen were positively correlated with the PR interval. Valenza G et al. demonstrated that brain regions, such as the frontal gyrus, insula, paracingulate and cingulate cortex, lateral occipital cortex, and precuneus cortex, as well as subcortical structures (putamen, thalamus, globus pallidus, amygdala, hippocampus, brainstem, and right caudate nucleus) were involved in the regulation of ANS and

mediated cardiovascular control (Valenza et al., 2017). Patients with ANS dysfunction can give rise to sympathoadrenal (SA) hyperactivity, which can cause elevated heart rates (Otte et al., 2005). Meanwhile, coupling with the decrease in parasympathetic tone may contribute to ventricular arrhythmias, and likely interpret the reason for higher cardiovascular mortality in patients with MDD and CVD (Halaris, 2017). Therefore, abnormal ReHo values in the left putamen may be involved in the regulation of ANS, and then affected the PR interval.

In line with a previous study (Xue et al., 2016), the ReHo values of the left ACC were decreased in patients with MDD compared with HCs. A VBM analysis found a decrease in gray matter volume in the left ACC of MDD compared with HCs (Chen et al., 2018). The ACC, a part of the neocortex, is involved in various cognitive functions such as misrecognition, emotional control, and adaptation to change (Allman et al., 2001; Gasquoine, 2013). ACC is involved in executive control in semantic processing through extensive connectivity with the sensory and motor cortices, and impaired connectivity with the ACC may lead to deficits in semantic performance (Zhao et al., 2017). In the present study, correlation analysis showed that the reduced ReHo values of left ACC were positively correlated with HAMD scores, $C - 2B + 100$ at reaction time in SCWT, and negatively correlated with Ce of SCWT and RP of WCST in the patients. Except for HAMD, they are cognitive indicators. RP is one of the best indicators of WCST to indicate cognitive flexibility (Heaton, 1981). SCWT tests the ability of individuals to overcome the occurrence of interference between two different dimensions of a stimulus through inhibitory control and selective attention mechanisms (Macleod, 1991). Previous studies have demonstrated that the DLPFC, ACC, and striatum are involved in SCWT tasks (Nee et al., 2007), and ACC is thought to monitor conflicts or errors during the SCWT tasks (Milham et al., 2001; Liu et al., 2006). Therefore, reduced ReHo values of the left ACC may contribute to cognitive impairment in MDD by directly affecting the salience network.

Decreased ReHo values were observed in the left precentral gyrus and were positively correlated with EPQ-N scores and negatively correlated with EPQ-L scores in the patients. Reduced ReHo values of the left precentral gyrus in patients with MDD have been found in the published literature (Zhang et al., 2021; Song et al., 2022). Previous studies have shown that patients with MDD who attempted suicide had fewer hemodynamic responses in the left precentral gyrus than patients with MDD without suicidal ideation and HCs (Tsujii et al., 2017). For EPQ, neuroticism has been identified as a risk factor for depression (Grav et al., 2012). Taking into account the higher score of the Lie subscale, the more stable and mature personality, Lie subscale is conducive to the development of behavior (Cao and Su, 2007).

The ITG plays an important role in visual object recognition, decision-making, and attentional impulse (Herath et al., 2001; Li and Kong, 2017). Some studies have shown that the left ITG is essential in lexical and phonological decision-making (Mechelli et al., 2003). In this study, the ReHo values of left ITG in patients with MDD increased, but no correlation with other indicators was observed. Kocsis K et al. found that the more severe depressive symptoms, the higher level of the asymmetry of ITG in patients with MDD (Kocsis et al., 2021). The results of a fractional Amplitude of Low Frequency Fluctuation (fALFF) study showed that the fALFF values of the left ITG were significantly increased in patients with MDD, and the fALFF values of the left ITG were correlated with the score of the Continuous Performance Test (CPT) second subtest (Huang et al., 2017). A voxel-based morphometry (VBM) study has shown a reduction in gray matter volume (GMV) in the right inferior temporal gyrus (Guo et al., 2014). Increased ReHo in the left ITG of patients with MDD may represent the presence of left–right hemisphere asymmetry, indicating that our results are consistent with those of previous studies.

Although there are valuable findings, there are still some limitations in this study. First, the sample size is relatively small. Second, the age of the two groups was mismatched, and mismatched age might have effects on our results although it was applied as a covariate in the analyses. Third, all correlations could not survive the Bonferroni correction although there were several correlations between abnormal ReHo and clinical and cognitive parameters in the patients. Thus, these results should be interpreted with caution. Finally, changes in ReHo values in patients with MDD after treatment were not tracked. Future studies with a view of the dynamic changes in ReHo values in patients with clinically cured MDD are needed to clarify whether the changes in ReHo values in patients with MDD are a trait phenomenon or a state marker.

Overall, this study is the first to evaluate the correlations between ReHo values and numerous indicators of MDD, including biological, clinical, psychological, and cognitive indicators. We found that the ReHo values were mainly significantly correlated with the cognitive indicators of patients with MDD, suggesting that the reduced ReHo values in brain regions of the salience network might be the underpinning of cognitive impairments in patients with MDD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Foshan Third People's Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YW, XL, and HY: methodology, data curation, formal analysis, and writing and editing. YO, WeW, WS, WC, YY, JL, WaW, HL, ZL, and XM: conceptualization and data curation. GX and WG: methodology, data curation, writing—review and editing, and funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.1090181/full#supplementary-material

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A retrospective study of psychotropic drug treatments in bipolar disorder at acute and maintenance episodes

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Background: Bipolar disorder (BD) is predominantly treated with psychotropic drugs, but BD is a complex medical condition and the contribution of psychotropic drugs is not clear. The objectives of this study are: (1) to present psychotropic drugs used in patients with BD; (2) to access changes of psychotropic drug treatments in acute and maintenance episodes.

Methods: The study retrospectively evaluated the medical records of inpatients in the Ningbo Kangning Hospital from January 2019 to December 2019. The medical history of each subject was collected completely, including sociodemographic (gender, age, marital status, and so on) and clinical characteristics at baseline and within 12 months of admission.

Results: The study ultimately included 204 patients with BD. After 12 months, 73.0% of the patients still took drugs. Mood stabilizers (72–90%) and antipsychotics (77–95%) were still the most important drugs in patients with BD. Antidepressants (34–40%) and benzodiazepines (20–34%) were the other frequently used drug classes. For mood stabilizers, 40–56% of patients were prescribed lithium. For antipsychotic, 54–65% of patients were prescribed quetiapine. Sertraline (6–9%) and fluoxetine (5–9%) were the antidepressant that most frequently prescribed. Lorazepam (10–18%) was the most commonly used benzodiazepine. In psychotropic polypharmacy, the most frequently taken was mood stabilizer plus antipsychotic co-treatment, about 36–44% of all patients. A total of 35–48% of patients treated by two psychotropic drugs and 24–36% received three.

Conclusion: The first 6 months after treatment is very important to medication adherence. Mood stabilizers and antipsychotic remained the primary treatment for BD. Antipsychotic is on the rise in the treatment of BD.

KEYWORDS

psychotropic drugs, bipolar disorder, acute, maintenance, retrospective

Introduction

Bipolar disorder (BD) is a common mental illness that affects more than 2% of the world's population (1). Most affected individuals experience illness-related disability, reduced psychosocial functioning, reduced quality of life, and increased economic costs (2, 3). Mortality studies indicate that BD, like schizophrenia, is associated with a loss of approximately 10–20 potential years of life (4). In addition, people with BD die from suicide more often than people with other mental disorders (5, 6), such as major depressive disorder (MDD). The most important unmet need in BD is accurate and timely diagnosis and prompt implementation of effective treatment (7).

Multiple nationally and internationally authored guidelines for BD have been published in recent years (8–12). The primary modalities of therapy in BD are psychotropic drugs, psychosocial counseling, neurostimulation therapies (e.g., electroconvulsive therapy), and lifestyle modification. Although psychotropic drugs have shown an effect on the neuroendocrine system and other faults (13), psychotropic drugs treatments are the foundation of any treatment plan and have been studied to a greater extent than other treatments. However, the exclusion of BD patients from randomized controlled trials – those most common in clinical practice (e.g., patients with multiple comorbidities and suicidal tendencies) – limits what can be inferred from these study findings to clinical practice (14). It is important to understand the real-world use of psychotropic drugs in patients with BD.

Mood stabilizers and antipsychotics are standard treatment for acute manic episodes (15). For acute BD mania, monotherapy with either mood stabilizers or antipsychotics is recommended, and the combination of a mood stabilizer with an antipsychotic is suggested for cases in which monotherapy is not sufficient (16). Although this polypharmacy treatment is also associated with common comorbidities (17), two or more medications with mood-stabilizing properties are usually part of the treatment regimen for BD (18). Mania is an adverse effect of antidepressant therapy in patients with BD (19). However, antidepressants are commonly used drugs in patients with BD. These are the reasons why antidepressants are commonly used in patients with BD. There are other reasons as well, for example, patients with BD usually develop during episodes of depression or mixed emotions, and depressive symptoms tend to dominate the course of the illness (20, 21). Benzodiazepines are also commonly prescribed to patients with BD. Some studies suggest that some specific anxiety disorders representing the phase of abnormal rhythm within the BD disease spectrum (22).

Few psychotropic drug treatments for BD have shown efficacy as maintenance treatments. In Scotland, the percentage of patients with BD receiving lithium declined between 2009 and 2016 (23). Lamotrigine has shown efficacy as a maintenance therapy for depression (24). Evidence of efficacy as a maintenance treatment for BD exists for quetiapine, but not for risperidone or aripiprazole (25). Maintenance treatments are important to control mood symptoms and to reduce relapse. Therefore, it is important to fully understand the efficacy of psychotropic drugs in maintenance treatment for patients with BD.

The incidence and prevalence of diagnosed BD have increased during the last 20 years (26), not least because of the launch of new treatments. It is not known whether this has affected the prescription pattern. With the expansion of available medications for BD, such as new generation antidepressants and antipsychotics, and the use of psychiatric indications for anticonvulsants, prescribers have many options. Effective treatment for patients with BD and good medication adherence to treatment are important for the prognosis of patients, which can reduce the recurrence rate, improve the quality of life of patients, and reduce the burden on family and society. We selected inpatients, and this study explored drug treatment patterns in BD during acute episodes and maintenance periods of approximately 12 months of psychotropic drug intake. From this study, we want to know the characteristics of psychotropic drug use and medication adherence of patients with BD, so as to provide evidence for psychiatrists in clinical medication.

Materials and methods

Data collection

This study was approved by the Ethics Committee of Ningbo Kangning Hospital. The study retrospectively evaluated the medical records of inpatients in Ningbo Kangning Hospital from January 2019 to December 2019. Because this was a retrospective, non-interventional study and all data were collected anonymously, informed consent was not required. All the patients included in the study needed to meet the International Classification of Diseases, Tenth Edition (ICD-10) criteria for BD. The diagnosis of BD was made by a psychiatrist during hospitalization, and all the patients received psychotropic drug treatments. We excluded patients with history of schizophrenia, epilepsy, alcohol, and psychoactive substance dependence, have a history of organic brain disease, serious physical disease or endocrine disease, pregnant or suspected pregnancy patients, and nursing patients. If multiple hospitalizations were found during the time of admission, the record from the most recent hospitalization was selected. If there was a record of hospitalization during the maintenance period, it was ruled out. The study had minimal inclusion criteria to better represent the patient heterogeneity of clinical practice.

The medical history of each subject was collected, including sociodemographic (sex, age, marital status, and so on), and clinical characteristics were assessed at baseline and within 12 months of admission. Subsequent assessment data were collected 3 months after the baseline, at 6 months, at 9 months, and at 12 months.

Medication classes

The psychotropic drugs mentioned in this study were mood stabilizers (MSs), antipsychotics (APs), antidepressants (ADs), and benzodiazepines (BZDs). Mood stabilizers were defined as valproate, lithium, lamotrigine, oxcarbazepine, or topiramate. Second-generation antipsychotics are also effective mood stabilizers, but they were classified separately in order to better classify the drugs taken and compare them with previous studies. Trazodone and mirtazapine were considered antidepressants, although they were often used to improve sleep. These included benzodiazepines, because they are commonly used in patients with BD. For each patient, the prescribed daily dose (PDD) was defined as the daily dose. The type of medication taken was defined as the daily use of any medication within the type of medication.

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TABLE 1 Sociodemographic and clinical characteristics of patients with bipolar disorder.

	Acute episode	Maintenance period				χ^2	*P*
	Baseline (*n* = 204)	3 months (*n* = 173)	6 months (*n* = 153)	9 months (*n* = 147)	12 months (*n* = 149)		
Sex							
Male	77 (37.7)	65 (37.6)	56 (36.6)	54 (36.7)	56 (37.6)	0.080	0.999
Female	127 (62.3)	108 (62.4)	97 (63.4)	93 (63.3)	93 (62.4)	0.080	0.999
Marital status							
Single	101 (49.5)	82 (47.4)	68 (44.4)	64 (43.5)	63 (42.3)	2.468	0.650
Married/spouse	83 (40.7)	76 (43.9)	70 (45.8)	68 (46.3)	71 (47.7)	2.103	0.717
Divorced	9 (4.4)	6 (3.5)	6 (3.9)	6 (4.1)	6 (4.0)	0.223	0.994
Widowed	8 (3.9)	7 (4.0)	7 (4.6)	7 (4.8)	7 (4.7)	0.250	0.993
Other	3 (1.5)	2 (1.2)	2 (1.3)	2 (1.4)	2 (1.3)	0.413	1.000
Disease course, months							
0–12	48 (23.5)	38 (22.0)	30 (19.6)	30 (20.4)	29 (19.5)	1.280	0.865
13–60	73 (35.8)	58 (33.5)	51 (33.3)	46 (31.3)	46 (30.9)	1.229	0.873
61–120	33 (16.2)	29 (16.8)	27 (17.6)	26 (17.7)	27 (18.1)	0.308	0.989
121–240	32 (15.7)	30 (17.3)	27 (17.6)	27 (18.4)	30 (20.1)	1.236	0.872
≥241	18 (8.8)	18 (10.4)	18 (11.8)	18 (12.2)	17 (11.4)	1.381	0.847
Age, years							
<18	27 (13.2)	19 (11.0)	17 (11.1)	15 (10.2)	16 (10.7)	0.997	0.910
18–59	154 (75.5)	133 (76.9)	115 (75.2)	111 (75.5)	112 (75.2)	0.185	0.996
≥60	23 (11.3)	21 (12.1)	21 (13.7)	21 (14.3)	21 (14.1)	1.096	0.895
Type of BD							
Mania	55 (27.0)	47 (27.2)	46 (30.1)	45 (30.6)	46 (30.9)	1.218	0.875
Major depression	108 (52.9)	96 (55.5)	81 (52.9)	79 (53.7)	77 (51.7)	0.519	0.972
Mixed state	35 (17.2)	26 (15.0)	24 (15.7)	21 (14.3)	24 (16.1)	0.625	0.960
Rapid cycle	3 (1.5)	1 (0.6)	1 (0.7)	1 (0.7)	1 (0.7)	1.265	0.927
Remission	2 (1.0)	2 (1.2)	1 (0.7)	1 (0.7)	1 (0.7)	0.775	1.000
Other	1 (0.4)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2.507	1.000
Educational background							
Primary school and below	12 (5.9)	9 (5.2)	9 (5.9)	9 (6.1)	9 (6.0)	0.161	0.997
Junior high school	81 (39.7)	68 (39.3)	57 (37.3)	56 (38.1)	57 (38.3)	0.307	0.989
Senior high school	45 (22.1)	38 (22.0)	38 (24.8)	35 (23.8)	35 (23.5)	0.563	0.967
Junior college or bachelor	62 (30.4)	54 (31.2)	46 (30.1)	44 (29.9)	44 (29.5)	0.124	0.998
Postgraduate or above	4 (1.9)	4 (2.3)	3 (2.0)	3 (2.0)	4 (2.7)	0.493	0.992
Psychiatric hospitalization, days							
≤14	61 (29.9)	47 (27.2)	38 (24.8)	38 (25.9)	39 (26.2)	1.388	0.846
15–28	72 (35.3)	62 (35.8)	57 (37.3)	55 (37.4)	57 (38.3)	0.437	0.979
29–56	63 (30.9)	56 (32.4)	50 (32.7)	46 (31.3)	45 (30.2)	0.315	0.989
≥57	8 (3.9)	8 (4.6)	8 (5.2)	8 (5.4)	8 (5.4)	0.647	0.958

TABLE 2 Numbers of different medication classes used in the treatment of patients with bipolar disorder.

Medication class	Acute episode	Maintenance period				χ^2	*P*
	Baseline (*n* = 204)	3 months (*n* = 173)	6 months (*n* = 153)	9 months (*n* = 147)	12 months (*n* = 149)		
Mood stabilizers	183 (89.7)	124 (71.7)	112 (73.2)	106 (72.1)	109 (73.2)	25.622	0.000
Antipsychotics	193 (94.6)	142 (82.1)	123 (80.4)	113 (76.9)	117 (78.5)	26.669	0.000
Antidepressants	77 (37.7)	69 (39.9)	57 (37.3)	51 (34.7)	50 (33.6)	1.754	0.781
Benzodiazepines	70 (34.3)	41 (23.7)	34 (22.2)	30 (20.4)	37 (24.8)	11.482	0.022

TABLE 3 The most commonly used drugs and their dosages in the treatment of patients with bipolar disorder, expressed as *n* (%) and mean (SD).

Medication	Acute episode		Maintenance period									
	Baseline (*n* = 204)		3 months (*n* = 173)		6 months (*n* = 153)		9 months (*n* = 147)		12 months (*n* = 149)		χ^2/H	*P*
	N (%)	Dose (mg)	*N* (%)	Dose (mg)	*N* (%)	Dose (mg)	*N* (%)	Dose (mg)	*N* (%)	Dose (mg)		
Mood stabilizers												
Lithium	115 (56.4)	738.3 ± 242.6	82 (47.4)	709.8 ± 242.7	71 (46.4)	684.5 ± 233.4	64 (43.5)	670.3 ± 231.4	60 (40.3)	696.7 ± 234.3	10.565/5.464	0.032/0.243
Valproate	106 (52.0)	747.6 ± 255.1	59 (34.1)	745.8 ± 252.1	51 (33.3)	670.6 ± 239.0	55 (37.4)	707.3 ± 274.4	53 (35.6)	697.2 ± 258.2	19.048/4.13	0.001/0.389
Lamotrigine	9 (4.4)	111.1 ± 60.1	9 (5.2)	111.1 ± 60.1	9 (5.9)	134.7 ± 72.3	7 (4.8)	164.3 ± 47.6	10 (6.7)	107.5 ± 60.2	1.097/4.836	0.895/0.304
Antipsychotics												
Quetiapine	132 (64.7)	233.0 ± 152.3	101 (58.4)	232.4 ± 144.2	90 (58.8)	224.7 ± 139.5	80 (54.4)	229.7 ± 138.0	85 (57.0)	232.4 ± 148.6	4.123/0.121	0.390/0.998
Olanzapine	41 (20.1)	8.9 ± 5.3	27 (15.6)	8.2 ± 4.4	19 (12.4)	8.0 ± 4.2	19 (12.9)	6.3 ± 4.0	19 (12.8)	7.4 ± 4.5	6.040/5.552	0.196/0.235
Aripiprazole	18 (8.8)	11.3 ± 6.0	11 (6.4)	10.7 ± 5.5	12 (7.8)	11.9 ± 5.6	11 (7.5)	11.6 ± 4.8	12 (8.1)	10.8 ± 5.3	0.833/0.552	0.934/0.968
Risperidone	3 (1.5)	3.3 ± 1.2	3 (1.7)	3.3 ± 2.1	4 (2.6)	2.6 ± 2.2	6 (4.1)	2.5 ± 1.4	4 (2.7)	3.0 ± 1.4	2.859/1.188	0.581/0.880
Clozapine	5 (2.5)	95.0 ± 90.8	4 (2.3)	150.0 ± 108.0	5 (3.3)	125.0 ± 109.0	7 (4.8)	125.0 ± 99.0	4 (2.7)	150.0 ± 108.0	2.046/1.660	0.740/0.798
Antidepressants												
Sertraline	19 (9.3)	97.4 ± 61.2	16 (9.2)	101.6 ± 64.9	14 (9.2)	100.0 ± 67.2	12 (8.2)	93.8 ± 72.4	9 (6.0)	105.6 ± 63.5	1.566/0.626	0.815/0.96
Fluoxetine	16 (7.8)	28.8 ± 10.2	15 (8.7)	27.3 ± 13.3	11 (7.2)	29.1 ± 13.8	8 (5.4)	25.0 ± 9.3	8 (5.4)	27.5 ± 14.9	2.123/0.975	0.713/0.914
Escitalopram	10 (4.9)	14.0 ± 4.6	8 (4.6)	12.5 ± 3.8	4 (2.6)	11.3 ± 2.5	4 (2.7)	11.3 ± 2.5	3 (2.0)	11.7 ± 2.9	3.418/2.003	0.490/0.735
Venlafaxine	7 (3.4)	150.0 ± 0.0	9 (5.2)	105.6 ± 42.9	8 (5.2)	131.3 ± 53.0	9 (6.1)	105.6 ± 72.4	7 (4.7)	132.1 ± 64.1	1.509/5.903	0.825/0.207
Bupropion	6 (2.9)	250.0 ± 77.5	10 (5.8)	187.5 ± 81.0	7 (4.6)	192.9 ± 73.2	6 (4.1)	225.0 ± 82.2	4 (2.7)	187.5 ± 75.0	2.833/3.334	0.586/0.504
Duloxetine	8 (3.9)	82.5 ± 21.2	6 (3.5)	55.0 ± 35.1	6 (3.9)	55.0 ± 35.1	7 (4.8)	47.1 ± 23.6	6 (4.0)	50.0 ± 15.5	0.356/8.706	0.986/0.069
Paroxetine	5 (2.5)	26.0 ± 13.4	3 (1.7)	40.0 ± 0.0	3 (2.0)	30.0 ± 10.0	3 (2.0)	26.7 ± 11.5	7 (4.7)	23.6 ± 7.5	3.615/5.376	0.461/0.251
Benzodiazepines												
Lorazepam	36 (17.6)	0.9 ± 0.5	21 (12.1)	0.9 ± 0.4	15 (9.8)	0.9 ± 0.4	17 (11.6)	0.9 ± 0.4	15 (10.1)	0.9 ± 0.5	6.854/0.477	0.144/0.976
Oxazepam	11 (5.4)	24.5 ± 19.0	2 (1.2)	30.0 ± 0.0	1 (0.7)	7.5 ± 0.0	1 (0.7)	30.0 ± 0.0	1 (0.7)	45.0 ± 0.0	12.308/5.329	0.006/0.255
Clonazepam	13 (6.4)	1.3 ± 0.6	9 (5.2)	1.6 ± 0.5	11 (7.2)	2.0 ± 0.8	5 (3.4)	1.8 ± 0.4	8 (5.4)	2.1 ± 0.8	2.383/9.218	0.666/0.056
Zopiclone	7 (3.4)	7.5 ± 0.0	5 (2.9)	7.5 ± 0.0	4 (2.6)	7.5 ± 0.0	5 (3.4)	6.8 ± 1.7	7 (4.7)	7.0 ± 1.4	1.213/2.908	0.892/0.573
Zolpidem	3 (1.5)	10.0 ± 0.0	4 (2.3)	12.5 ± 5.0	5 (3.3)	11.0 ± 5.5	4 (2.7)	10.0 ± 0.0	7 (4.7)	9.3 ± 1.9	3.541/2.161	0.468/0.706

χ^2: Difference at baseline, 3, 6, 9, and 12 months. H: Difference in dose at baseline, 3, 6, 9, and 12 months. *P*: *P*-value of the number used drugs and their dosages in the treatment of patients. Only one of the classes of drugs taken by 4% or more of the patients was included.

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TABLE 4 Drug classes and combinations used in treating patients with bipolar disorder, expressed as *n* (%).

	Acute episode	Maintenance period					
Combinations by class	Baseline (*n* = 204)	3 months (*n* = 173)	6 months (*n* = 153)	9 months (*n* = 147)	12 months (*n* = 149)	χ^2	*P*
MS	3 (1.5)	8 (4.6)	10 (6.5)	14 (9.5)	15 (10.1)	15.552	0.004
MS + AP	90 (44.1)	62 (35.8)	60 (39.2)	55 (37.4)	53 (35.6)	3.864	0.426
MS + AD	2 (1.0)	8 (4.6)	4 (2.6)	5 (3.4)	1 (0.7)	7.580	0.091
MS + BZD	0 (0)	2 (1.2)	2 (1.3)	2 (1.4)	3 (2.0)	4.299	0.322
MS + AP + AD	28 (13.7)	18 (10.4)	15 (9.8)	18 (12.2)	18 (12.1)	1.680	0.797
MS + AP + BZD	29 (14.2)	12 (6.9)	9 (5.9)	7 (4.8)	8 (5.4)	15.616	0.003
MS + AD + BZD	5 (2.5)	1 (0.6)	3 (2.0)	0 (0)	3 (2.0)	5.144	0.233
MS + AP + AD + BZD	26 (12.7)	13 (7.5)	8 (5.2)	5 (3.4)	8 (5.4)	14.105	0.007
AP	4 (2.0)	16 (9.2)	10 (6.5)	10 (6.8)	14 (9.4)	13.066	0.010
AP + AD	6 (2.9)	14 (19.2)	14 (9.2)	9 (6.1)	7 (4.7)	7.802	0.099
AP + BZD	0 (0)	3 (1.7)	3 (2.0)	5 (3.4)	3 (2.0)	7.255	0.087
AP + AD + BZD	10 (4.9)	5 (2.9)	3 (2.0)	4 (2.7)	6 (4.0)	2.692	0.619
AD	1 (0.5)	5 (2.9)	6 (3.9)	6 (4.1)	4 (2.7)	6.902	0.126
AD + BZD	0 (0)	5 (2.9)	5 (3.3)	5 (3.4)	3 (2.0)	8.865	0.046
BZD	0 (0)	1 (0.6)	1 (0.7)	2 (1.4)	3 (2.0)	4.588	0.225

AD, antidepressant; AP, antipsychotic; MS, mood stabilizer; BZD, benzodiazepine.

TABLE 5 Number of drugs prescribed to patients being treated for bipolar disorder, expressed as *n* (%).

	Acute episode	Maintenance period					
Number of drugs	Baseline (*n* = 204)	3 months (*n* = 173)	6 months (*n* = 153)	9 months (*n* = 147)	12 months (*n* = 149)	χ^2	*P*
1	6 (2.9)	25 (14.5)	20 (13.1)	26 (17.7)	34 (22.8)	33.047	0.000
2	71 (34.8)	76 (43.9)	74 (48.4)	69 (46.9)	55 (36.9)	10.199	0.037
3	74 (36.3)	51 (29.5)	37 (24.2)	35 (23.8)	39 (26.2)	9.498	0.050
4	46 (22.5)	11 (6.4)	12 (7.8)	10 (6.8)	14 (9.4)	35.410	0.000
≥ 5	7 (3.4)	10 (5.8)	10 (6.5)	7 (4.8)	7 (4.7)	2.097	0.718
Mean number (SD)	2.9 ± 0.9	2.5 ± 1.0	2.5 ± 1.0	2.3 ± 1.0	2.4 ± 1.1	45.168	0.000

Polypharmacy was defined as the use of two or more psychotropic drugs. Polypharmacy might involve the same class of drugs, such as two antidepressants, or different classes of drugs, such as mood stabilizers and antipsychotics. Fifteen types of medication classes were analyzed, including four types of monotherapies, six types with two different classes of drug co-treatments, four types with three different classes of drug co-treatments, and one type with four different classes of drug co-treatment. For all patients, the numbers of drugs used were collected at baseline and at each follow-up assessment. The changes in the drug numbers were observed from the collection of these data.

Statistical analysis

Data on sociodemographic, clinical characteristics, numbers of different medication classes, their dosage of psychotropic drugs, drug combinations, and number of psychotropic drugs were compared between groups. Continuous variables that did not conform to the normal distribution were reported as median (1st quartile = Q1, 3rd quartile = Q3), and those that conform to the normal distribution were reported as means ± the standard deviation (SD). Categorical variables were reported in numbers (percentages). Chi-square test was used to compare categorical variables. For the most commonly used drugs, only one of the classes of drugs taken by ≥4% or more of the patients was included. If the number of cases was less than 5, then the outcome from Fisher's exact test was used. Data were analyzed using two-tailed significance estimates. All data was analyzed using SPSS 21.0 software (Statistical Package for Social Sciences, SPSS Inc.) and the statistical significance was set at *P*-value < 0.05.

Results

The study ultimately included 204 patients with BD, of whom, 108 (52.9%) were diagnosed with bipolar depression, 55 (27.0%) with bipolar mania, 35 (17.2%) with mixed state, and 3 (1.5%) with rapid cycle; 2 (1.0%) were in remission and 1 (0.4%) were not classified. Of the 204 patients, 77 (37.7%) were male and 127 (62.3%) were female, and the age at enrollment was 29.0 (20.0, 44.8) years old; 101 (49.5%) were single, and 83 (40.7%) were married. The median disease course

was 48.0 (19.5, 120) months, and the patients reported 21 (13, 32) days of psychiatric hospitalization for BD. The sociodemographic and clinical characteristics of the patients during the maintenance period are shown in Table 1. There were no significant sociodemographic or clinical characteristics among the groups ($P > 0.05$).

Table 2 presents the four medication classes received by patients for each 3-month assessment period. After 12 months, 73.0% of the patients still took medications, and 27.0% of the patients stopped taking medications. Three and 6 months post-discharge were important times at which medication use was discontinued. Mood stabilizers (72–90%) and antipsychotics (77–95%) were still the most important drugs in patients with BD. Antidepressants (34–40%) and benzodiazepines (20–34%) were the other frequently used drug classes. There was no significant difference in antidepressants used during acute episodes and maintenance periods ($P > 0.05$). There were, however, significant differences in mood stabilizers, antipsychotics, and benzodiazepines used ($P < 0.05$).

Table 3 shows the most common drugs used and their daily mean dosage, displayed separately for each 3-months period. For mood stabilizers, 40–56% of BD patients were prescribed lithium, and 33–52% of patients were prescribed valproate. For antipsychotics, 54–65% of BD patients were prescribed quetiapine, and 12–20% of the patients were prescribed olanzapine. Sertraline (6–9%) and fluoxetine (5–9%) were the antidepressants that were most frequently used. Lorazepam (10–18%) was the most commonly used benzodiazepine. There were no changes in the prescription rate of the most common drugs during the 12-month study period, but the prescription rates for lithium, valproate, and oxazepam decreased. Among the major drugs, the mean doses of lithium, valproate, quetiapine, sertraline, and lorazepam were 738.3, 747.6, 233.0, 97.4, and 0.9 mg, respectively. There were no significant changes in the daily mean dosage among the BD patients over 12 months.

Considering drug combinations, there were 15 unique combinations by medication class (Table 4). The most frequently taken was MS plus AP co-treatment, accounting for approximately 36–44% of all patients. Twelve months after discharge, the use of MS and AP alone gradually increased. The use of MS + AP + BZD and MS + AP + AD + BZD decreased gradually over the same period, and the use of AD + BZD changed significantly, but not linearly.

As shown in Table 5, 35–48% of the patients were treated with two drugs and 24–36% received three drugs. While only 2.6% of the patients received one drug at baseline, this increased to 22.8% at the 12th month. The overall average number of drugs used was approximately 2.5.

Discussion

This study found that the first 6 months after the initiation of treatment are very important to medication adherence. Poor medication adherence is a common problem among patients with BD, causing disability and suffering as well as widespread financial costs. Psychotropic adherence was evaluated with medication possession ratio in patients with BD, and about 50% of patients were non-adherence (27, 28). The barriers to adherence are numerous and span multiple levels, including factors related to the pathology of BD, as well as factors specific to the individual's genetic, psychological, and social environment. Treatment Settings, the health care system, and broader health policies may all influence medication adherence in patients with BD (29). According to medical records, we found that a quarter of inpatients with BD had poor medication adherence. We were surprised to find that this kind of behavior was generally observed within 6 months after treatment. If a patient can adhere to a medication regimen for 6 months, then this adherence could be maintained.

The study also found that mood stabilizers and antipsychotics remained the primary treatment for BD, with 90% of patients using mood stabilizers during an acute episode and approximately 72% of patients using mood stabilizers during the maintenance period. Ninety-five percent of patients used antipsychotics during acute episodes, and approximately 80% used antipsychotics in the maintenance period. Antipsychotics were prescribed at a higher rate than mood stabilizers in both the acute episodes and maintenance periods and thus played the most important role in the treatment of BD. There were many differences in drug use in BD patients. Some previous studies have suggested that mood stabilizers are the primary treatment for BD (30, 31). Meta-analysis data provide some evidence that antipsychotics might be superior to lithium or divalproex in reducing the time required for manic symptoms (32). We clearly observe that treatment is changing over time and that antipsychotics are on the rise in the treatment of BD.

Despite the widespread use of antidepressants in BD, there is controversy surrounding the inclusion of antidepressant medications in management of the disorder (33). The study found that more than 37% of BD patients used antidepressants, and there was no significant difference between the acute episodes and maintenance periods. For the treatment of depressive symptoms, clinicians prefer antidepressants to mood stabilizers that have an anti-depression effect. Although there is a risk to antidepressant use in BD, the improvement in depressive symptoms achieved is incomparable to that of other drugs. In Japan, about 40% of patients with BD are treated with antidepressants. Antidepressants are commonly used in combination with mood stabilizers, antipsychotics, or both. Those taking antidepressants took fewer mood stabilizers, more anti-anxiety medications and more hypnotics than those not taking antidepressants (34).

Although benzodiazepines are not used to treat BD, many people with BD have anxiety and sleep symptoms, so they are often used to treat these secondary symptoms. Although impairment in memory and processing speed was found in patients with BD, benzodiazepine users showed additional neurocognitive impairment in executive function, regardless of whether they received benzodiazepine treatment. These findings support limiting the use of benzodiazepines in patients with BD (35). Our study found that the acute use rate was 34% and the maintenance use rate was 23%. The use during maintenance periods was obviously lower than that during acute episodes. The problem of benzodiazepine addiction is still worthy of attention (36).

In our study, the most commonly used mood stabilizers were lithium and valproate. The most commonly used antipsychotic was quetiapine. Antidepressant use was more dispersed, with sertraline relatively more frequently used, at approximately 8%. The most commonly used benzodiazepine was lorazepam, at approximately 12%. The significant differences between acute episodes and maintenance periods were observed with lithium, valproate, and oxazepam. The proportion of oxazepam used was small, and the influencing factors were not clear. The usage of lithium and valproate during maintenance periods was significantly lower than that in acute episodes. Some previous studies in recent years have shown

a decrease in lithium use (37). We found that not only lithium but also valproate showed a decrease. In terms of drug dosage, we did not find significant changes between the acute episodes and maintenance periods. Among the major drugs, the mean doses of lithium, valproate, quetiapine, sertraline, and lorazepam were 738.3, 747.6, 233.0, 97.4, and 0.9 mg, respectively. This can provide a reference for psychiatrists. For antipsychotics used in BD patients, there is a key point we must know. A previous study suggested that aripiprazole was associated with a longer time to hospitalization than ziprasidone, olanzapine, quetiapine, or risperidone in BD patients (38).

There is an increased risk of diabetes mellitus associated with antipsychotic and psychotropic polypharmacy use in BD (39). In our study, drug combinations were still very common in BD, with MS + AP being the predominant drug class combinations, with approximately 36–44% of patients receiving this treatment and no significant changes in acute episodes and maintenance periods. In terms of drug class use, MS, MS + AP + BZD, MS + AP + AD + BZD, AP, and AD + BZD had significant changes in the acute episodes and maintenance periods. MS and AP increased significantly, MS increased from 2 to 10%, and AP increased from 2 to 9%. MS + AP + BZD and MS + AP + AD + BZD decreased significantly, MS + AP + BZD decreased from 14 to 5%, and MS + AP + AD + BZD decreased from 13 to 3%. AD + BZD showed no linear change. From our study, we can see that the treatment during acute episodes and maintenance periods changes, and relatively simple drug use in the maintenance period is more common. The selection, sequence, and combination of anti-manic agents must be tailored to each patient and informed by their illness presentation, comorbidities, previous history, drug costs, treatment preferences, and the availability of safety monitoring (40).

At present, drug treatment is still the main clinical for BD. In order to achieve rapid and effective outcomes, clinicians often use polypharmacy for BD patients (41). Our study found that the average number of medications used by BD patients was 2.5, with more medication used during acute episodes than during maintenance periods. There were 24–36% of patients who used three drugs and 35–48% of patients who used two drugs. The proportion of patients using one drug showed a significant upward trend, and the proportion of those using four drugs showed a downward trend. Recently, there has been a significant increase in polypharmacy. While some of these combinations have been supported by clinical trials, the efficacy of many combinations has not been proven. These trends increase patients' risk of drug-drug interactions with uncertain benefits in terms of quality of care and clinical outcomes (42).

There were some limitations to this study. First, the sample size of this study was small, and the data were from only one hospital. This affects the credibility of the findings to some extent, and a larger sample size and the inclusion of patients from more hospitals are needed to validate the present result. Sub-analysis such as who were received 2–3 medications and those treated with more than 3 medications would be quite interesting. Second, BD is a complex group of disorders that includes bipolar depression, bipolar mania, mixed state, and rapid cycle, as well as cases in remission and those not classified. Different types may have different treatment drugs. A study of each type is needed. Third, we followed patients with BD for 1 year. We were still not studying patients for a long enough duration, and drug treatment for BD will require much longer observational studies. Finally, there are many different factors that may influence drug choice, such as physician prescribing habits, drug costs, regulatory impact, insurance plan prescribing, drug marketing, and patient preferences, which were not considered in this study. However, from this study, we know about the characteristics of psychotropic drug use and medication adherence of patients with BD at acute and maintenance episodes. These provide reference for psychiatrists in clinical medication. In this way, patients with BD may receive more effective treatment and reduce the burden on patients and society.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ningbo Kangning Hospital Ethics Committee. The Ethics Committee waived the requirement of written informed consent for participation.

Author contributions

PJ wrote the manuscript, conceived, designed, performed the experiments, and analyzed and interpreted the data. JS, CZ, and XM performed the experiments and contributed to reagents, materials, and analysis tools or data. XZ conceived and designed the experiments, contributed to reagents, materials, and analysis tools or data, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Abnormal amplitude of low-frequency fluctuation values as a neuroimaging biomarker for major depressive disorder with suicidal attempts in adolescents: A resting-state fMRI and support vector machine analysis

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Objective: Major depressive disorder (MDD) is associated with suicidal attempts (SAs) among adolescents, with suicide being the most common cause of mortality in this age group. This study explored the predictive utility of support vector machine (SVM)-based analyses of amplitude of low-frequency fluctuation (ALFF) results as a neuroimaging biomarker for aiding the diagnosis of MDD with SA in adolescents.

Methods: Resting-state functional magnetic resonance imaging (rs-fMRI) analyses of 71 first-episode, drug-naive adolescent MDD patients with SA and 54 healthy control individuals were conducted. ALFF and SVM methods were used to analyze the imaging data.

Results: Relative to healthy control individuals, adolescent MDD patients with a history of SAs showed reduced ALFF values in the bilateral medial superior frontal gyrus (mSFG) and bilateral precuneus. These lower ALFF values were also negatively correlated with child depression inventory (CDI) scores while reduced bilateral precuneus ALFF values were negatively correlated with Suicidal Ideation Questionnaire Junior (SIQ-JR) scores. SVM analyses showed that reduced ALFF values in the bilateral mSFG and bilateral precuneus had diagnostic accuracy levels of 76.8% (96/125) and 82.4% (103/125), respectively.

Conclusion: Adolescent MDD patients with a history of SA exhibited abnormal ALFF. The identified abnormalities in specific brain regions may be involved in the pathogenesis of this condition and may help identify at-risk adolescents. Specifically, reductions in the ALFF in the bilateral mSFG and bilateral precuneus may be indicative of MDD and SA in adolescent patients.

KEYWORDS

amplitude of low-frequency fluctuation, major depressive disorder, suicidal attempts, resting-state fMRI, support vector machine

1. Introduction

Major depressive disorder (MDD) is an extremely debilitating neuropsychiatric disease that causes characteristic and often severe emotional dysregulation (Wu et al., 2020). MDD is strongly associated with age and adolescents in the United States exhibit lifetime and 12-month MDD prevalence rates of 11 and 7.5%, respectively (Avenevoli et al., 2015). Adolescents suffering from MDD are also at risk of a range of other comorbid psychiatric conditions, suicide attempts (SAs; Doruk Camsari et al., 2019), substance abuse, and reduced social skills (Nardi et al., 2013); thus, the disease is a major focus of clinical psychiatry and public health-focused research throughout the world (Chen et al., 2020). MDD is the most common disorder present in adolescents that commit or attempt suicide (Nock et al., 2013), with suicide remaining the second most common driver of mortality among individuals 10–19 years of age (Breslin et al., 2020). Despite the severe toll that adolescent MDD can have on patients and those around them, the neurophysiological basis for this condition is not completely understood.

A range of magnetic resonance imaging (MRI) strategies have been used to assess patients with MDD. These include functional MRI (fMRI), magnetic resonance spectroscopy, structural MRI, and diffusion tensor imaging (Gao et al., 2021). Of these, fMRI offers value as a safe, noninvasive, reproducible tool that can aid in diagnosing disease through the assessment of minute shifts in blood oxygenation-level-dependent (BLOD) MRI signaling linked to brain activity (Gore, 2003). fMRI includes both resting-state (rs-fMRI) and task-based formats (Gao et al., 2021), with rs-fMRI performed in a quiet setting while subjects have their eyes closed and are not performing any tasks. Research by Biswal et al. suggests that the spontaneous resting-state BLOD signals observed under these conditions are reflective of basal neuronal activity (Biswal et al., 1995). Accordingly, rs-fMRI offers value as a means of examining spontaneous brain function and detecting any abnormalities or aberrant functional connectivity within the central nervous system (Biswal et al., 1995; Biswal, 2012). Unlike task-based fMRI analyses, rs-fMRI permits the evaluation of individuals not performing complex tasks and is thus better suited to the assessment of individuals unable to complete cognitively demanding tasks due to neurological or psychiatric disorders (Takamura and Hanakawa, 2017). For these reasons, fMRI had been used to study patients with a range of diseases and disorders, including depression (Guo et al., 2022), bipolar disorder (Vargas et al., 2013), schizophrenia (Whitfield-Gabrieli et al., 2009), epilepsy (Gao et al., 2022b), attention deficit hyperactivity disorder, abnormal brain development (Jolles et al., 2011), migraine (Wang et al., 2022), mild cognitive impairment (Gao et al., 2022c), and Parkinson's Disease (Mi et al., 2021).

The two parameters that are most commonly calculated from BLOD signals recorded during rs-fMRI analyses include the amplitude of low-frequency fluctuation (ALFF) and functional connectivity (FC) (Zhang et al., 2014). Of these, ALFF is an indicator of the intensity of spontaneous local neuronal activity under these basal conditions. Shifts in spontaneous brain activity are assessed by fast Fourier transform of time-series data into the frequency domain and then examining the average amplitude from 0.01 to 0.08 Hz to compare changes in BOLD signals (Zang et al., 2007). Unlike FC, ALFF is a frequency-specific signal that is related to oscillatory phenomena, and directly reflects the intensity of spontaneous neural activity in a given region of the brain. While some studies have explored ALFF values in MDD patients, there is limited analysis of the results using support vector machine (SVM) techniques. SVM machine learning algorithms classify high-dimensional data points through the maximization of margins between classes (Pereira et al., 2009). SVM methods are frequently employed in psychiatric and neurological settings due to their high degree of classification accuracy and ability to process high-dimensional data (Gaonkar et al., 2015; Li et al., 2021).

Here, an SVM approach was employed to identify brain regions showing differences in ALFF values between adolescent MDD patients with a history of SA and healthy control individuals. The relationships between these values and patient depression and suicide scale scores were also assessed, and the utility of these changes in ALFF values as a neuroimaging biomarker of MDD with SA in adolescents was examined.

2. Materials and methods

2.1. Participants

A total of 71 first-episode drug-naïve adolescent depression patients were recruited from the Department of Psychiatry of Wuhan Mental Health Center. Patients were diagnosed with depression by two experienced psychiatrists based on DSM-IV criteria. To be eligible for study inclusion, patients had to be 7–17 years of age, right-handed, meet the diagnostic criteria for an acute episode of depression, have a history of SA within the past 14 days, be free of serious physical illnesses, be free of the alcohol and/or substance abuse or dependence, and be free of other Axis I disorders including schizophrenia, bipolar disorder, and substance-induced mood disorders. In addition, 54 age- and sex-matched healthy control individuals were recruited from the Wuhan Mental Health Center medical examination center. These controls were right-handed, had no history or family history of psychiatric disorders, and were free of any severe physical illness. All participants provided written informed consent for study participation. The Ethics Committee of Wuhan Mental Health Center approved this research, which was conducted in accordance with the guidelines of the Declaration of Helsinki.

SA was defined as any self-destructive behavior intended to terminate one's own life that did not result in death (O'Carroll et al., 1996; Li et al., 2021). The patients included in this study were confirmed to have a history of SA through interviews with experienced psychiatrists, who also collected relevant details including the numbers of SAs and the dates on which they had occurred. When ambiguous results were obtained, the psychiatrists also made inquiries with the parents or clinicians of that patient to confirm these results. The Suicidal Ideation Questionnaire Junior (SIQ-JR; Keane et al., 1996) scale was conducted on the same day as the rs-fMRI to evaluate the severity of suicidal ideation, while the child depression inventory (CDI; Akimana et al., 2019) was used to assess depression severity.

2.2. Image acquisition

An Achieva 3 T MRI scanner (Philips, The Netherlands) was used for all imaging acquisition. The rs-fMRI data were preprocessed using MATLAB DPARSF software (Wang et al., 2017), as previously described (Gao et al., 2022a). Further details are provided in the Supplementary material.

TABLE 1 Characteristics of the participants.

Characteristics	Patients (n=71)	HCs (n=54)	p value
Gender (male/female)	71 (39/32)	54 (24/30)	0.245
Age, years	13.97 ± 1.51	14.17 ± 1.48	0.472
Years of education, years	6.79 ± 2.16	7.24 ± 2.28	0.261
CDI	30.27 ± 7.68	7.94 ± 2.64	0.000
SIQ-JR	65.58 ± 9.44	-	-

The value of p for gender distribution was obtained by the Chi-square test. The p-values were obtained by two sample t-tests. HC, healthy controls; CDI, child depression inventory; SIQ-JR, Suicidal Ideation Questionnaire Junior.

2.3. ALFF analysis

ALFF analyses were performed with Rest software[1] as reported previously (Zou et al., 2008). Further details are provided in the Supplementary material.

2.4. Classification analysis

SVM methods were used to evaluate the ability of ALFF values in specific brain regions to differentiate between MDD patients with a history of SA and healthy control individuals. The SVM analysis was conducted using the LIBSVM package in MATLAB; further information is provided in the Supplementary material.

2.5. Statistical analysis

Age, CDI scores, and years of education were compared between MDD patients and control individuals using two-sample t-tests, whereas gender distributions were compared with Chi-square tests. SPSS 22.0 was used for statistical analyses. Correlations between abnormal ALFF values and specific clinical findings were assessed *via* Pearson correlation analyses. $p < 0.05$ were considered significant.

A voxel-by-voxel covariance analysis of individual whole-brain ALFF maps was used to detect differences between the two study cohorts. Analyzed covariates included age, years of education, and framewise displacement. REST was used for the GRF correction of results at $p < 0.01$ (cluster significance: $p < 0.01$, voxel significance: $p < 0.001$).

3. Results

3.1. Participant characteristics

A total of 71 first-episode MDD patients with a history of recent SAs were enrolled in the study, together with 54 healthy control individuals were enrolled. The clinical and demographic characteristics of the participants are shown in Table 1. No significant differences in age, sex, or education level were observed between the groups.

3.2. ALFF differences between groups

Differences in ALFF values were compared between MDD patients and controls using two-sample t-tests, revealing significantly lower ALFF values in the bilateral medial superior frontal gyrus (mSFG) and bilateral precuneus of MDD patients with a history of SA compared with the controls (Figure 1; Table 2).

3.3. SVM results

An SVM approach was used to analyze decreases in the ALFF values of the bilateral mSFG and bilateral precuneus in MDD patients with a history of SA. This showed that reduced ALFF values in the bilateral precuneus offered the highest diagnostic accuracy of 82.4% (103/125), with a sensitivity and specificity of 91.5% (65/71) and 70.4% (38/54), respectively (Figure 2). The accuracy value for the reduced ALFF values in the bilateral mSFG was 76.8% (96/125) (data not shown).

3.4. Correlation results

The associations between ALFF values and other clinical variables in MDD patients were assessed through Pearson correlation analyses. This revealed the ALFF values in the bilateral mSFG and bilateral precuneus were negatively correlated with CDI scores (Figure 3), while there was also a negative correlation between ALFF values in the bilateral precuneus and SIQ-JR scores (Figure 4). ALFF values were not significantly correlated with patient age or years of education (data not shown).

4. Discussion

This is the first report of the use of an SVM technique to detect alterations in rs-fMRI-derived ALFF values in adolescent MDD patients with a history of SA compared with healthy controls. Significant reductions in the ALFF values were found in the mSFG and precuneus of MDD patients compared with the controls. Further analysis using SVM methods confirmed that these neuroimaging alterations may be of diagnostic value for the identification of adolescents with MDD.

The prefrontal cortex is positioned anteriorly to the premotor and motor portions of the frontal lobe (Lewis, 2004) and includes the mSFG, orbital SFG, and dorsolateral SFG (Liu et al., 2021). The default mode network (DMN) consists of an interconnected series of regions in the brain that exhibits higher levels of activity under resting conditions than during task completion. The mSFG is a DMN hub (Franco et al., 2009) and has been reported to be associated with aberrant neurological activity in patients with MDD (Guo et al., 2018). The mSFG also serves as an essential region of the brain necessary for emotional processing, executive function, the detection of causality, and for sequence learning (Van Overwalle, 2009). Previous studies have explored the association between the mSFG and MDD, with Peng et al., for example, reporting increased mSFG gray matter volume in these patients (Peng et al., 2016) while Liu et al. reported an association between

1 http://www.resting-fmri.sourceforge.net

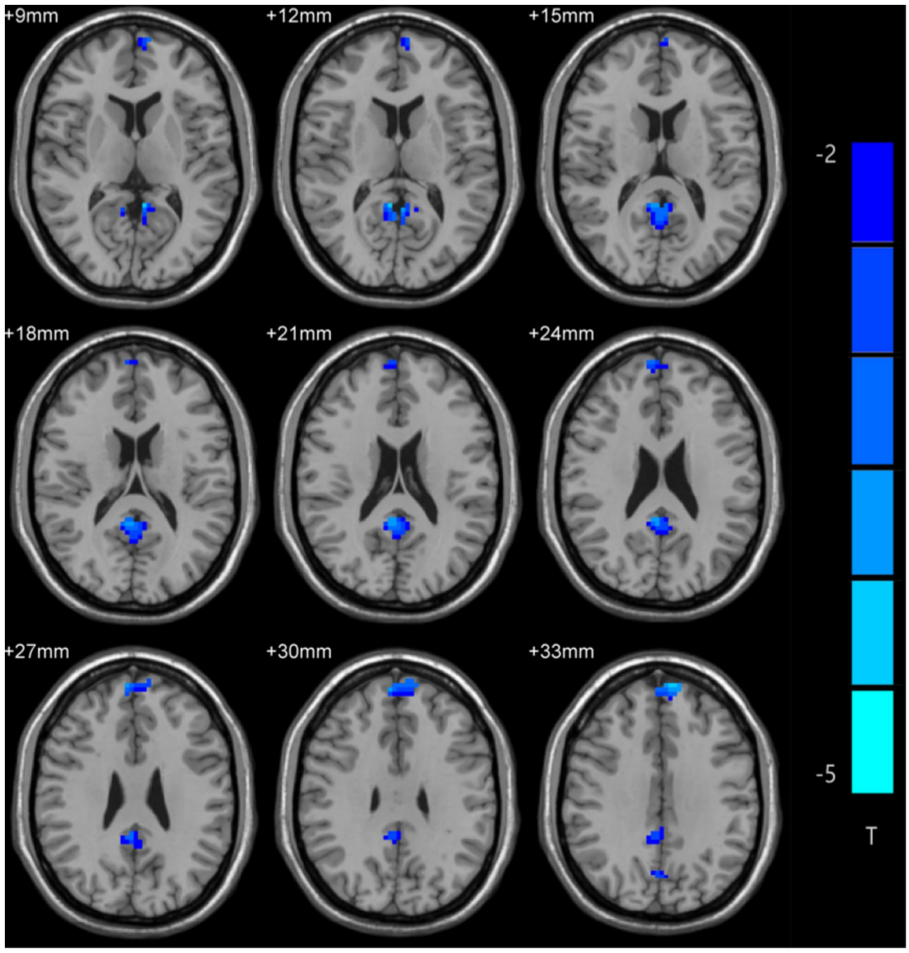

FIGURE 1
Amplitude of low-frequency fluctuation (ALFF) differences across groups. Blue color denotes low ALFF, and the darker the color, the lower the ALFF value of the brain area.

TABLE 2 Signification differences in ALFF values between the groups.

Cluster location	Peak (MNI)			Number of voxels	*T* value
	X	Y	Z		
Bilateral mSFG	±9	57	39	103	−5.79
Bilateral precuneus	±3	−66	39	253	−4.97

ALFF, amplitude of low-frequency fluctuation; mSFG, medial superior frontal gyrus; MNI, Montreal Neurological Institute.

dysfunction of the right mSFG and the cognitive processing of negative emotion in MDD (Liu et al., 2021). Here, ALFF values in the bilateral mSFG were found to be lower in MDD patients. In line with these results, a case–control rs-fMRI study of first-episode drug-naïve adolescent MDD patients showed lower ALFF values in the left medial frontal lobe (Gong et al., 2014). However, one voxel-based meta-analysis found higher ALFF values in the SFG in MDD patients than in controls (Gong et al., 2020). These differences may be linked to variations in study cohorts, duration of illness, medication use, and scanning parameters. For example, while higher bilateral SFG ALFF values were reported in early-onset depression, reduced values were found in late-onset depression (Guo et al., 2013). Another analysis that focused on non-suicidal self-harm also observed significantly lower bilateral mSFG ALFF values in adolescents suffering from MDD (Huang et al., 2021). Moreover, lower ALFF values in the right ventral medial frontal gyrus were reported in MDD patients with a history of SA compared with non-suidical patients (Fan et al., 2013). This may suggest a close relationship between ALFF values in the frontal gyrus and the risk of self-harm or suicide in MDD. Here, the SVM results indicated a 76.8% accuracy in the use of the these values to differentiate between adolescent patients with MDD and a history of SA and healthy controls. Correlation analysis showed that the mSFG ALFF values were negatively correlated with the and CDI scores but were unrelated to the SIQ-JR scores. Changes in the ALFF values in the mSFG may thus be closely related to the pathophysiology of MDD and/or suicidal ideation in these patients.

The precuneus has a unique anatomical location within the posteromedial parietal cortex buried in the interhemispheric fissure. It is thus rarely injured in isolation and it is particularly challenging to study (Cavanna and Trimble, 2006). The functions of the precuneus include self-awareness, cognition, autobiographical memory, and visuospatial processing (Zhang and Li, 2012; Tanglay et al., 2021). Much like the mSFG, the precuneus functions as a core DMN hub, and prior work suggests a close

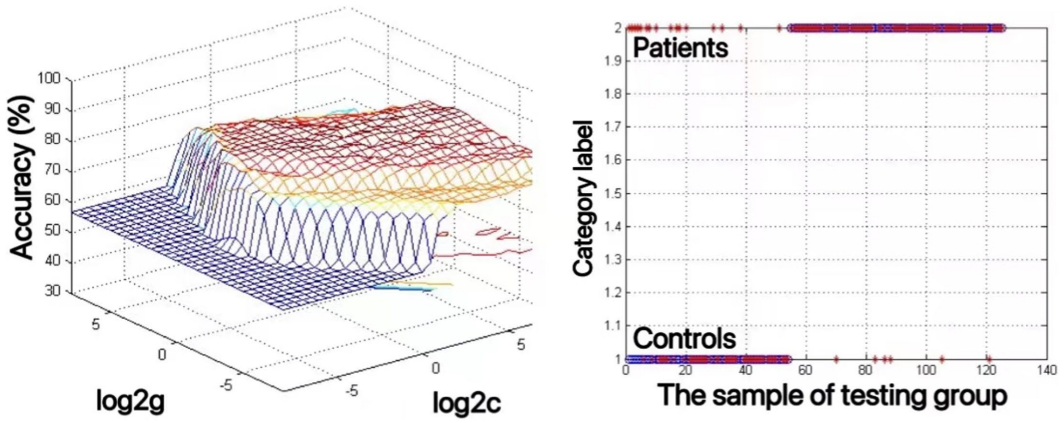

FIGURE 2
The use of decreased ALFF values in the bilateral precuneus to differentiate adolescents with major depressive disorder with suicidal attempts from healthy controls. Visualization of classifications through support vector machine (SVM) techniques using the ALFF values in the bilateral precuneus. Left: SVM parameters selection result of 3D view; Right: Classification map of the ALFF values in the bilateral precuneus.

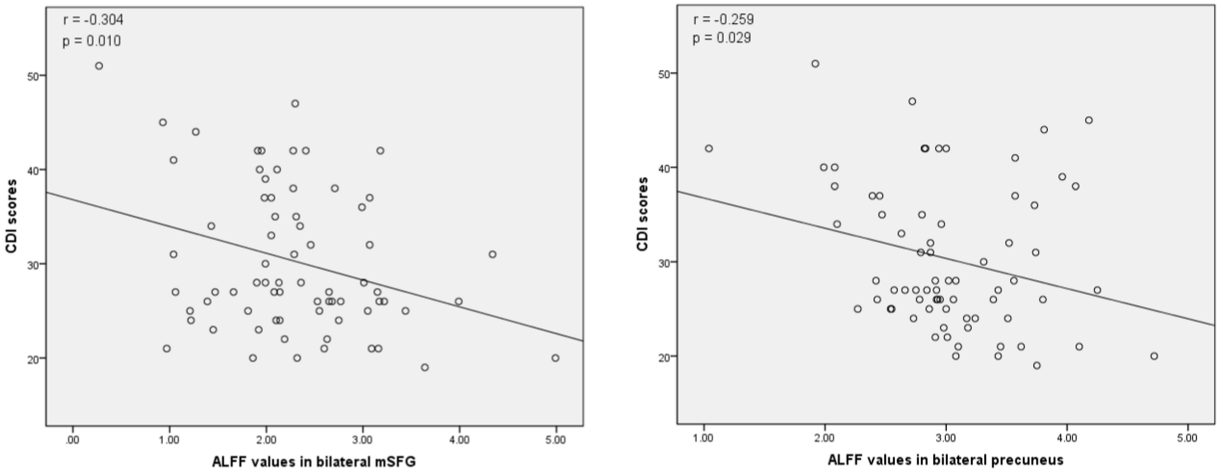

FIGURE 3
Correlations between abnormal ALFF and child depression inventory (CDI) scores. Left: Negative correlation between the ALFF values in the bilateral medial superior frontal gyrus (mSFG) and CDI scores. Right: Negative correlation between the ALFF values in the bilateral precuneus and CDI scores.

relationship with MDD. For example, in one rs-fMRI study, ALFF values in the left precuneus were found to be abnormal in individuals affected by social anxiety disorders and to be negatively correlated with the clinical symptoms experienced by these patients (Yuan et al., 2018). Lower ALFF values in the right precuneus have also been reported in MDD, which were found to remain below those of healthy controls even after remission, suggesting that ALFF values may represent a valuable biomarker for MDD (Wang et al., 2020). Consistently, other studies have proposed the application of ALFF as a diagnostic neuroimaging biomarker of MDD in both adolescent and adult populations (Gong et al., 2014; Li et al., 2018; Gong et al., 2020). Patients with depression accompanied by suicidal tendencies also exhibit reductions in right precuneus FC compared with controls (Shu et al., 2022). Consistent with these findings, the present study found that adolescent MDD patients with a history of SA showed lower ALFF values in the precuneus relative to healthy controls, and negative correlations were observed between the precuneus ALFF values and both CDI and SIQ-JR scores. The accuracy of the SVM results was 82.4%, indicating that the precuneus may represent a key mediator of MDD and SA pathogenesis. A reduced precuneus ALFF value should thus be explored as a neuroimaging biomarker for the diagnosis of MDD with suicidal tendencies in adolescents.

5. Summary and conclusion

MDD and suicidality represent growing public health problems throughout the world, especially among adolescents. Despite this pressing issue, the current understanding of MDD in adolescents is less understood compared with adults. The advent of novel neuroimaging technologies has led to the establishment of rs-fMRI as a valuable noninvasive means of aiding patient diagnosis in clinical

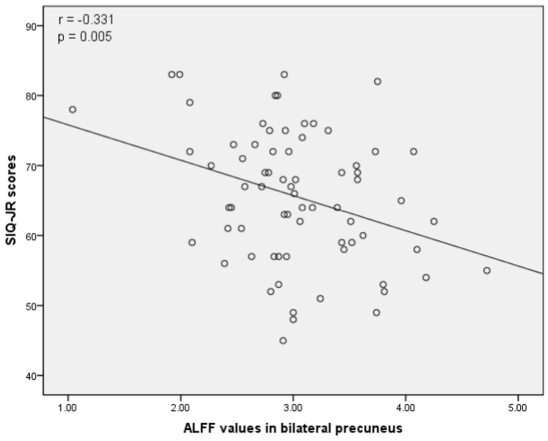

FIGURE 4
Correlations between abnormal ALFF and Suicidal Ideation Questionnaire Junior (SIQ-JR) scores. A negative correlation was found between the ALFF values in the bilateral precuneus and SIQ-JR scores.

settings. ALFF values, in particular, enable researchers to detect abnormalities in spontaneous brain activity through the monitoring of brain energy metabolism (Jing et al., 2013). Here, an SVM algorithm, which is commonly used for data analysis in biomedical contexts, was employed, demonstrating the value of reduced ALFF values in the bilateral mSFG and bilateral precuneus as neuroimaging biomarkers capable of identifying adolescent MDD patients with a history of SA.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Wuhan Mental Health Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YZ: investigation, resources, data analysis, manuscript writing and submitting. YS: investigation, resources, software, manuscript writing. CC: investigation, data curtion, writing-review. SY: data curtion, writing-review and editing. MC: conceptualization, methodology. TL: project administration, supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1146944/full#supplementary-material

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Development, validation and psychometric evaluation of the Chinese version of the biopsychosocial impact scale in orofacial pain patients

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Background: The objective of this study was to develop the Chinese version of the biopsychosocial impact scale (BPIm-S) to assess functional limitation and psychosocial distress in orofacial pain (OFP) patients in mainland China, and investigate the factor structure, reliability and validity, measurement invariance, as well as scores differences across genders, age and educational status among OFP patients.

Methods: The BPIm-S was developed and evaluated in four stages: (1) concept selection and item generation; (2) a pilot study assessing face and content validity; (3) the factors structure, reliability, convergent validity, and measurement invariance; and (4) concurrent validity and clinical responsiveness. Exploratory (EFA) and confirmatory factor analyses (CFA) were performed on data gathered from 406 OFP patients to assess construct validity. Composite Reliability (CR) and the Average Variance Extracted (AVE) were used to assess internal convergent validity. CR, internal consistency, and split-half reliability were also performed to determine the reliability. Multigroup CFA (MGCFA) was used to assess measurement invariance across genders, age and educational status. Mann–Whitney test compared scores across different genders, age and educational status. Participants completed the BPIm-S, visual analog scale (VAS), brief pain inventory facial (BPI-F), General Anxiety Disorder-7 (GAD-7) and Patient Health Questionnaire-9 (PHQ-9), and spearman 's correlation coefficient was used to evaluate the concurrent validity and item-total correlations. A total of 12 patients with OFP completed the BPIm-S twice to test clinical responsiveness. To conduct the CFA and measurement invariance analysis, Mplus 8.4 was used. IBM SPSS Statistics 21 software and SPSSAU, a web-based data science algorithm platform tool, were used for all additional studies.

Results: For the preliminary version, 17 items were chosen. A total of four items were removed following the pilot research. The remaining 13 items of the BPIm-S comprised an overall summary scale. Excellent reliability (Item-to-total correlations ranged from 0.763 to 0.912) and strong internal consistency (Cronbach's α = 0.970, functional limitation, 0.962, and psychosocial distress,

0.977) were discovered. CFA also validated the structural validity of the 13-item scale. EFA was performed and a two-factor structure was investigated. In addition, MGCFA corroborated the measurement invariance of the BPIm-S across gender, age, and educational status. Patients over the age of 30, those with a medium level of education, and those with a low level of education showed substantially greater levels of functional limitation and psychological distress (Wilcoxon test, $p < 0.001$). Both concurrent validity and clinical responsiveness were assessed to be of good quality.

Conclusion: The BPIm-S demonstrated good psychometric qualities and is a reliable tool that can now be used by clinicians to evaluate functional limitation and psychosocial distress among OFP patient.

KEYWORDS

chronic orofacial pain, scale development, Chinese patients, factor analysis, measurement invariance, clinical responsiveness

1. Introduction

Oral health is a critical component of general health (Petersen and Kwan, 2004). Oral health-related quality of life (OHRQoL) refers to the role of oral conditions or diseases on quality of life, which is closely related to the impact of pain or discomfort, physical, psychological, and social functions on wellbeing (Geels et al., 2008). Various studies have shown a connection between periodontal disease and other, more serious health issues, including endocarditis, stroke, and diabetes (Hiraki et al., 2020). Depression, anxiety is only some of the psychiatric issues that can coexist with burning mouth syndrome (Stohler, 2001; Kim et al., 2020). Throughout the world, increasing attention has been paid to the relationship between oral health and general health, including physical and mental health, particularly in China as research and policy regarding oral health have developed (Petersen, 2003). It has been reported that the Chinese government has released a series of policies on health, including the Healthy China 2030 blueprint and the Chronic Diseases Program in 2017 (Kong, 2017; Li and Chen, 2020; Li et al., 2020). These policies all involve oral health promotion as one of their main components. They also aim to encourage the development of oral health behaviors and increase the public's oral health literacy.

Orofacial pain (OFP) is one of the most complained about oral and maxillofacial problems. The global prevalence of OFP is estimated to be between 14% and 42% (McMillan et al., 2010). And it is associated with healthcare costs, loss of productivity and reduced quality of life, with a high social and personal burden (Durham et al., 2016). Although the epidemiology of OFP have been well-studied in many countries, limited surveillance data are available in China (Leung et al., 2008). This suggests that OFP would be the area of great concern and profound impact on oral health and general health in China. Moreover, OFP is a typical type of psychosomatic disorder in oral diseases (Shamim, 2014). Long-term OFP has been demonstrated in studies to be associated with sleeping issues, cardiovascular problems, indicating that OFP may be part of a general health condition (Lee and Auh, 2022). Also, approximately 30% of OFP patients exhibit psychiatric symptoms, which often go undetected and untreated (Toyofuku, 2016). Thus, it is important to identify patients with OFP at an early stage and to treat them with appropriate diagnosis.

The International Headache Society (IHS) published the International Classification of Orofacial Pain, the first edition (ICOP) in 2020 (IOP, 2020). ICOP proposed that in addition to traditional biological factors, psychosocial factors are not only powerful predictors of pain, function and quality of life of patients with chronic pain. Additionally, psychological variables are strong predictors of reactions to medical treatments such as pain relief surgery and medication. In the course of the illness of OFP patients, complex psychological conditions often aggravate the distress of the disease (Festa et al., 2021), but the existing research on this model is not deep enough, which has brought great obstacles to clinical diagnosis, intervention and treatment. Therefore, the biopsychosocial model has become the most comprehensive model in the field of OFP management.

Given that biopsychosocial disabilities have been observed in patients with OFP (Randall et al., 2016). The measurement of biopsychosocial disturbance is also an integral part of OFP assessment. It is critical for clinicians to take into account patient-reported outcome measures (PROMS) when diagnosing and evaluating treatment outcomes (Kyte et al., 2015). Current PROMS that measure function and disability in patients with OFP including Mandatory Function Improvement Questionnaire (MFIQ) (Stegenga et al., 1993), Craniofacial pain and disability inventory (CF-PDI) (Madrid et al., 2014), The 8-item and 20-item Jaw Functional Limit Scale (JFLS) (Ohrbach et al., 2008) and so on, which most focus on physical pain and disabilities but lack of the psychosocial dimension. Compared with the above instruments, although the Manchester Orofacial Pain Disability Scale (MOPDS) graded the degree of both physical and psychosocial disabilities, it still is lack of characteristic tests, like measurement invariance, clinical responsiveness and so on (Aggarwal et al., 2005; Kallás et al., 2013). The Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) proposed that PROMS should have validity, reliability and responsiveness (Prinsen et al., 2018). Due to the large number of OFP people on the Chinese

mainland, research into the use of PROMS in this population is essential. This questionnaire should include the biopsychosocial dimension to reflect the functional limitation and psychosocial distress of OFP patients. Pain assessment involves the use of subjective and objective measures and the subjective measures involve the use of diagnostic daily pain diary where patients verbalize or describe their pain. Objective measures include clinicians observing the patient's response to pain according to PROMS, such as the extent to which aspects of life are affected by pain or psychological changes (IOP, 2020). PROMS assessment must be performed systematically and using rigorously validated questionnaires to minimize the non-physiological variability inherent in such measures. Therefore, a psychometric validated PROMS that can be used to assess symptoms, related functions and the impact of OFP on quality of life in OFP patients is very necessary.

1.1. Assessing the OFP

The comprehensive evaluation of physical and psychological variables needs to rely on accurate screening, and use a relatively short, accurate instrument that can be used by people with different characteristics but studies using unverified scales are prone to the risk of bias (Marshall et al., 2000). In addition, among OFP patients, their perception of OFP is vulnerable to various social and cultural factors (Lin et al., 2013), so it is recommended to make cultural modifications to prevent cultural bias. There is a need for a Chinese scale able to assess the physiological and psychosocial dimensions of Chinese OFP patients, and its structure is explored and verified to make the scale more useful.

Many studies have shown that OFP is related to gender, age and different educational status. Shinal and Fillingim (2007) pointed out that women of childbearing age are more likely to have OFP than men. Dussor et al. (2018) proposed that the oral and facial morbidity of men and the elderly is high. In addition, our previous research has also proved that education will also affect OFP, for example, the high incidence of OFP can be observed among college students (Feng et al., 2022). Given the above results, it cannot be ruled out whether the population is affected by latent variables (gender, age, education, etc.) because they didn't use the same and accurate assessment instruments. Therefore, the scale should provide measurement invariance data (Kline, 2015). Appropriate assessment instruments contain measurement invariance, which indicates that personal traits unrelated to the structure evaluated by the scale do not influence individual project ratings (Gregorich, 2006). Psychological test score differences are meaningful after assessing the scale's measurement invariance in gender, age, and education. We aim to explore a suitable model structure, and test the reliability of the scale, especially after in-depth analysis of its invariance in terms of gender, age and educational status, to compare the differences between groups, which could make sure that the scale could be utilized as an important tool for assessing the impact of OFP and help doctors to make individualized clinical treatment.

PROMS represents an important measure of the impact of illness and its treatment on symptoms and functions. The questionnaire score should respond to the clinically obvious disability, that is, certain changes in the questionnaire score should reflect the corresponding changes in the clinical situation (Gillespie et al., 2014). Therefore, it is necessary to test the clinical reactivity of the newly developed PROMS.

In this study, we built on past research to create and test a new scale to measure the functional restriction and psychological effect of OFP on patients' lives. This research aimed to create a simple assessment scale for OFP patients that could be used to evaluate the complex impact of OFP on patients' everyday life and assist physicians in ordinary clinical practice.

2. Materials and methods

2.1. Theoretical framework

The ICOP guidelines suggest that the biopsychosocial model is strongly embedded as a concept in the understanding and assessment of OFP (IOP, 2020). The model suggests that OFP is increasingly understood as a complex biopsychosocial phenomenon that is highly associated with physical disability as well as a high prevalence of psychosocial distress. Physical disability (functional limitation) is reflected in the impact on quality of life related to oral health, i.e., chewing, mouth opening and speaking, in addition to the impact on life activities (Liu et al., 2021). And psychosocial distress demonstrated that patients with OFP often suffer from anxiety and depression (Wang et al., 2015).

2.2. Participants

This research was authorized by the Experimentation and Ethics Committee of the Second Xiangya Hospital of Central South University (KQ2019FY01). The study was conducted in compliance with the tenets of the Declaration of Helsinki. Participants in this research were recruited from the Department of Stomatology at Central South University's Second Xiangya Hospital, and all gave their permission before to participation. People who are fluent in Chinese are eligible. According to ICOP criteria (IOP, 2020), participants had to be diagnosed with definite OFP. The diagnostic criteria were validated by OFP physicians, temporomandibular doctors and endodontics experts according to the ICOP criteria (**Table 1**). The exclusion criteria for clinical samples were: (1) those who could not read and understand the scale correctly; (2) oral cancer patients; and (3) any other concurrent Axis I disorders according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (American Psychiatric Association, 2013); any organic brain disorder, severe head trauma, or history of substance abuse.

TABLE 1 Diagnostic criteria for OFP used in the studies[a].

Criteria[b]
1. OFP for at least 3 months (considered as chronic pain, according to the ICOP)
2. Baseline pain score ≥3 on a ten-point visual analog scale (VAS)

[a]The criteria complied with those defined by the ICOP.
[b]OFP severity is considered abnormal when either (1) or (2) applied.

2.3. Measurement

2.3.1. Instrument development

According to Boateng et al. (2018) development and psychometric testing of scale is one of most critical in much of the work of health, social, and psychological sciences. It includes four stages: (1) concept is selected and items are generated; (2) the scale is constructed; (3) the factors of the scale are captured, reliability, validity, and measurement invariance are tested, and compare the scores of different sociodemographic characteristics; and (4) clinical adaptation is assessed. The biopsychosocial impact scale (BPIm-S) was developed using the exploratory sequential research design to assessed the OFP health life related functional-psychosocial quality (**Figure 1**).

2.3.2. Stage I concept selection and item generation

2.3.2.1. Reviews of previous qualitative insights and OFP literature

On the basis of a survey of the relevant literature, current theories and models, and accessible measuring techniques, a precise conceptualization of the notion was first formulated (Boateng et al., 2018). We had a literature review related to OFP, trigeminal neuralgia, epidemiology, maxillofacial pain, temporomandibular, primary headache and so on, which were searched for in PubMed, China National Knowledge Infrastructure (CNKI) and other databases (**Supplementary Table 1**). Items based on the articles' functional and psychological views on OFP were developed and extracted. The item pool of 53 items was generated from the literature review and personal interviews.

2.3.2.2. Structured interview by target population and experts

Individuals interview were then performed with patients having a verified diagnosis of OFP in order to find observable manifestations of the idea, as opposed to depending only on a theoretical perspective. The participants (n = 15 patients with OFP) were later interviewed, and the following topics were covered: overall impression, thoroughness of instructions, and understandability of the questionnaire. They were also questioned whether it addressed all significant components of their pain-related life discomfort. Two hypothetical conceptual dimensions, functional distress and psychological distress, were derived from the examination, comparison, and combination of the original 27 items.

Further screening of items experts in dentistry, rehabilitation medicine, epidemiology, biostatistics, sociology, and psychology were invited to further screen the items. A total of 17 items were

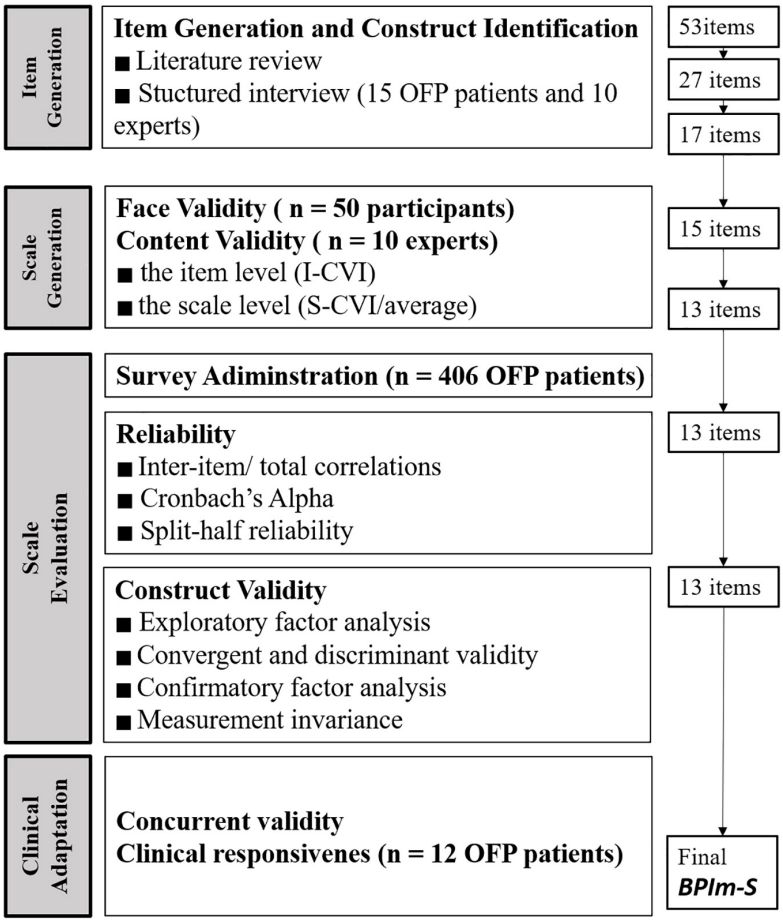

FIGURE 1
Phases in the development of the scale.

finally retained, which served as the first draft of the questionnaire (BPIm-S first draft).

2.3.3. Stage II scale development

2.3.3.1. Face validity–Evaluation by target population

To assess whether the questions reflected the study domain and met the necessary criteria, to confirm that the questions in the generated scale were appropriate and understandable to the targeted respondents, a cognitive interview was performed with 50 OFP patients before the survey was sent.

First-round BPIm-S completion times averaged 3 min and 19 seconds across participants. Items that were not part of the OFP, items that overlapped with other items, and items with confusing representations were removed. Using the results of the cognitive interviews, we revised the grammar and the available responses. More than seventy percent of patients replied "not relevant" to two questions about behavior disturbance (not doing chores and eating more often).

2.3.3.2. Content validity–Evaluation by experts

Delphi methodology was used to conduct experts investigation in this study. Ten specialists examined the scale to see whether the generated items adequately measured the targeted variables. The research group included two OFP physicians (Guo yue, He Zhi-jing), two temporomandibular doctors (Feng Yun-zhi, Liu Yin-chen), one anesthesia specialist (Wang Ya-ping), two endodontics experts (Gao Yi-jun, Li Wen-hui), two psychosocial research scientists (Chen Jin-dong, Yuan Hui), a statistician (Zhou Ying-hui). Through the whole process of refining and concluding the questionnaire, they contributed valuable insight and input.

The content validity index (CVI) was calculated at both the item (I-CVI) and scale (S-CVI/average) levels as part of the evaluation of the scale's content validity. Ten experts used a four-point scale ranging from 1 (not relevant) to 4 (very clear) to assess the relevance and clarity of the underlying topic or concept. Item relevance was determined using the Polit and Beck-proposed value range, whereby an I-CVI > 0.78 indicates relevance and an S-CVI of 0.80 or more indicates an appropriate scale (Polit and Beck, 2006).

TABLE 2 Characteristics of validation study participants (*N* = 406).

	Median-age, (interquartile range)	*N* (%)/(95% CI)
Age (years)		
	34 (24, 52)	
Gender		
Male		165 (40.6%)/(35.7%,45.3%)
Female		241 (59.4%)/(54.7%,64.3%)
Education status		
High education (undergraduate and above)		214 (52.7%)/(48.0%,57.6%)
Medium and low education (high school and junior high school)		192 (47.3%)/(42.4%,52.0%)

Two items (items 9 and 11) were eliminated for the value range recommended by Polit and Beck (2006) to determine an item's significance. Some items were also changed to improve their clarity based on the opinions and recommendations of the experts. Item 13 "Have you ever been recommended for help because of OFP" had little to do with psychology. Item 17 "Have you ever felt punished for OFP (sense of punishment)" seemed to be difficult for Chinese people to understand, as the topic is more likely to reflect the psychosocial distress of theistic believers. Thus, items 9 and 11 had a confusing representation were removed (**Supplementary Table 2**). The S-CVI/AVE of the 13-item of BPIm-S was 0.954 points.

2.3.4. Stage III scale evaluation

2.3.4.1. Participant recruitment

The 406 participants met the requirements of being at least 18 years old and Chinese-literate. Any patients who met the ICOP criteria for OFP were included in the study. The doctor will decide if the OFP patient needs additional assessment or referral to a specialist care facility.

2.3.4.2. Reliability

2.3.4.2.1. Item analysis and item-total correlations

We calculated the average, standard deviation, minimum, and maximum for each item. The data normality was examined using the Shapiro-Wilk test (Kim, 2012).

We used the theory of classical testing (CTT) to estimate inter-item and total item correlations, which is used to check the relationships that exist between the items in the pool (Crocker and Algina, 1986).

2.3.4.2.2. Exploratory factor analysis

Exploratory factor analysis (EFA) was used to test the underlying structures within the BPIm-S. For EFA, 5 or 10 subjects

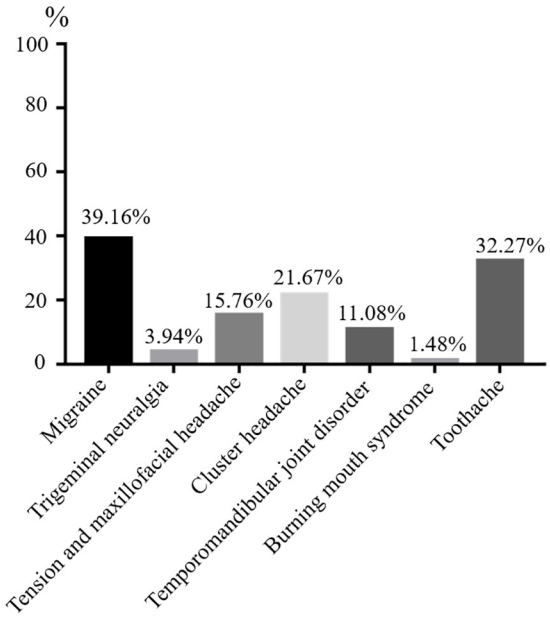

FIGURE 2
Diagram of OFP patient distribution.

TABLE 3 Descriptive statistics of the responses given to the items of the BPIm-S by the participants.

Item	Median	Interquartile	Min	Max	Item-total correlations	Cronbach's α if item deleted
Item 1	2	(1, 2)	1	4	0.799	0.968
Item 2	2	(1, 2)	1	4	0.776	0.969
Item 3	2	(1, 2)	1	4	0.774	0.969
Item 4	2	(1, 2)	1	4	0.763	0.970
Item 5	2	(1, 2)	1	4	0.796	0.969
Item 6	2	(1, 3)	1	4	0.892	0.967
Item 7	2	(1, 3)	1	4	0.904	0.967
Item 8	2	(1, 3)	1	4	0.906	0.966
Item 9	2	(1, 3)	1	4	0.883	0.967
Item 10	2	(1, 3)	1	4	0.875	0.967
Item 11	2	(1, 3)	1	4	0.912	0.966
Item 12	2	(1, 3)	1	4	0.879	0.967
Item 13	2	(1, 3)	1	4	0.889	0.967

per item are recommended regardless of the number of items (Gorsuch, 1990). To ensure that EFA and confirmatory factor analyses (CFA) were performed independently (Lee, 2016), 193 subjects were selected using IBM SPSS Statistics' random sampling method for EFA (Child, 1990).

2.3.4.2.3. Convergent validity

Both the convergent validity of the measure were assessed using the method developed by Fornell and Larcker (1981). If there is a high average variance extracted (AVE) and composite reliability (CR) between the scale's items, then the convergent validity of the scale is established.

2.3.4.2.4. Confirmatory factor analysis

We tested the factorial structure obtained by the EFA with the remaining 213 were used for CFA sample using CFA.

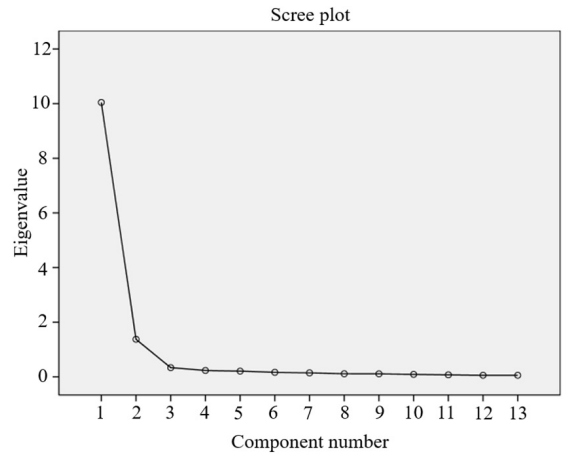

FIGURE 3
The scree plot of the BPIm-S factors.

2.3.4.2.5. Factorial invariance across genders, age, and education level

Multigroup CFA (MGCFA) was used to probe the feature of measurement invariance (Munro, 2005). CFA's model was used in these measurement invariance tests. MGCFA allows users to evaluate the relative merits of various degrees of model constraint. Age, gender, and status of education were the demographics studied, and four tiers of measurement invariance were examined. The following degrees of invariance were examined as part of the analyses: First, the concept of "configural invariance," which indicates that there is no significant difference in the clustering of items and the factors that they represent across groups; second, "metric invariance," which indicates that factor loadings are comparable across groups; third, "scalar invariance," which indicates that intercept are comparable across groups; and fourth, "residual invariance," which indicates that the residual variances are not significantly different across groups.

2.3.5. Stage IV clinical adaptation

2.3.5.1. Concurrent validity–Evaluation through scales

Concurrent validity refers to a measure's capacity to identify a simultaneously evaluated criteria (Bowen and Masa, 2015). We examined the concurrent validity of BPIm-S questionnaire against other commonly used scales for assessing functional limitation and psychosocial distress. A total of five questionnaires were filled out by the participants: the final 13-item version of the BPIm-S, brief pain inventory facial (BPI-F), MOPDS, General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9). The BPI-F is a measure of facial functions (Sandhu et al., 2015), the MOPDS was found to be reliable to evaluate the functional limitation (Aggarwal et al., 2005), while the GAD-7 (Spitzer et al., 2006), and PHQ-9 (Smarr and Keefer, 2011) were well-validated tools used to screen and diagnose generalized psychosocial disorder in clinical practice. It was assessed by evaluating the spearman correlation coefficients between the BPIm-S score and the scores of the BPI-F, MOPDS, GAD-7, and PHQ-9.

2.3.5.2. Clinical responsiveness–Evaluation by patients

A total of 12 patients with OFP (3 females, 9 males; median age, 25 years) (P25, P75: 22, 52; type of OFP disease: migraine, toothache, tension and maxillofacial headache, burning mouth syndrome) who underwent physical therapy (hot compress) were collected for evaluating the clinical responsiveness. Hot compress treatment was performed in six sessions of 30 min duration each before bedtime, three times per week for 2 weeks. All participants were able to answer questionnaires without assistance.

2.4. Data analysis

In the structured interview by target population and experts' phase, OFP patients were interviewed by the dentists and their responses were collated. The experts scored each item based on its relevance to the OFP, its objective measurability, and its scientific interpretation as well. The numbers 3, 2, and 1 indicate "consistent," "general," and "inconsistent," respectively. Items with a mean <2.000 and a coefficient of variation (CV) greater than 0.400 are excluded from the analysis. Then we conducted face and content validity tests on the first draft of the BPIm-S. A CVI calculation will be used to determine the face validity of the assessment (Petrick, 2002). Finally, a 13-item of BPIm-S was formed.

In the item analysis and item-total correlations phase, to determine if the data distribution is normal, the Shapiro-Wilk test was used. Data with a *p*-value of greater than 0.05 are considered to fit a normal distribution ($\alpha = 0.05$) (Kim, 2012). There were four different types of analysis performed on each item: the median, (P25, P75), minimum, and maximum. Internal reliability index was calculated using Cronbach's α. Internal consistency reliability assesses the homogeneity of items belonging to the same scale or domain, which was estimated using Cronbach's alpha ($\alpha \geq 0.7$, acceptable), and split-half reliability ($r \geq 0.7$, acceptable) (Cohodes et al., 2022).

TABLE 4 Exploratory factor analysis of the BPIm-S scale items.

The BPIm-S domain	Item	Factor 1	Factor 2
Functional limitation			
	Item 1	0.825	
	Item 2	0.866	
	Item 3	0.859	
	Item 4	0.878	
	Item 5	0.806	
Psychosocial distress			
	Item 6		0.830
	Item 7		0.858
	Item 8		0.877
	Item 9		0.807
	Item 10		0.883
	Item 11		0.887
	Item 12		0.861
	Item 13		0.865

Following item selection and reliability analyses, an EFA was run in IBM SPSS Statistics 21 software and CFA were run in Mplus 8.4. version. Kaiser-Meyer-Olkin and Bartlett tests were used to determine the adequacy of the sampling of the EFA (Vetterlein et al., 2022). Then, the latent factors of the BPIm-S were extracted *via* the maximum-likelihood EFA with varimax rotation. The number of extractable factors was determined using parallel analysis. The 3-indicator rule stipulates that each factor must have at least three items. We removed items with communality values less than 0.2.

Next, discriminant validity was assessed with the web-based data science algorithm platform tool SPSSAU. The AVE > 0.7, CR > 0.5 indicating good convergent validity, and the square root of AVE is greater than the correlation coefficient between the factors, indicating a good discriminant validity of the test.

Confirmatory factor analyses and measurement invariance analyses were performed with Mplus 8.4 version the $\chi 2$ statistic, standardized root mean square residual (SRMR), a Tucker-Lewis index (TLI), and a root mode square error of approximation (RMSEA) were used to estimate the model fit. Following Bryne (Byrne, 2011), we considered the fit of the factorial model to the data was considered adequate when CFI and TLI ≥ 0.90. In addition, SRMR < 0.05 and RMSEA ≤ 0.1 were considered to indicate a satisfactory fit (Steiger, 1990). In MGCFA, Goodness-of-fit statistics were estimated for each model and for each model relative to the previous, less restricted, model. The fit of the model was assessed using the CFI, TLI, SRMR, and RMSEA fit indices. we evaluated ΔCFI and ΔRMSEA between the more and less constrained models. ΔCFI and △TLI larger than 0.01 and ΔRMSEA larger than 0.015 indicated a significant worsening of fit (Chen, 2007).

Concurrent validity was assessed by evaluating the spearman correlation coefficients between the BPIm-S score and the scores of the BPI-F, MOPDS, GAD-7, and PHQ-9. A total of 12 patients with OFP who underwent physical therapy (hot compress) were collected for evaluating the clinical responsiveness. All participants were able to answer questionnaires without assistance. The scores before and after the hot press treatment were compared by using the 2-tailed paired Mann–Whitney test to evaluate responsiveness. The significance level was set at 0.05.

3. Results

3.1. Demographic characteristics

A total of 406 participants were recruited for scale evaluation in stage III of this study [Median age (P25, P75), 34 years (24, 52)], The doctor will decide if the OFP patient needs additional assessment or referral to a specialist care facility. More than 50% of respondents were female ($n = 241$) and over 30 years old ($n = 220$). Regarding the education level of the participants, 214 participants (52.71%) were high education and 192 (47.29%) graduated from high school or lower (**Table 2** and **Supplementary Table 3**). The most frequently diagnosis of OFP was migraine ($n = 159$), followed by toothache ($n = 131$), cluster headache ($n = 88$), tension and maxillofacial headache ($n = 64$), temporomandibular joint disorder ($n = 45$),

trigeminal neuralgia (n = 16), and burning mouth syndrome (n = 6) (Figure 2).

3.2. Item analysis and item-total correlations

In this population sample, the Shapiro-Wilk test of normality of distribution did not indicate a normal distribution (W = 0.897, p < 0.05). The BPIm-S comprises 13 items that describe 2 dimensions: functional limitation, psychosocial distress. The format for the questions is "Have you ever had difficulty concentrating because of orofacial pain" The items are graded on a five-point Likert scale, from 0 (never) to 4 (very frequently). The median BPIm-S score was 25 (13, 31) (range 13–52). Item-total correlations analysis was performed using the spearman correlation index. Adequate spearman correlation was found between the items and the whole, with values ranging from 0.763 to 0.912 (Table 3).

3.3. Reliability analysis

After factor analysis, the overall Cronbach's α value for the scale was 0.970, indicating a very high degree of reliability. Cronbach's α would decrease if any of the 13 items were removed (Table 3). Cronbach's α scores for the two variables were as follows: 0.962 for functional limitation and 0.977 for psychological suffering. The internal consistency of scale was determined by split-half reliability. The split-half reliability coefficient of FPIm-S was 0.880. They were deemed satisfactory for both the overall score and the dimension scores.

3.4. Exploratory factor analysis

The remaining 13 scale items' underlying variables were uncovered by EFA. Kaiser-Meyer-Olkin (KMO) value of 0.945 (p < 0.001) was found in the preliminary factor analysis, which is above the minimum required value of 0.5 and shows the sufficiency of scale items for factor analysis. Bartlett's test of sphericity also verified the factorability of the 13 items (χ^2 = 3818.156; p < 0.01). Figure 3 indicates that 2 components were moderately distinguishable and explained 87.845% of the variance. As reflected in Table 4, factor 1 had 5 items, and factor 2 had 8 items for a total of 13 items. Also, the factor loading of each item were above 0.8 in their dimensions.

3.5. Construct validity evaluation

Construct validity was established *via* convergent validity. By engaging the AVE and CR, the convergent validity was tested. The CR was 0.927 for functional limitation and 0.957 for psychosocial distress. The AVE was 0.718 for functional limitation and 0.738 for psychosocial distress. AVE scores for all variables were greater than 0.50 and lower than the CR, hence establishing convergent validity.

3.6. Confirmatory factor analysis

The CFA findings indicated that a two factor model provided an excellent sufficient fit to the OFP topics, and the results were as follows: χ^2 = 142.641, df = 64, χ^2/df <5, CFI = 0.956, TLI = 0.947, SRMR = 0.036 and RMSEA = 0.076.

TABLE 5 Model comparisons for measurement invariance testing across gender, age, education level groups in OFP patients (N = 406).

Model	χ^2 (df)	CFI	TLI	SRMR	RMSEA	ΔCFI	ΔTLI	ΔRMSEA
Invariance across gender groups								
Model 1	272.934 (128)	0.960	0.951	0.033	0.075			
Model 2	295.386 (139)	0.957	0.951	0.038	0.074	−0.003	0.000	−0.001
Model 3	316.008 (150)	0.954	0.952	0.038	0.074	−0.003	0.001	0.000
Model 4	347.823 (163)	0.949	0.951	0.037	0.075	−0.005	−0.001	0.001
Invariance across age groups								
Model 1	299.855 (128)	0.950	0.939	0.034	0.081			
Model 2	321.545 (139)	0.947	0.940	0.044	0.080	−0.003	0.001	−0.001
Model 3	341.483 (150)	0.944	0.942	0.045	0.079	−0.003	0.002	−0.001
Model 4	373.855 (163)	0.938	0.941	0.046	0.080	−0.006	−0.001	0.001
Invariance across educational status groups								
Model 1	271.658 (128)	0.956	0.946	0.035	0.074			
Model 2	292.479 (139)	0.953	0.947	0.046	0.074	−0.003	0.001	0.000
Model 3	314.279 (150)	0.950	0.948	0.049	0.073	−0.003	0.001	−0.001
Model 4	329.055 (163)	0.949	0.951	0.050	0.071	−0.001	−0.003	−0.002

Model 1, configural invariance; Model 2, metric invariance; Model 3, scalar invariance; Model 4, residual invariance. χ^2, chi-squared test; df, degrees of freedom; CFI, comparative fit index; TLI, Tucker-Lewis index; SRMR, standardized root mean square residual; RMSEA, root mean square error of approximation.

3.7. Measurement invariance across genders, age, and education level

Table 5 shows the fit measures of the multi-group models for testing measurement invariance across age, genders and education level. Considering genders, the data were extremely well matched by the two-factor model configural invariance model (CFI = 0.960, TLI = 0.951, SRMR = 0.033, RMSEA = 0.075). A satisfactory fit was shown using a limited metric invariance model (CFI = 0.957, TLI = 0.951, SRMR = 0.038, RMSEA = 0.074). The data were well-fitted by the scalar invariance model (CFI = 0.954, TLI = 0.952, SRMR = 0.038, RMSEA = 0.074). Last but not least, the residual invariance was compared to the scalar invariance, suggesting that invariance remained constant with each additional model constraint (CFI = 0.949, TLI = 0.951, SRMR = 0.037, RMSEA = 0.075), suggesting that measurement invariance may be considered to be across genders. Similar results were found for age and educational status indicating that the structure, factor loadings and item intercepts are invariant across age and educational status. The measurement invariance held when the fitting change met the following conditions: $\triangle$CFI $\leq$ 0.01, $\triangle$TLI $\leq$ 0.01 and $\triangle$RMSEA $<$ 0.015 (Table 5).

Mann–Whitney test for scores of BPIm-S between sex, age and educational status level is shown in Table 6. The results showed that there was no significant difference between male and female in the total score ($p > 0.05$), functional limitation ($p > 0.05$) and psychosocial distress ($p > 0.05$) of the scale; People over the age of 30 had a significantly higher total score ($p < 0.001$), functional limitation ($p < 0.05$), and psychosocial distress ($p < 0.001$) on the scale than those under the age of 30 did; likewise, those with a medium or low education level had a significantly higher total score ($p < 0.001$), functional limitation ($p < 0.001$), and psychosocial distress ($p < 0.001$) than those with a high education level did.

3.8. Concurrent validity

Concurrent validity was evaluated through comparisons of the final 13-item version of the BPIm-S questionnaire scores with BPI-F, MOPDS, GAD-7, PHQ-9 (Table 7). Correlations of BPIm-S scores with the BPI-F, MOPDS, GAD-7, PHQ-9 ranged from 0.554 to 0.781 ($p < 0.001$). The BPIm-S exhibited adequate-to-good concurrent validity in relation to this scale.

TABLE 6 Scores of the BPIm-S between genders, age and different education status groups.

The BPIm-S	Male	Female	Z-scores[a]	>30	≤30	Z-scores[a]	High education	Medium and low education	Z-scores[a]
Total	22 (13, 30)	25 (14, 31)	−1.46	26 (15, 35)	18 (13, 26)	−5.14***	17 (13, 26)	28 (18, 37)	−7.07***
Functional limitation	7 (5, 10)	9 (5, 11)	−1.38	10 (5, 12)	7 (5, 10)	−2.49*	7 (5, 10)	10 (5, 12)	−3.83***
Psychosocial distress	15 (8, 20)	16 (8, 20)	−1.39	16 (9, 24)	11 (8, 16)	−5.82***	10 (8, 16)	18 (12, 24)	−7.80***

[a]Comparison between scores by Mann–Whitney test.
*$p < 0.05$, ***$p < 0.001$.

TABLE 7 Correlations of the BPIm-S score with scales for chronic pain interference, pain severity, and other psychosocial variables.

The BPIm-S	BPI-F	MOPD	PHQ-9	GAD-7
Functional limitation	0.628***	0.622***	0.598***	0.554***
Psychosocial distress	0.687***	0.744***	0.781***	0.743***
Total	0.710***	0.749***	0.772***	0.729***

BPI-F, the brief pain inventory-facial; MOPDS, Chinese version of Manchester orofacial pain disability scale; GAD-7, the anxiety disorder assessment; PHQ-9, the patient health questionnaire-9.
***$p < 0.001$.

TABLE 8 Responsiveness evaluated in the 12 patients of the hot pressed treatment group.

	Median (interquartile)		
Scale	Before treatment	After hot pressed treatment	Z-scores[a]
BPIm-S (total scores)	18.00 (14.00, 25.75)	4.00 (2.00, 5.00)	−3.062**
BPIm-S (functional limitation scores)	7.50 (5.00, 10.00)	2.50 (2.00, 3.00)	−3.063**
BPIm-S (psychosocial distress scores)	10.50 (9.00, 15.50)	1.00 (0.00, 2.00)	−3.063**
BPI-F	28.00 (21.00, 29.75)	8.50 (1.00, 9.75)	−3.064**
MOPDS	29.50 (27.00, 37.50)	13.50 (2.75, 19.00)	−3.061**
PHQ-9	13.00 (9.50, 17.00)	2.50 (1.25, 4.00)	−3.071**
GAD-7	8.00 (7.25, 13.00)	2.50 (0.50, 3.75)	−2.983**

BPI-F, the brief pain inventory-facial; MOPDS, Chinese version of Manchester orofacial pain disability scale; GAD-7, the anxiety disorder assessment; PHQ-9, the patient health questionnaire-9.
[a]Comparison between scores by Wilcoxon signed-rank test.
**$p < 0.01$.

3.9. Clinical responsiveness

Responsiveness was evaluated in 12 OFP patients who underwent the hot-pressed treatment. After receiving therapy, patients demonstrated considerable improvements on the BPIm-S (total scores, functional limitation scores, and psychosocial distress scores), BPIm-F, MOPD, PHQ-9, and GAD-7 (**Table 8**).

4. Discussion

Patients with OFP have reported worse health-related quality of life due to the condition's detrimental impact on their ability to do daily activities and their emotional wellbeing (Aguiar et al., 2021). The absence of a Chinese scale able to assess the impact of OFP patients further confounded difficult for doctors to make individualized clinical treatment. Exploring an accurate instrument to assess the physical and psychosocial impairment of OFP was critical. It was the first time to develop the BPIm-S to assess the OFP health life related functional-psychosocial quality through the exploratory sequential research design, which also was proved to be an appropriate PROMS instrument for OFP clinical studies.

Based on the biopsychosocial model suggested by ICOP guidelines and extensive review of the literature on the OFP, we developed the Chinese Version of the BPIm-S in patients with OFP through the principle of item selection, with preliminary and further screening of the items by patients, as well as two rounds of evaluation using the Delphi method. Fifty patients with OFP were asked to review the scale for face validity, and the results showed that two questions had "not relevant" responses from more than 70% of the patients. Because doing housework not always was a daily activities (Platt et al., 2020), and increasing the mealtime always was influenced by work or others (Habib et al., 2020). Experts further verified the construct validity through their experience and deleted two items that are not related to OFP in the sociopsychological dimension. Finally, 13 items across 2 components (functional limitation and psychosocial distress) of the evaluation index system were selected to create the BPIm-S.

Since the BPIm-S was firstly developed and used in the Chinese clinical population, we firstly explored its reliability to evaluate the internal consistency (Rattray and Jones, 2007). The inter-total correlations between the BPIm-S items demonstrated their consistency, usefulness, and lack of redundancy. According to the results of Cronbach's α, the scale's internal consistency was quite high (Bonett and Wright, 2015). Our results showed that the BPIm-S with 13 items was still a reliable and stable instrument for measuring and assessing the influence of Chinese patients with OFP, which guaranteed follow-up psychometric research.

We further explored the factor structure of the BPIm-S, and the EFA analyses identified two domains, functional limitation and psychosocial distress. Factor 1 is labeled "functional limitation" because it contains five items that reflect the functional limitation caused by symptom onset in OFP patients. Examples of such behaviors include mouth opening restrictions, painful eating. This factor corresponds to previous studies describing physical disabilities associated with OFP patients. Factor 2 contains eight items and is labeled as "psychosocial distress" because it involves distress that mainly embodies the psychosocial dimension of OFP patients. Also, we also proved the internal convergence validity through CR and AVE, suggesting that the two-factor structure in the BPIm-S did not intersect and could be calculated as independent dimensions. We further used CFA to evaluate the two-factor structure instrument of the FPIm-S, The CFA verified the EFA output and provided an initial proof of the construct validity of the FPIm-S.

The novel contribution of the present study lies in the analysis of measurement invariance, which previously had been lacking. Measurement invariance was also established across gender, age, and educational status groups to further support the reliability of the 2-factor model. The BPIm-S exhibited high levels of configural, metric, scalar, and residual invariance across male and female OFP patient samples, as validated by our MGCFA analysis. Two measures evaluating functional limitation and psychosocial distress showed that BPIm-S was conceived identically in women and men, lending credence to the notion of configural invariance. Metric invariance was also supported, which meant that the same units of measurement apply to both sexes. Further, the current scalar invariance setup suggested that disparities in scores between males and females may be understood as representing real group differences in latent variables, which offered a common baseline for both sexes. It is only when the units and reference points are the same that comparisons across groups become relevant. Consequently, the assumption of metric equivalence and scalar equivalence in order to do a latent mean comparison (Hermida, 2015). Finally, the cross-gender difference in latent variable variation was mirrored in the support for the residual invariance across both women and men (Shah and Goldstein, 2006). The outcomes depend on age and education level in a similar fashion. In conclusion, this study's findings corroborate the measurement invariance of the FPBIm-S, suggesting its efficacy and interpretability across demographics such as gender, age, and education level. The findings of the present study allow researchers to apply the HRFS in a wider variety of research designs. Measurement invariance is an important prerequisite for comparisons between groups.

We utilized the Mann–Whitney to compare means across categories such as gender, age, and level of education, there was no significant difference in the results of the measurement invariance test between the gender. Males and females did not vary significantly in terms of total score, functional limitation component, or psychological distress dimension, according to these findings. However, previous studies have shown that the prevalence and symptoms of OFP tend to be higher among females than among males (Cairns, 2007). This is inconsistent with the findings of this study. Since the measurement invariance between the gender has already been studied. In this case, since we can rule out potential interference caused by gender differences, the results can be relied upon. In terms of age, the total score, functional limitation, and psychosocial distress of the scale of people over 30 years old were significantly higher than those of people under 30 years old. This is consistent with previous studies (Salman Roghani et al., 2019). In terms of educational status, the total score, functional limitation and psychosocial distress of the medium education and low education population were significantly higher than those of the High education population. A similar result has been obtained in a previous study, this may be because people with

higher educational status have higher self-perception ability in OFP management (Taqi et al., 2021).

To test the concurrent validity, spearman correlation coefficients of BPIm-S and BPI-F, MOPD, PHQ-9, and GAD-7 scores were calculated. All scales correlate well with the BPIm-S, indicating adequate concurrent validity. This study further investigated the responsiveness of the BPIm-S and BPI-F, MOPD, PHQ-9, and GAD-7 scores to clinical outcomes in OFP patients after hot compress treatment. The BPIm-S was shown to be sensitive to changes in clinical outcomes, indicating that it is a valid tool for gauging improvement in the health of OFP patients and the efficacy of treatment. The results of this investigation give further support for the use of the FPIm-S, expanding the findings of earlier studies in both applied and research contexts, and so contribute to the ongoing validation of the FPIm-S in clinical settings.

Assessment of clinical outcomes with PROMs is increasingly important in the evaluation of patients (Dawson et al., 2010). The process of the BPIm-S completion prompts patients to reflect on their health and in doing so, patients develop a deeper understanding of how their condition affects them. By answering the questions on the BPIm-S, patients are prompted to think about their health and get insight into the impact of their disease. Proactive use of the BPIm-S during follow-up may enhance patient involvement leading to increased satisfaction with care. Work still needs to be done to understand how the BPIm-S can be utilized effectively to improve patient outcomes.

Despite the thorough approach used to create a psychometrically sound scale, a few research limitations were discovered that must be carefully considered. A small sample size was the limitation. More measurement invariance of clinical samples can be verified, such as work status, etc. After that, a longitudinal study can be conducted with the target population to study the reliability of the FPIm-S for OFP disease follow-up.

5. Conclusion

This research examines physical and psychosocial search using a standard constructed and tested measure, a review of OFP, concept analysis, and structured interviews. The tool consists of 13 questions divided into two categories: Functional limitation and psychosocial distress. The instrument, BPIm-S, displayed strong psychometric qualities and clinical responsiveness; hence, it may be used to investigate and quantify the distress in OFP patients' functional limitation and psychological distress.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Experimentation and Ethics Committee of the Second Xiangya Hospital of Central South University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YF and Z-YO-Y: conceptualization, methodology, resources, and writing—original draft preparation. D-DX and Y-FY: validation. Z-YO-Y, YF, and N-XC: formal analysis. Z-YO-Y and X-LS: investigation. D-DX, YC, and JZ: data curation. YF, Y-QZ, and Z-YO-Y: writing—review and editing. YF, BF-K, and JZ: visualization. YG and Y-ZF: supervision, project administration, and funding acquisition. All authors read and agreed to the published version of the manuscript.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1101383/full#supplementary-material

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The mediating effect of somatic symptom disorder between psychological factors and quality of life among Chinese breast cancer patients

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Objective: We conducted this cross-sectional study to explore the mediating and predicting role of somatic symptom disorder (SSD) between psychological measures and quality of life (QOL) among Chinese breast cancer patients.

Methods: Breast cancer patients were recruited from three clinics in Beijing. Screening tools included the Patient Health Questionnaire-15 (PHQ-15), the Patient Health Questionnaire-9 (PHQ-9), the General Anxiety Disorder-7 scale (GAD-7), the Health Anxiety Scale (Whiteley Index-8, WI-8), the Somatic Symptom Disorder B-Criteria Scale (SSD-12), the Fear of Cancer Recurrence scale (FCR-4), the Brief Illness Perception Questionnaire (BIPQ-8), and the Functional Assessment of Cancer Therapy-Breast (FACT-B). Chi-square tests, nonparametric tests, mediating effect analysis, and linear regression analysis were used for the data analysis.

Results: Among the 264 participants, 25.0% were screened positive for SSD. The patients with screened positive SSD had a lower performance status, and a greater number of patients with screened positive SSD received traditional Chinese medicine (TCM) ($p<0.05$). Strong mediating effects of SSD were found between psychological measures and QOL among patients with breast cancer after adjusting for sociodemographic variables as covariates ($p<0.001$). The range of the percentage mediating effects was 25.67% (independent variable=PHQ-9) to 34.68% (independent variable=WI-8). Screened positive SSD predicted low QOL in physical (B=−0.476, $p<0.001$), social (B=−0.163, $p<0.001$), emotional (B=−0.304, $p<0.001$), and functional (B=−0.283, $p<0.001$) well-being, as well as substantial concerns caused by breast cancer (B=−0.354, $p<0.001$).

Conclusion: Screened positive SSD had strong mediating effects between psychological factors and quality of life among breast cancer patients. Additionally, screened positive SSD was a significant predictor of lower QOL among breast cancer patients. Effective psychosocial interventions for improving QOL should consider the prevention and treatment of SSD or integrated SSD caring dimensions for breast cancer patients.

KEYWORDS

breast cancer, psycho-oncology, medication effect, quality of life, somatic symptom disorder

1. Introduction

Breast cancer is the most common malignant tumor in women worldwide. According to the latest data, breast cancer ranks first in cancer incidence among Chinese women, and the mortality rate ranks fourth (1, 2). The incidence and mortality of breast cancer in China have been increasing in the past 10 years; therefore, improvements in the quality of life (QOL) of these patients are becoming increasingly important from both clinical and research perspectives. Chinese breast cancer patients are generally younger than patients in developed countries, with the median age at the time of diagnosis of breast cancer in China being approximately 50 years of age, which is 10 years earlier than that in the United States and the European Union (3).

The diagnosis of breast cancer affects the physical and mental health, QOL, and social function of patients, and they often face serious psychological distress and emotional problems, such as anxiety, depression, and fear (4, 5). Moreover, due to the disease itself and treatment-related adverse reactions, various physical and psychological symptoms can result in a considerable symptom burden, which seriously affects patients' QOL and social functions (6). Studies have shown that the symptom burden of breast cancer patients is closely related to anxiety and other emotional problems (7), and cancer-related somatic symptoms are also affected by physical status, cognition, emotion and other factors (8). Some patients experience somatic symptoms, although these symptoms are not well explained by existing medical diseases. In recent years, the physical symptoms of patients with mental illness have become more and more obvious and diverse, especially the impact of new coronary pneumonia in recent years (9). The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) defines this condition as somatic symptom disorder (SSD), which is characterized by persistent somatic symptoms (lasting for more than 6 months) that are accompanied by excessive thoughts, feelings, and behaviors that are related to the symptoms but disproportionate to the seriousness of the symptoms (10).

Studies have shown that patients with SSD suffer from multiple disturbances of physical and psychological symptoms, which affect their quality of life. The influencing factors of quality of life are multidimensional, including the severity of somatic symptoms, the number of somatic symptoms, and disease cognitions. A high number of somatic symptoms, a high level of somatic symptom disorder and a negative illness perception will significantly reduce the quality of life of cancer patients (11, 12). Li reported the prevalence of and risk factors for SSD among Chinese breast cancer patients by SCID interview, which provided a greater understanding about this issue and aroused our interest in exploring the influence of SSD on quality of life in this group (13). Therefore, we reanalyzed these data to understand the mediating and predicting role of SSD between psychological variables and QOL in Chinese breast cancer patients and to explore the applicability of the SSD-12 as a screening tool in clinical oncology.

2. Methods

2.1. Participants

A total of 273 participants were recruited from three clinics (two breast cancer clinics and one psychiatric clinic) in two hospitals in Beijing, China, from February 2019 to October 2019. All patients who entered one of the three clinics were informed of this study and invited to participate by research assistants. Eligible patients who came to the clinics were recommended to join the study by the doctors. The patients who agreed to join were asked to fill out the self-reported questionnaires. Participation was voluntary, and the patients signed informed consent forms and agreed to the evaluation and processing of the collected data. This study was approved by the Ethics Committees of Peking University Cancer Hospital (2019YJZ06).

The inclusion criteria included age $\geq$ 18 years, pathological diagnoses of breast cancer and adequate Chinese reading and writing skills. The exclusion criteria included severe cognitive impairments, psychosis, and acute suicidal tendencies.

2.2. Assessment instruments

The Somatic Symptom Disorder B-Criteria Scale (SSD-12) (14) is a self-assessment scale developed from the B criteria for an SSD diagnosis that is used to quantitatively evaluate patients' feelings and coping styles in relation to physical discomfort. It includes 12 items, and each item is rated from 0 (never) to 4 (frequently), with total scores ranging from 0 to 48. The Chinese version of the SSD-12 has also been verified to have good reliability and validity, and a score of 16 is recommended as the cut-off value (15). The SSD-12 was used to divide the sample into a non-SSD group (score $<$ 16) and an SSD group (score $\geq$ 16). Although the SSD-12 could not fully meet all diagnosis criteria for SSD, we used the SSD-12 as the main screening tool in this reanalysis study because the SSD-12, as a patient-reported outcome (PRO) measurement, is preferable for psychosocial distress screening in oncology practice and provides valuable referral recommendations to multidisciplinary professionals.

The Patient Health Questionnaire-15 (PHQ-15) (16) was used to evaluate the number of somatic symptoms and the degree of distress experienced in the past 4 weeks. It includes 15 somatic symptoms or symptom clusters. Each item is rated as 0 (no trouble), 1 (few troubles), or 2 (many troubles), with total scores ranging from 0 to 30. The optimal cut-off points of 5, 10, and 15 represented low, medium, and high somatic symptom severity, respectively (16). The Chinese version of the PHQ-15 has good reliability and validity (17).

The Patient Health Questionnaire-9 (PHQ-9) (18) was designed to evaluate the degree of depression experienced in the past 2 weeks. It includes 9 items, and each item is rated from 0 (not at all) to 3 (nearly every day), with total scores ranging from 0 to 27. The Chinese version of the PHQ-9 was validated in outpatients with multiple somatic symptoms, and the optimal cut-off point for moderate depression in Chinese outpatients was 10 (19).

The General Anxiety Disorder-7 (GAD-7) was used to assess anxiety levels experienced in the past 2 weeks. It includes 7 items rated from 0 to 3, with total scores ranging from 0 to 21. The Chinese version of the GAD-7 has been validated in general hospital outpatients, and the cut-off points for mild, moderate, and severe anxiety disorder were 4, 9, and 12, respectively (20).

The Health Anxiety Scale (Whiteley index-8, WI-8) is a brief scale for assessing disease belief and health concern experienced

in the past four weeks and includes 8 items. Each item is rated from 1 to 5, with a total score ranging from 8 to 40. Higher scores indicate a higher degree of anxiety (21). The cut-off point for the WI-8 was 19 (22).

The Fear of Cancer Recurrence (FCR-4) includes 4 items, and each item is rated from 0 to 4, with total scores ranging from 0 to 16. Higher scores indicate a greater fear of cancer recurrence, and no cut-off point has been recommended (23). The Chinese version of the FCR-4 has not yet been validated.

The Brief Illness Perception Questionnaire (BIPQ-8) was used to assess the cognitive and emotional representations of patients with regard to their own diseases. It includes the following 8 items: influence, duration, personal control, treatment control, symptom identification, concern, understanding, and emotional response. Each item is rated from 0 to 10. No cut-off value was suggested; higher scores indicate higher degrees of feeling threatened and negative illness perceptions. One study explored the Chinese version of the BIPQ-8 among local cancer patients and proved that the BIPQ-7 (item 7 "how well do you feel you understand your illness" was deleted) had good validity and reliability (24). No further study using this changed version was reported, especially in the breast cancer group in China. We used the original version of the BIPQ-8 in this study.

The Functional Assessment of Cancer Therapy-Breast (FACT-B) was used to evaluate the QOL of breast cancer patients over the past week. It included four subscales and an additional scale with 37 items. The four subscales included physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB) and functional well-being (FWB). The breast cancer subscale (BCS) was an additional subscale that contained 10 items related to breast cancer. Each item was rated from 0 to 4. Higher scores indicated higher QOL, and no cut-off point was recommended by the development group. The Chinese version of the FACT-B has also been validated in breast cancer patients (25).

All investigators were trained to use the assessment instruments and became competent in conducting consistent evaluations.

2.3. Statistical analyses

Statistical analyses were performed via SPSS 26.0 (IBM Corporation) and SAS 9.4 (SAS Institute Inc.). Regarding the descriptive statistics, the continuous variables that were normally distributed are expressed as the means ± standard deviations; otherwise, the variables are represented by medians and quartiles, and the count data are expressed as rates. According to the specific data types and distribution characteristics, t-tests or nonparametric tests (Kruskal–Wallis H test) were used to analyze the discrepancies in the sociodemographic characteristics, medical conditions, and psychosocial variables between the SSD group and the non-SSD group. Univariate and multivariate linear regression analyses were used to explore the predictive role of SSD for QOL among breast cancer patients.

Mediation analyses were used in this study to examine the underlying relationship between SSD, psychological measures, and QOL. Two mediation models were used. Model 1 directly estimated the mediating effects of SSD between psychological measures and QOL without adjusting for any covariates. Model 2 estimated the mediating effects after adjusting for the following covariates: age, BMI, health insurance, residence, marital status, actual life situation, income, employment, activities in winter, activities in summer, smoking exposure, and alcohol exposure. Mediation analyses were conducted using the CAUSALMED procedure in SAS.

3. Results

3.1. Sociodemographic characteristics and medical conditions

A total of 331 breast cancer patients were enrolled in this study, and 273 patients agreed to participate and signed informed consent forms. Nine patients withdrew due to a lack of time or poor health status. In total, 264 patients completed all the self-assessment questionnaires, with 66 patients (25.0%) being screened positive for SSD (see Figure 1 study flowchart). The sociodemographic characteristics and medical conditions are shown in Table 1. Furthermore, there were no significant differences in the sociodemographic characteristics between the patients with and without screened positive SSD. The patients with screened positive SSD had a lower performance status than those without SSD ($t = 2.171$, $p = 0.031$). In addition, more patients with screened positive SSD reported having received traditional Chinese medicine (TCM) treatments ($\chi^2 = 5.046$, $p = 0.025$) than patients without screened positive SSD.

3.2. Comparison of psychosocial measures and QOL between patients with and without screened positive SSD

Compared to the non-SSD group, the screened positive SSD group had significantly higher levels of somatic symptoms, general anxiety, health anxiety, depression, fear of cancer recurrence, and negative illness perception, as well as lower QOL ($p < 0.001$; Table 2).

3.3. The predictive role of screened positive SSD on quality of life of breast cancer patients

FACT-B scores (PWB, SWB, EWB, FWB, FACT-G-Total, FACT-B-TOI, and FACT-B-Total) were used as the dependent variables, and SSD-12 was entered as an independent variable in the linear regression analysis to explore the influence of SSD on QOL in breast cancer patients. The results are shown in Table 3. Screened positive SSD was a significant predictor of lower scores in all of the dimensions of the FACT-B, FACT-B-TOI, FACT-G-Total, and FACT-B-Total in breast cancer patients ($p < 0.001$). Additionally, a more severe presentation of screened positive SSD resulted in lower physical, social, emotional, and functional well-being, as well as more significant special concerns caused by breast cancer, thus resulting in lower QOL among breast cancer patients. After adjusting for the PHQ-15, PHQ-9, GAD-7, WI-8, FCR-4, and BIPQ-8 as covariates in the linear regression analysis, the SSD-12 still served as a strong predictor for lower physical

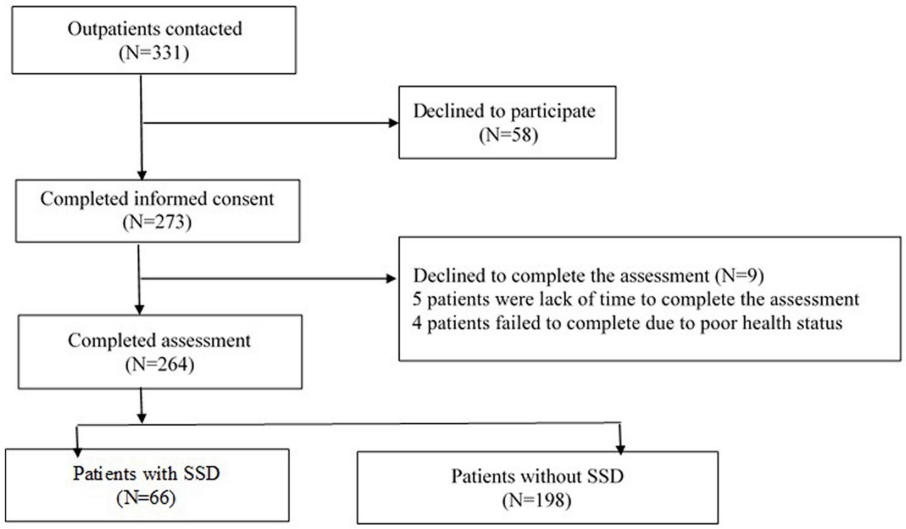

FIGURE 1
Study flowchart.

($R^2 = 0.0.833$, $p < 0.001$), social/family ($R^2 = 0.555$, $p = 0.002$), and functional well-being ($R^2 = 0.734$, $p = 0.002$), as well as lower levels of BCS ($R^2 = 0.733$, $p = 0.003$) and FACT-B-TOI ($R^2 = 0.876$, $p = 0.020$).

3.4. Mediating effects of screened positive SSD between psychosocial measures and QOL

Two mediation models were derived in the statistical analyses. In these models, somatic symptoms, general anxiety, depression, health anxiety, fear of cancer recurrence, and negative illness perception were independent variables; QOL was the dependent variable. Model 1 (without any covariates) showed that screened positive SSD had significant mediating effects between these psychological measures and QOL. The mediating effects ranged from the lowest of 25.668% (between depression and QOL) to the highest of 34.678% (between health anxiety and QOL). When incorporating covariates such as age, body mass index (BMI), health insurance, residence, marital status, living situation, income, employment, activities in summer or in winter, smoking exposure, and alcohol exposure in Model 2, significant mediating effects remained. The mediating effects ranged from the lowest of 26.836% (between depression and QOL) to the highest of 34.435% (between health anxiety and QOL). Detailed parameters are shown in Table 4; Figure 2.

4. Discussion

SSD in cancer has been recognized by psycho-oncologists. Grassi et al. suggested that special diagnostic criteria for SSD in cancer should integrate conventional psychiatric and psychosomatic criteria and that specific psychosocial interventions should be validated in cancer patients (26). Our results showed that the rate of screened positive SSD among breast cancer patients was 25.0%, which was lower than that in outpatients of general hospitals in China (33.8%) (27). This may indicate that the prevalence of SSD is divergent based on different populations; additionally, breast cancer patients may have more physical symptoms due to the disease itself and treatments, which may result in cancer patients and family members preferring to consider any discomfort as a physical symptom rather than a psychological issue. Moreover, patients can rebalance their health in a manner in which their health anxiety may be lower than that observed among patients in general hospitals (28). It is necessary to mention that this prevalence result came from the brief screening tool of the SSD-12. Although the SSD-12 has good reliability and validity, it cannot meet the diagnostic accuracy of psychiatric interviews. The SSD-12 results have clinical reference value, but they cannot be considered an SSD diagnosis. The descriptive results obtained from this study for SSD need to be interpreted appropriately. We found that a higher percentage of TCM exposure was reported in patients with SSD than in patients without SSD. In Chinese culture, an important role of TCM is "improving immunity." Some cancer patients may choose TCM to improve their immunity and relieve symptoms, including somatic symptoms, while receiving anticancer treatments (29). As it is thought that cancer patients inevitably suffer from more severe symptoms, SSD is often ignored by oncologists and family caregivers. Therefore, we hope to present the phenomenon of SSD prevalence in breast cancer patients to highlight the need to pay more attention to this issue. The identification of SSD in breast cancer patients has both benefits and potential risks. The benefits are that more attention can be given to the psychological care of breast cancer patients with physical symptoms to help patients alleviate distress and improve their physical symptoms and quality of life. However, there are also some potential risks, such as that these physical symptoms may be caused by disease progression or anticancer therapies that might be ignored under the consideration of SSD. Therefore, we must be more careful when considering the diagnosis of SSD in cancer patients. Toussaint et al. suggested using combined scores of ≥23 in the SSD-12 and ≥9 in the PHQ-15 for psychiatric outpatients (30).

TABLE 1 Sociodemographic characteristics and medical conditions.

Variables		SSD group (n=66) M±SD/n (%)	Non-SSD group (n=198) M±SD/n (%)	t [a]/χ^2	P
Age		50.94 ± 10.24	50.99 ± 10.20	0.035	0.972
BMI		23.14 ± 3.11	23.22 ± 3.24	0.157	0.876
KPS		90.15 ± 10.45	93.06 ± 9.05	2.171	0.031*
Residence	Urban	53 (80.3)	151 (76.3)	0.458	0.498
	Rural	13 (19.7)	47 (23.7)		
Health insurance	Yes	56 (84.8)	180 (90.9)	1.910	0.167
	No	10 (15.2)	18 (9.1)		
Marital status	Single/married but separated/divorced/widowed	9 (13.6)	20 (10.1)	0.630	0.427
	Married	57 (86.4)	178 (89.9)		
Living status	Living alone	4 (6.1)	13 (6.6)	0.021	0.885
	Living with others	62 (93.9)	185 (93.4)		
Education	Junior middle school and lower	15 (22.8)	42 (21.2)	0.424	0.515
	Senior middle school	12 (18.2)	53 (26.8)		
	University and above	39 (59.1)	103 (52.0)		
Family monthly income	8,000 RMB and lower	18 (27.3)	50 (25.2)	0.105	0.746
	Higher than 8,000 RMB	48 (72.7)	148 (74.8)		
Employment	Employed	23 (34.8)	85 (42.9)	1.332	0.248
	Unemployed/retired/housewife/others	43 (65.2)	113 (57.1)		
TNM stage	0	5 (7.6)	2 (1.0)	1.002	0.317
	1	14 (21.2)	20 (10.1)		
	2	11 (16.7)	40 (20.2)		
	3	35 (53.0)	42 (21.2)		
	4	65 (98.5)	89 (44.9)		
	Missing	1 (1.5)	5 (2.5)		
Surgery	Yes	51 (77.3)	163 (82.3)		
	No	15 (22.7)	35 (17.7)		
Chemotherapy	Yes	61 (92.4)	179 (90.4)	0.244	0.622
	No	5 (7.6)	19 (9.6)		
Radiation therapy	Yes	24 (36.4)	137 (69.2)	0.697	0.404
	No	42 (63.6)	61 (30.8)		
TCM therapy	Yes	20 (30.3)	34 (17.2)	5.046	0.025*
	No	46 (69.7)	162 (81.8)		
	Missing		2 (1.0)		

[a]Independent sample t-test; *$p < 0.05$.

However, Cao et al. suggested using DSM-V B criteria (SSD-12 or WI-8 alone) in Chinese general hospital settings (31). Cao et al. also suggested the use of a score ≥ 13 in the SSD-12 alone. Considering that the increasing sensitivity of a screening tool would both increase the potential negative risk of ignoring the symptoms caused by cancer and anticancer treatments and increase the screening burden in the oncology department, we finally used a score ≥ 16 in the SSD-12 suggested by Li[15] in this paper.

The psychosocial measures for depression, anxiety, health anxiety, fear of cancer recurrence, and negative cognitive and emotional representations of disease in the patients with SSD were also significantly higher than those in the patients without SSD, thu indicating that symptom-related emotional distress is more prominent in the patients with SSD, which is similar to the results by other researchers (32, 33). Therefore, it is necessary to conduct a comprehensive assessment of psychological dimensions such as anxiety and depression, in addition to evaluating somatic symptoms. Furthermore, the QOL of the patients with SSD was significantly lower than that of the patients without SSD, which indicates that QOL in the patients with SSD was generally affected. Similar conclusions were obtained in a study on QOL in outpatients with SSD in general hospitals in China (34).

The current study found that screened positive SSD was a redictor of lower QOL in breast cancer patients; specifically,

TABLE 2 Comparison of somatic symptoms and other psychological variables between patients with and without SSD.

Measures	M±SD	SSD group (n=66)	Non-SSD group (n=198)	t^a	p
PHQ-15	5.81 ± 3.98	9.77 ± 3.68	4.49 ± 3.11	11.408	<0.001***
PHQ-9	5.93 ± 4.70	10.06 ± 4.17	4.56 ± 4.01	9.558	<0.001***
GAD-7	5.30 ± 4.34	9.32 ± 3.97	3.96 ± 3.56	10.277	<0.001***
WI-8	14.99 ± 6.07	21.95 ± 4.59	12.67 ± 4.54	14.355	<0.001***
FCR-4	6.62 ± 3.95	9.74 ± 4.29	5.58 ± 3.22	8.333	<0.001***
BIPQ-8	36.25 ± 12.17	44.12 ± 12.49	33.63 ± 10.89	6.527	<0.001***
FACT-B	101.17 ± 20.35	83.15 ± 13.37	107.17 ± 18.68	−9.651	<0.001***

[a]Independent sample t-test; ***$p < 0.001$.

TABLE 3 Predictive role of SSD (SSD-12) on QOL (dimensions of FACT-B) - results from univariate and multivariate linear regression analyses.

	R^2	F	p	Unstandardized coefficients B	
				Constant	SSD-12
PWB univariate analysis	0.529	294.038	<0.001***	25.325	−0.476
Multivariate analysis	0.833	82.926	<0.001***	30.804	−0.201
SWB univariate analysis	0.062	17.435	<0.001***	22.993	−0.163
Multivariate analysis	0.555	16.294	0.002**	27.391	0.185
EWB univariate analysis	0.362	148.722	<0.001***	19.213	−0.304
Multivariate analysis	0.824	77.351	0.313	24.944	0.031
FWB univariate analysis	0.210	69.807	<0.001***	18.965	−0.283
Multivariate analysis	0.734	42.609	0.002**	24.784	0.140
BCS univariate analysis	0.414	185.051	<0.001***	29.049	−0.354
Multivariate analysis	0.733	42.362	0.003**	33.627	−0.120
FACT-B-TOI univariate analysis	0.525	289.156	<0.001***	73.338	−1.113
Multivariate analysis	0.876	133.983	0.020*	89.215	−0.181
FACT-G-total univariate analysis	0.396	171.639	<0.001***	86.496	−1.226
Multivariate analysis	0.870	114.207	0.137	107.923	0.155
FACT-B-total univariate analysis	0.466	228.230	<0.001***	115.544	−1.580
Multivariate analysis	00893	143.951	0.754	141.551	0.035

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. PWB, physical well-being; SWB, social/family well-being; EWB, emotional well-being; FWB, functional well-being; BCS, breast cancer subscale. FACT-B-TOI, FACT-B Trial Outcome Index (Score = PWB + FWB + BCS). FACT-G-Total, Functional Assessment of Cancer Treatment-General Scale Total (Score = PWB + SWB + EWB + FWB). FACT-B-Total, Functional Assessment of Cancer Treatment-Breast Cancer Total (Score = PWB + SWB + EWB + FWB + BCS). Each FACT subscale score was included into both univariate and multivariate linear regression analysis specifically. In univariate linear regression analysis, the SSD-12 was the independent variable, and all FACT subscales were dependent variables. All residuals were confirmed to be normally distributed. In multivariate linear regression analysis, SSD-12, PHQ-15, PHQ-9, GAD-7, FCR-4, WI-8, and BIPQ-8 scores were included as independent variables. The variance inflation factor (VIF) of the SSD-12 was 3.008.

screened positive SSD interfered with all dimensions of QOL, as it caused lower physical, social, functional, and emotional well-being, as well as increasing specific concerns related to breast cancer. Additionally, we performed a multivariate linear regression analysis, which showed that even though confounding factors existed, SSD could also predict lower physical, social/family, and functional dimensions of QOL, as well as lower BCS and FACT-B-TOI scores. Other studies have also demonstrated a predictive role of somatic symptoms for health outcomes (11, 35). Therefore, specific care for SSD and the distress caused by SSD should be considered in high-quality cancer care to improve the QOL of cancer patients. The former study also indicated that psychological factors were associated with the QOL of breast cancer patients and suggested the incorporation of these factors in cancer care (36). Moreover, multidisciplinary interventions are recommended to improve QOL by reducing the distress caused by SSD and emotional problems (37).

Significant mediating effects of SSD were verified in this research, which suggested that SSD played an important role in the process by which psychosocial measures influence QOL for patients with breast cancer. Research on cancer patients with SSD is not sufficient. Most of the studies remain in the stage of presenting descriptive outcomes. More research on the mechanism of SSD in cancer, whether it has a profound impact on quality of life or survival, how to identify it properly and in a timely manner, and which kind of psychosocial interventions would be more effective are necessary in the future. This is the first study to explore how SSD affects quality of life in Chinese breast cancer patients. Both direct and indirect effects were verified in

TABLE 4 Two mediation effect models of SSD between psychosocial variables and quality of life in patients with breast cancer.

	Mediation effect (Model 1)					Adjusted mediation effect (Model 2)				
	Total effect (95% CI)	Natural direct effect (5% CI)	Natural indirect effect	Percentage mediated	Pr>|Z|	Total effect (95% CI)	Natural direct effect	Natural indirect effect	Percentage mediated	Pr>|Z|
PHQ-15	−0.734 (−0.816, −0.652)	−0.502 (−0.606, −0.398)	−0.232 (−0.309, −0.155)	31.599 (20.982, 42.217)	<0.0001	−0.748 (−0.832, −0.664)	−0.513 (−0.617, −0.408)	−0.235(−0.312, −0.158)	31.444 (21.104,41.785)	<0.0001
GAD-7	−0.760 (−0.839, −0.682)	−0.549 (−0.645, −0.452)	−0.211 (−0.281, −0.141)	27.809 (18.600, 37.019)	<0.0001	−0.754 (−0.833, −0.675)	−0.543 (−0.641, −0.444)	−0.211 (−0.283, −0.140)	28.019 (18.499,37.540)	<0.0001
PHQ-9	−0.778 (−0.854, −0.703)	−0.579 (−0.670, −0.488)	−0.200 (−0.265, −0.135)	25.668 (17.366, 33.970)	<0.0001	−0.759 (−0.836, −0.682)	−0.555 (−0.647, −0.463)	−0.204 (−0.270, −0.138)	26.836 (18.189,35.483)	<0.0001
WI-8	−0.716 (−0.800, −0.632)	−0.468 (−0.593, −0.343)	−0.248 (−0.347, −0.149)	34.678 (20.550, 48.807)	<0.0001	−0.722 (−0.807, −0.637)	−0.473 (−0.598, −0.349)	−0.249 (−0.347, −0.151)	34.435 (20.595,48.27)	<0.0001
BIPQ	−0.744 (−0.825, −0.664)	−0.526 (−0.613, −0.439)	−0.218 (−0.281, −0.156)	29.314 (21.242, 37.386)	<0.0001	−0.728 (−0.809, −0.646)	−0.510 (−0.597, −0.424)	−0.217 (−0.279, −0.155)	29.855 (21.684,38.025)	<0.0001
FCR-4	−0.729 (−0.812, −0.647)	−0.495 (−0.593, −0.398)	−0.234 (−0.305, −0.163)	32.051 (22.342, 41.761)	<0.0001	−0.735 (−0.818, −0.652)	−0.503 (−0.601, −0.405)	−0.232 (−0.303, −0.161)	31.523 (21.901, 41.144)	<0.0001

***$P < 0.001$. Model 1: Mediation effect model without any covariates. Model 2: Mediation effect model with covariates (age, BMI, health insurance, residence, marital status, living situation, income, employment, activities in summer or in winter, smoking exposure, and alcohol exposure).

our sample, which emphasized the importance of identifying and caring for SSD among breast cancer patients. Patient-reported outcome (PRO) management, including common symptom management, has been integrated into oncology clinical guidelines or as a requirement for medical assessment by authorized organizations in many countries, as it has certainly influenced both quality of life and survival in cancer patients (38–40). SSD is the overlapping dimension of physical and psychological symptoms in the monitoring process among cancer patients, which indicates that clinicians should understand some physical symptoms in cancer patients from a psychological perspective and provide rational psychosocial care for patients with SSD.

4.1. Study limitations

Several limitations should be acknowledged. This was a cross-sectional study, which was unable to determine the causal relationship between SSD and QOL. We selected two breast cancer clinics, including one psychiatric clinic and one psychological clinic, where the patients may have more emotional and mental problems than in other clinics. Studies incorporating larger and more diverse cancer samples, as well as longitudinal studies, are recommended to further understand the relationship between SSD and QOL. Many cancer patients have more than one concomitant disease, especially advanced cancer patients who have received or are undergoing conventional anticancer treatments. However, we collected information on all somatic symptoms but did not distinguish between symptoms derived from cancer and those derived from treatments and those that resulted from concomitant diseases. We would like to consider this issue in future studies on SSD. Strict diagnostic criteria for SSD are needed and are preferable if the study purpose is to verify a confirmed diagnosis of SSD. Patient-reported outcomes (PROs) have been highlighted in oncological clinical trials (41) and integrated clinical cancer care (39), and distress reported by patients' self-reported physical and psychosocial distress screening has been included in many clinical practice guidelines (42, 43). Swift and timely recognition of cancer patients' distress with brief PRO measurements has been recommended as the first step. We would like to use the SSD-12 as the main measurement in our data analysis to indirectly verify the practicability of the utility of the SSD-12 among breast cancer patients. Additionally, interventional studies on SSD in cancer patients would provide more benefits to high-quality cancer care.

4.2. Clinical implications

SSD can be easily mistaken as a physical symptom among cancer patients, which results in both overmedication and insufficient psychosocial care. In our study, we demonstrated a significantly higher level of SSD among breast cancer patients, and its direct and indirect effects on QOL warrant greater attention to this unique issue among cancer patients.

4.3. Conclusion

Breast cancer patients with SSD had higher levels of somatic symptoms, general anxiety, health anxiety, depression, negative

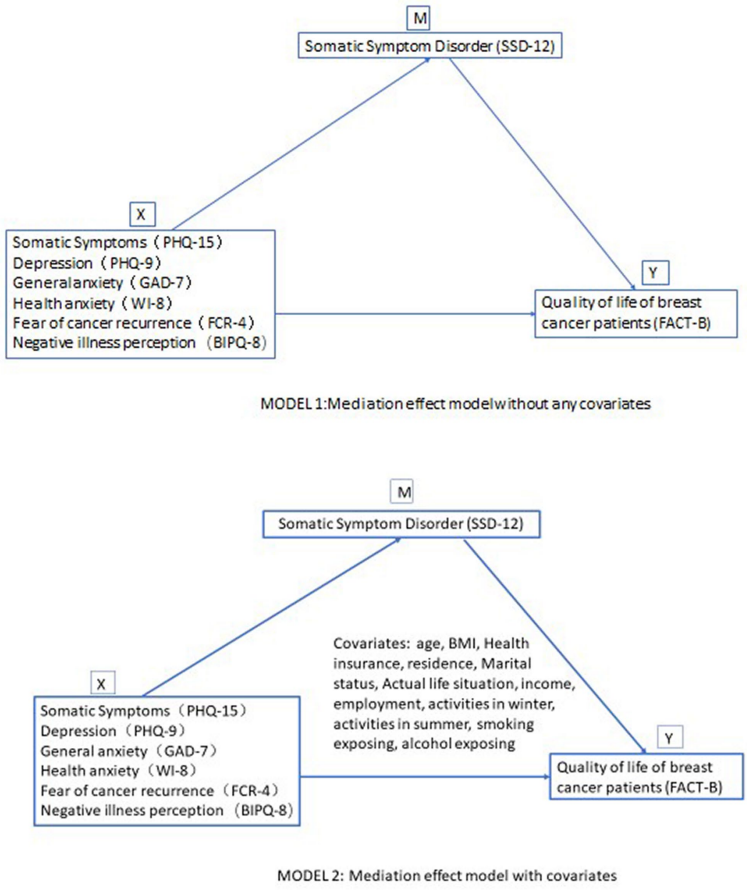

FIGURE 2
Models of the mediation effect of SSD.

illness perception, fear of cancer recurrence, and lower QOL. SSD had both a direct negative influence (significant independent predictor of low QOL) and an indirect negative influence (strong mediation effect) on QOL among breast cancer patients.

Data availability statement

The datasets presented in this article are not readily available because it is not allowed by the Regulations of the People's Republic of China on the Management of Human Genetic Resources. Requests to access the datasets should be directed to the corresponding author for further application to the authorized Department of Management of Human Genetic Resources in China.

Ethics statement

This study was approved by the Ethics Committees of Peking University Cancer Hospital (2019YJZ06). The patients/participants provided their written informed consent to participate in this study.

Author contributions

LT supervised this study and revised this manuscript. YZ and ZL conducted this study and wrote this manuscript. YP, YH, LS, YW, and SH helped in the study process like collecting data and coordinators training. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

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Implementing biofeedback treatment in a psychosomatic-psychotherapeutic inpatient unit: a mixed methods evaluation of acceptance, satisfaction, and feasibility

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Introduction: Feedback-based therapies such as biofeedback have a benefit in patients with mental health disorders. While biofeedback is heavily researched in outpatient settings, it has been rarely investigated in psychosomatic inpatient settings. The implementation of an additional treatment option in inpatient settings holds special requirements. The aim of this pilot study is the evaluation of additional biofeedback treatment in an inpatient psychosomatic-psychotherapeutic unit to derive clinical implications and recommendations for the future implementation of biofeedback offers.

Methods: The evaluation of the implementation process was investigated using a convergent parallel mixed methods approach (following MMARS guidelines). Quantitative questionnaires measured patients' acceptance and satisfaction with biofeedback treatment after receiving 10 sessions in addition to treatment as usual. After 6 months during implementation, qualitative interviews were conducted with biofeedback practitioners, i.e., staff nurses, examining acceptance and feasibility. Data analysis was conducted using either descriptive statistics or Mayring's qualitative content analysis.

Results: In total, 40 patients and 10 biofeedback practitioners were included. Quantitative questionnaires revealed high satisfaction and acceptance in patients regarding biofeedback treatment. Qualitative interviews showed high acceptance in biofeedback practitioners but revealed several challenges that were encountered during the implementation process, e.g., increased workload due to additional tasks, organizational and structural difficulties. However, biofeedback practitioners were enabled to expand their own competencies and take over a therapeutic part of the inpatient treatment.

Discussion: Even though patient satisfaction and staff motivation are high, the implementation of biofeedback in an inpatient unit requires special actions to be taken. Not only should personnel resources be planned and available in advance of implementation but also be the workflow for biofeedback practitioners as easy and quality of biofeedback treatment as high as possible. Consequently, the

implementation of a manualized biofeedback treatment should be considered. Nevertheless, more research needs to be done about suitable biofeedback protocols for this patient clientele.

KEYWORDS

biofeedback, neurofeedback, psychosomatic, implementation, mixed methods, inpatient

1. Introduction

Feedback is an essential component in psychotherapeutic interventions: it facilitates learning, increases motivation, and modifies thoughts or behavior (1). Biofeedback (BFB) as psychophysiological therapy is taught through cognitive changes (2), such as improving self-efficacy (3) or learning coping strategies. Typically, BFB is provided on parameters like muscle tone, respiratory rate, heart rate, skin conductance, skin surface temperature, or brain activity (i.e., neurofeedback, NFB) (4). The effectiveness of BFB has been investigated in several somatic and mental health disorders. The most common use of feedback-based therapies is in fields such as epilepsy (5), migraine (6), strokes (7), attention deficit / hyperactivity disorder (8), autism spectrum disorder (9), major depression and anxiety disorders (10), as well as addiction (11) and psychotic disorders (12). However, BFB has been rarely investigated in the specialty of psychosomatic medicine, the core idea of which is that mind and body both contribute an essential part to human function and which represents an independent specialty in Germany (13, 14). In the context of psychosomatic illnesses (i.e., somatoform/functional disorders, somatopsychic disorders, eating disorders, posttraumatic stress disorders, depressive disorders), several studies examined the use of BFB, e.g., to affect pain perception. In a patient case study, duration of the headaches and decreased intensity were related to increased alpha activity (8–12 Hz) (15). Glombiewski et al. could show in their meta-analysis on BFB including seven studies (321 patients) that BFB training significantly reduced pain intensity compared to controls with a large effect (2). NFB has shown promise in alleviating overall symptoms of posttraumatic stress disorder (PTSD) (16). Especially patients with PTSD who did not respond to previous treatments were able to benefit from NFB (16). Moreover, BFB had a positive impact on several eating disorders (e.g., food craving, rumination) (17). Not only were feedback-based techniques related to significant modifications in sympathetic responses to food stimuli but also to brain activity in different areas of the reward system (17).

Overall, current literature suggests a benefit of BFB and/or NFB in patients with various psychosomatic illnesses. However, while BFB has already been heavily researched in the outpatient setting (18–21), the usage of BFB and/or NFB in an inpatient setting for mental health disorders has been rarely investigated. To our knowledge, only one study examined the usage of BFB in inpatients with eating disorders (22). Another study investigated the use of BFB in combat veterans suffering from PTSD (23).

Abbreviations: BFB, Biofeedback; NFB, Neurofeedback; PTSD, Posttraumatic stress disorder; TAU, Treatment as usual; PL, Project leader.

Noteworthy, the demands on a therapy offer in the inpatient setting differ from those in the outpatient setting. While the outpatient setting is characterized by weekly therapy sessions, the inpatient setting consists of several different daily therapy offers provided over several weeks. This leads to tightly scheduled appointments and therapies and units might be understaffed. This leads to higher organizational demands, which can affect the implementation and feasibility of an additional treatment offer such as BFB. Up to now, there are no studies examining the implementation process of BFB treatment in psychosomatic-psychotherapeutic inpatient settings, the associated challenges, and the acceptance of patients and BFB practitioners.

Within the scope of this pilot study, patients in our psychosomatic-psychotherapeutic unit received regular BFB treatment sessions in addition to the treatment as usual (TAU). We will then examine quantitatively the acceptance and satisfaction of patients with BFB treatment. Moreover, we will use qualitative interviews to investigate the acceptance of BFB practitioners and feasibility in conducting BFB treatment. We will then combine these methods to evaluate the ability to implement this new treatment offer into our psychosomatic-psychotherapeutic inpatient settings in a mixed methods investigation.

The aim of this pilot study is the evaluation of additional BFB treatment in an inpatient psychosomatic-psychotherapeutic unit by investigating acceptance, satisfaction, and feasibility of BFB treatment. On this basis, we will derive clinical implications and develop recommendations for action for the future implementation of BFB offers in psychosomatic-psychotherapeutic inpatient settings.

2. Method

To assess acceptance, satisfaction, and feasibility of a BFB treatment in addition to the TAU, we conducted a convergent parallel mixed methods approach, which involves collecting qualitative and quantitative data simultaneously, and then combining and comparing these multiple data sources (24), by using quantitative questionnaires for patients as well as qualitative semi-structured interviews for BFB practitioners. Both quantitative and qualitative data were collected parallel during the implementation process and analyzed separately. Integration of the results will lead to a more comprehensive evaluation of the implementation process. In conducting and reporting this pilot study we followed the *Mixed Methods Article Reporting Standards (MMARS)* by the American Psychological Association (25). Evaluation was granted exemption from ethical review by the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen (No. 19-8893-BO). The study was conducted in accordance with the Declaration of Helsinki.

2.1. Study design and procedure

Implementation of the BFB treatment started in November 2021 as an additional routine treatment program in the inpatient unit of the LVR-University Hospital, Clinic for Psychosomatic Medicine and Psychotherapy (for further information regarding inpatient therapy see below in section 2.2 Setting or above in the introduction). Prior to this, the equipment was set up and instructions and manuals were created to assist BFB practitioners, i.e., staff nurses, in delivering the treatment. Due to the pilot character of this study, the BFB was an ordered new activity, for which the BFB practitioners received valences. The implementation started with a training of the BFB practitioners by the project leader (PL). Technical as well as theoretical basics were explained, and the conduction of sessions was exemplified and practiced. The BFB practitioners and the PL were supervised by a certified BFB instructor (author AK). Recruitment of patients took place during the first week of their admission to the inpatient unit *via* an information sheet. If patients expressed interest, they were referred to the PL, who then conducted the educational interview and obtained written informed consent. Inclusion criteria were a psychosomatic diagnosis (i.e., somatoform/functional disorders, somatopsychic disorders, eating disorders, posttraumatic stress disorders, depressive disorders), written informed consent, and age between 18 and 70 years. Exclusion criteria were neurological or central nervous disorders or insufficient language skills. BFB treatment appointments were made individually with patients by the nursing staff or PL. BFB sessions were conducted between November 25, 2021, and August 03, 2022. During the BFB treatment, different BFB practitioners conducted BFB sessions with each patient. Patients received 10 sessions of BFB treatment twice a week over a period of 5 weeks. After the last session, patients were asked to answer self-report questionnaires and they were given the opportunity to attend a follow-up meeting with the PL to clarify open questions. On March 1, 2022, a student assistant helped in assistance with the implementation and execution of the sessions. After 6 months following the start of implementation, the PL conducted qualitative semi-structured interviews with all BFB practitioners after they gave written informed consent.

2.2. Setting

The study site was an inpatient unit providing care for adults aged 18–70 years, within a psychosomatic-psychotherapeutic clinic in a university hospital. Patients either remained as full inpatients or stayed overnight in the clinic or spent only the therapy day in the clinic as part-time inpatients. The length of stay inpatient ranges from 6 weeks to 3 months. The psychosomatic diagnoses of patients vary and include eating disorders and obesity, somatoform disorders, PTSD, psycho-cardiologic, and affective diagnoses. Patients receive a comprehensive therapy program (i.e., TAU) ranging from therapeutically guided interactional group therapy and individual sessions to psychoeducation, art therapy, expressive painting, skills groups, sports and movement therapy, needs-oriented social work discussions, regular nursing individual sessions, medical care by ward physicians and regular visits by senior physicians (see A1 example schedule in the supplements). The BFB was offered in addition to the TAU.

2.3. BFB intervention

The BFB treatment was conducted using the NeXus-10B Set device and the corresponding software BioTrace (Mind Media, 2022) to collect psychophysiological information for BFB with a total of 10 channels. Trained parameters varied depending on the psychosomatic diagnosis and individually reported symptoms based on previous literature. Patients with somatoform disorders received electromyographic BFB (2) with positioning the electrodes in the neck-shoulder area. Patients with affective disorders, eating disorders or obesity, or PTSD received NFB treatment (16, 17, 26–28) with positioning the electrode on coordinate Cz and conducting alpha-frequency training to cause a relaxed brain state as well as theta-and beta-reduction to reduce arousal. Patients with psycho-cardiologic disorders received either electromyographic BFB or heartrate-variability training (29). The treatment took place in a multipurpose room, which was not used for other purposes during BFB sessions. Patients sat on a relaxation chair in distance of 1.5 m to the screen. As stimuli, patients saw a puzzle or a relaxing video, which continued depending on the degree of match with the target condition, i.e., reduction of muscle tone, increase of alpha-and reduction of theta- and beta-frequency, or increase of heartrate variability. Trained parameters were displayed as colored bar charts on the left side of the screen. The performing staff was present during the training but did not manipulate the feedback process or give verbal feedback. Patients were given a printout of every session to take it home. The BFB intervention comprised 10 training sessions, each lasting 40–45 min, taking place in the inpatient unit.

2.4. Measurement instruments

Data were collected using (a) anonymous quantitative self-report questionnaires answered by patients and (b) qualitative semi-structured interviews answered by the performing staff.

2.4.1. Quantitative data collection of patients

The quantitative questionnaire consisted of sociodemographic items, which were collected during patient admission (i.e., questionnaires in the preparation phase), as well as validated instruments answered by the patients after their last BFB session. The patients' satisfaction with the received BFB treatment was measured according to the Patient Satisfaction Questionnaire (ZUF-8) using 8 items on a 4-point Likert Scale, which results in a theoretical scale range of 8 to 32 ((30); see supplements A2, A3). It has a high internal consistency with Cronbach's $\alpha = 0.90$ (31). Kriz et al. defined a cut-off value of 23.5 in a psychosomatic cohort indicating high satisfaction (31). An adaptation of the System Usability Scale (SUS) was used to measure the usability of the BFB treatment with 10 items on a 5-point Likert Scale (32) (see supplements A4, A5). Reliability analysis indicated an acceptable internal consistency with Cronbach's $\alpha = 0.70$.

Based on Bangor, Kortum, and Miller, the SUS score can be translated into acceptance ranges with scores of about 73% representing good acceptance, 85% representing excellent acceptance, and 100% representing the best imaginable acceptance, respectively (33). However, acceptance can be assumed of scores >63 (33). Furthermore, acceptance and feasibility were measured with a self-generated questionnaire containing 9 items (see supplements A6, A7).

Items no. 1, 2, 4, and 5 were rated on a 6-point Likert scale (very displeasing, displeasing, partly displeasing, partly pleasing, pleasing, very pleasing). Items no. 3, 6, 7, 8, and 9 were rated on a 5-point Likert scale (not applies at all, rather not applies, partly true, rather true, totally true).

2.4.2. Qualitative data collection of BFB practitioners

The qualitative semi-structured interviews consisted of 12 interview questions to obtain a detailed opinion and possible suggestions for improvement of the BFB treatment offer from the BFB practitioners (see supplements A8, A9). The interview questions were derived based on the objectives of the study, which were to examine BFB practitioners' acceptance and feasibility of conducting BFB treatment, and to identify problems and obstacles as well as develop opportunities for improvement. The interviews took between 6 and 17 min and were conducted by the PL. All interviews were audio-recorded and transcribed verbatim.

2.5. Data analysis

2.5.1. Quantitative data analysis

Statistical analyses of quantitative data were performed using the Statistical Program for Social Sciences SPSS version 26 (IBM, New York). Figures were created using the R packages likert and ggplot. After identifying outliers (± 1 SD) *via* boxplots and exclusion from the dataset, the analyses were conducted. Simple descriptive statistics and internal consistency were computed for all quantitative questionnaire data. Acceptance and feasibility were described using frequencies.

2.5.2. Qualitative data analysis

All qualitative interviews were transcribed verbatim and then served as the foundation for consecutive data analysis. The software MAXQDA 2022 (Verbi Software, 2019) was used for qualitative data analysis. All interviews were analyzed using Mayring's method of structured content analysis (34). First, an initial deductive category system was derived from the semi-structured interview guideline. Then, in order to develop the further category system, two analyzing researchers (author 1 and author 2) coded two interviews. These researchers differed in age to enable different perspectives of the content analysis. After discussing the developed category system, it was used as a basis for coding all interviews. During the analysis, the researchers independently added, removed, or changed categories based on the text material. Until saturation of the category system was reached, relevant but still missing categories were added inductively. All interview quotations were translated from German into English language for publication purpose (for original see supplements A10).

3. Results

3.1. Quantitative patient questionnaires

3.1.1. Sample characteristics

A total of 40 psychosomatic patients were included to start BFB treatment (23 female, 17 male) with a mean age of 46.28 years (SD = 13.95, median = 49.0, range: 21–69). Table 1 shows the demographic information. Due to sudden and earlier discharge of the clinic, seven patients were not able to fill in the questionnaires after

TABLE 1 Demographic data of patients.

	n	Percentage (%)
Gender		
Female	23	57.5
Male	17	42.5
Marital status		
Single	12	30
Partnership	3	7.5
Married	19	47.5
Divorced	3	7.5
Living situation		
Alone	9	22.5
With partner	16	40
Alone with child(ren)	1	2.5
With partner and child(ren)	9	22.5
With parents	1	2.5
Other	1	2.5
Education		
High school diploma	24	60
Secondary school degree („*Realschule*“)	10	25
Secondary school degree („*Hauptschule*“)	2	5
Special-needs school	1	2.5
Missing	3	7.5
Employment status		
Employed	29	72.5
Unemployed	5	12.5
Retired	3	7.5
Missing	3	7.5
Sick leave		
Yes	17	42.5
No	19	47.5
Missing	4	10
Psychosomatic disorder		
Somatoform disorder (F45.x)	11	27.5
Depression (F32.x/F33.x)	12	30
Psychocardiologic disorder (F45.30)	11	27.5
Posttraumatic stress disorder (F43.1)	3	7.5
Eating disorder (F50.x)	2	5
Obesity (E66.x)	1	2.5
N = 40		

TABLE 2 Descriptive statistics of the quantitative self-report questionnaires ZUF-8, SUS, and acceptance and feasibility answered by patients.

Outcome		*N*	*M*	*SD (SE)*
ZUF-8		24	24.29	3.87 (0.791)
SUS		29	72.32	11.84 (2.2)
Acceptance & Feasibility	1. "I found the processing of the questionnaires in the preparation phase to be..."	29	3.41	0.825 (0.153)
	2. "I found the intervention to be..."	33	3.52	0.906 (0.158)
	3. "The intervention was feasible for me without any problems."	33	3.18	0.769 (0.134)
	4. "I found the challenges of the session to be..."	33	3.76	0.830 (0.145)
	5. "I found the basic conditions during the intervention to be..."	34	3.53	0.929 (0.159)
	6. "I found the intervention to be helpful in distracting from thoughts."	32	2.69	0.931 (0.165)
	7. "I found it helpful to be able to take the documentation of the session with me on paper."	30	1.83	1.289 (0.235)
	8. "I would like to continue a biofeedback offering at home."	33	2.03	1.237 (0.215)
	9. "I would recommend this study."	32	2.75	1.016 (0.180)

Measurement of patients' experiences regarding BFB training. ZUF-8, Patient Satisfaction Questionnaire, SUS, System Usability Scale. All analyses were conducted outlier corrected.

BFB treatment. Moreover, four patients discontinued due to a lack of motivation and understanding the therapy concept. However, based on the pilot character of this study, demographic data of all included subjects will be reported. Subjects had various psychosomatic disorders (see Table 1). Each patient completed at least one BFB session, with an average of 8.63 sessions attended (range 1–10). 65% of the patients completed all 10 BFB sessions. See A11 in supplementary material for the type of feedback each patient received.

3.1.2. Patient satisfaction and acceptance

Table 2 shows the descriptive statistics of the quantitative data. Patients' satisfaction with BFB ranged from 15 to 32, with a mean of 24.29 (SD = 3.87), which exceeds the cut-off value of 23.5 (31). In our sample, 18 patients exceeded the cut-off value of 23.5, six patients showed values below the cutoff. The internal consistency of the adapted ZUF-8 in our sample was excellent, with Cronbach's $\alpha = 0.903$. The perceived system usability ranged from 55 to 97.5, with a mean of 72.32 (SD = 11.84).

Figure 1 shows the evaluation of the self-generated questionnaire regarding acceptance and feasibility. 86.2% of the patients found the preparation of the questionnaires in the beginning as at least partly pleasant. Most of the patients (84.8%) perceived the intervention as at least partly pleasant. Only 15.2% of the patients perceived the intervention as unpleasant. 97% of the patients also indicated that the intervention had been at least partially feasible without problems. Only three patients (9.1%) indicated that the challenges of the sessions were partly unpleasant. Almost all patients (97.1%) perceived the basic conditions during the sessions as at least partly pleasant. Most of the patients (84.3%) found the intervention at least partially helpful in distracting from thoughts. 53.4% found it at least partially helpful to take the results of the session home. Most of the patients (66.7%) would like to continue BFB training at home. 93.7% of the patients at least partially recommended BFB.

3.2. Qualitative interviews with BFB practitioners

In total, 10 BFB practitioners (i.e., staff nurses) were involved in the implementation process of BFB by either conduction of sessions, planning BFB appointments, or managing ward-related processes in order to facilitate conduction of BFB. All of them were interviewed, nobody declined the interview. The student assistant was not interviewed to avoid conflict of interest due to involvement in project organization. Due to data privacy, we did not gather sociodemographic information of the BFB practitioners of the clinic. The duration of the interviews took between 6 and 17 min (mean 8 min 59.8 s, SD 3 min 36 s).

3.2.1. Positive feedback to BFB implementation

During the interviews, different positive aspects of the implementation were mentioned. For example, the relationship with patients could be positively influenced. Moreover, an effect of the therapy on the patients' symptoms were observed. Furthermore, the technical equipment was rated as very good. Four of 10 BFB practitioners felt supported during implementation. Supporting factors were instructions and manuals, supervisors, and colleagues as well as student assistants.

"On the contrary, I would even say that (there's) curiosity; this method is not known by everyone, and that this method enabled another contact with the patients." (Interview 8: 11).

Moreover, most BFB practitioners (8 of 10) were able to expand their area of expertise since a new therapy method was learned.

"Yes, definitely. It's been a new therapy method for me. I think it's great, it's evidence-based." (Interview 8: 15).

3.2.2. Suitability of the BFB treatment

The majority of BFB practitioners (9 out of 10) felt that BFB treatment was suitable for the services offered in our wards. They stated it was not a replacement for traditional services, but a supplement.

"It's a good complement to the therapies that are offered here." (Interview 8: 3).

One BFB practitioner considered BFB treatment not suitable for the patient group of this setting.

3.2.3. Obstacles and barriers

3.2.3.1. Technical difficulties

Seven BFB practitioners named technical problems due to high complexity. Occasionally software problems occurred in the

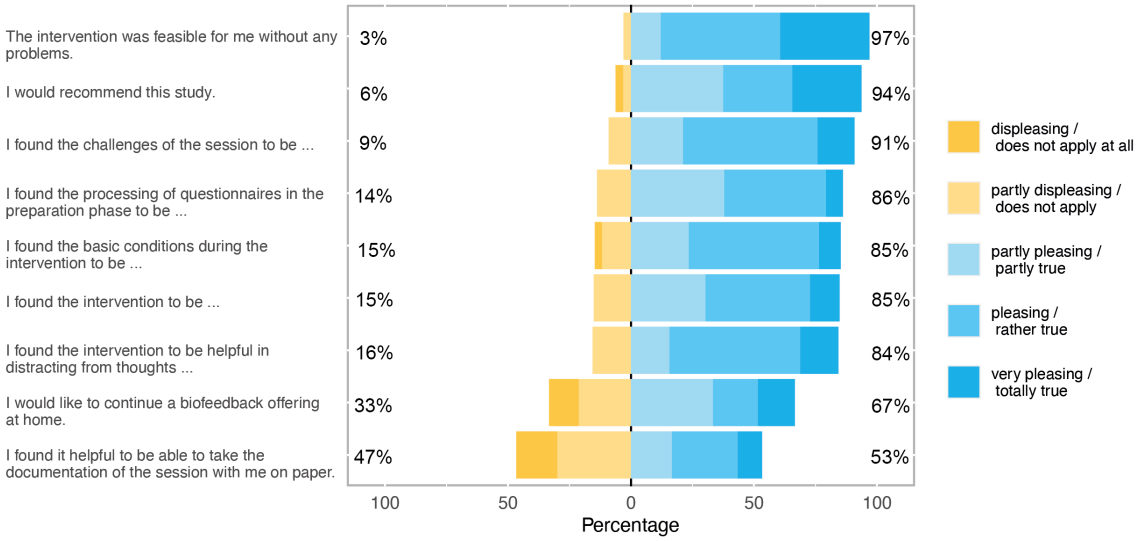

FIGURE 1
Evaluation of the self-generated questionnaire regarding patients' acceptance and feasibility of biofeedback treatment. Deviations in the direction of approval and rejection are shown on the right and left in percental frequencies. Percentages have been rounded to whole numbers. Items appear in order of approval.

presentation of the program as well as error messages. Furthermore, the setup of the BFB device required specific knowledge. In addition, data saving and printing of the session were prone to error.

"Yes, sometimes in the technical area, where the presentation of the program is not good in that something could not be seen on the monitor, where we then somehow also first clicked around a bit, until then you came to what you actually know." (Interview 4: 5).

3.2.3.2. Limits of own competencies

Three BFB practitioners reached the limits of their own competencies when they did not perform BFB treatment for an extended period of time due to illness or vacation. Changes in the process were thus difficult to integrate.

"Well, I was now and then away for longer periods of time during the time of introduction, so I was not engaged with it. I noticed that it (is) difficult to get back into it when I have not done it for a while." (Interview 3: 7).

Limits to one's own competencies were also evident regarding computer skills (3 of 10 BFB practitioners).

3.2.3.3. Structural difficulties

Structural problems arose in case of not sufficiently clarified responsibilities and missing space for clarifying communication. Furthermore, there was double occupancy of the room used for BFB treatment, which could not be avoided and resulted in canceling the BFB session. Moreover, it turned out to be a challenge implementing this new treatment in the nursing team so that all BFB practitioners reached the same level of competence and acquire background knowledge. Further, some problems occurred while ordering materials. In addition, eight BFB practitioners named time management as challenging due to frequently changing TAU schedules. There was not enough time scheduled for an appointment to accommodate patient delays as well as deal with technical issues. Therefore, it was not always possible to keep appointments due to a lack of time and increased workload. Structural problems also existed regarding personnel resources. Due to staff shortages, it was not possible to perform all scheduled BFB treatments. There were also missed appointments due to illness or vacation.

"So, for example, I was alone on the ward for quite a few days, I just could not keep the appointments." (Interview 2: 10).

The increased workload due to BFB treatment presented a strain to the nursing team, as the workload could not be appropriately accommodated at the given time.

"We all are involved in other routine processes, and this had to be mastered in addition, so to say. And, of course, that has also led to resistance." (Interview 10: 9).

Managing the staff was described as challenging during implementation, especially countering frustrations and maintaining staff motivation (2 of 10 BFB practitioners).

"Yes (...). Well, you have to bring everyone together. And it's always the case that one person is more motivated than the other. (...) That you find a common ground there." (Interview 9: 13).

Moreover, one employee mentioned that the Sars-CoV-2 pandemic led to particular everyday challenges due to constantly changing regulations and increased workload, which made implementing a new therapy much more difficult.

Additionally, the relationship with the patients might have been impaired due to the insecurities of BFB practitioners in performing the novel treatment, which they had no prior experience with. However, most BFB practitioners (8 of 10) felt that BFB treatment did not impair the relationship with patients.

3.2.4. Joy

Seven BFB practitioners enjoyed the implementation of BFB treatment because they learned something new, the benefits for the patients were observable, and the calm relaxation environment created a pleasant working. Frustration arose at times when organizational and structural problems occurred.

"Yes, it was fun. In the beginning, I was a bit skeptical. Something new is always like that... you have to look first. But when you see that the patients do benefit from it (…), then it's fun, sure." (Interview 5: 26).

3.2.5. Suggestions for improvement

As technical suggestions for improvement the change of the software and the creation of more modern feedback (videos, graphics) were mentioned.

"I think these video sequences could be a little more modern, the graphics could be a little cleaner, smoother. It still looks so much like 80s/90s software somehow. Then I think it would be more appealing (...) for the patients." (Interview 8: 18).

Another suggestion for improvement relates to the own competencies. Nine BFB practitioners would like to have more intensive training and an official advanced training. Furthermore, self-experience sessions are desired, in which BFB treatment can be tried by oneself. In this way, more background knowledge could be acquired and thus self-confidence could be increased.

"I could imagine doing such a training (...). Basically, to see what else is possible in the bio/neurofeedback area and also to improve my theoretical background knowledge again, (…) that there is a better outcome for the patients when they have a treatment with me (...)." (Interview 8: 20).

Furthermore, two BFB practitioners would like to have a second BFB device so that more patients can train in parallel. This would lead to an increase in efficiency. In addition, three BFB practitioners wish more support, e.g., in the form of up-to-date manuals and instructions as well as easily reachable contact persons who can help with technical problems or theoretical questions. The compliance of BFB practitioners would be particularly promoted if there was a contact person in their own team.

"Yes, if something should actually not work, that you could contact someone who can then help in that moment. For example, if we have IT (support) here, if we have computer problems or something. That we can reach someone." (Interview 5: 18).

In addition, two BFB practitioners suggest a standardization of the meetings to be able to develop more security and routine. Furthermore, the room used for BFB should be designed more appealing and friendly to support a relaxed training. Regarding appointment coordination, eight BFB practitioners stated that time slots for BFB treatment should be fixed. Furthermore, a calendar should be created to which all BFB practitioners have access to create more transparency regarding scheduling. Regarding personnel planning, one employee suggested to clearly clarify who covers an absentee in case of vacation or illness. Furthermore, an actual-target analysis should be conducted to balance staff resources and BFB sessions offered.

To promote patient rapport and adherence, two BFB practitioners suggested that the first BFB session should include enough time for intensive education and answering of questions. Moreover, it would be beneficial to have the same staff member conducting therapy with a particular patient. Furthermore, there should be a permanent contact person for patients who can be reached on short notice.

"Actually, we should have a short conversation with the patients. That one schedules a few minutes more time in the first session. We have this information leaflet, but they have so many questions that you actually have to give answers before the first session." (Interview 1: 24).

4. Discussion

The aim of the present study was to evaluate the implementation process of an individual BFB treatment in addition to the TAU in an inpatient psychosomatic unit. Therefore, the acceptance, satisfaction, feasibility, and ability of implementing this new treatment offer were investigated by applying a convergent parallel mixed methods design. The results of the present quantitative patient assessment exceeded the defined cutoff-value of 23.5 (31) indicating satisfaction of the patients with the BFB treatment. Moreover, based on Bangor et al., system usability suggests a moderate to high acceptance of patients with the BFB treatment (33). The self-generated instrument for measuring acceptance also indicates a high satisfaction and acceptance of patients with the BFB treatment. Most of the patients perceived the sessions as pleasant and expressed their wish to continue BFB treatment after discharge of the clinic. The results of the qualitative interviews with BFB practitioners revealed that most of the BFB practitioners find BFB as suitable for the psychosomatic inpatient unit. The introduction of this treatment enabled the BFB practitioners to expand their own competencies and to take over a therapeutic part of the inpatient treatment of psychosomatic patients. Moreover, BFB treatment allowed BFB practitioners for a different way of relating to the patients resulting in treating the psychosomatic disorder from another perspective. However, the results of the present study revealed several challenges emerging during the implementation process ranging from technical to organizational and structural difficulties. Therefore, technical background knowledge was helpful and partly essential in conducting the sessions. Moreover, not sufficiently clarified responsibilities and a lack of routines showed to be demanding. In addition, tight schedules meant that there was no buffer left for patient delays or spontaneously occurring events. Staff shortages led to cancelling of appointments in case of vacation or illness. However, the biggest challenges revealed to be the increased workload due to additional tasks within the framework of this implementation. The results of both qualitative and quantitative measures show that acceptance and satisfaction with the BFB treatment among both patients and BFB practitioners was high. Although many difficulties were encountered during implementation, BFB practitioners also showed a high level of acceptance. To our estimation, the perceived difficulties during the introduction of BFB are comparable to typically occurring challenges in implementation processes. However, it has become clear that BFB in the psychosomatic-psychotherapeutic inpatient setting must be able to meet special demands. On the one hand, fixed structures narrow the space for novelty. In addition, psychosomatic departments usually treat very heterogeneous groups of patients, to whose different needs one must adapt individually. Typically, inpatient treated patients suffer from a more severe symptom burden than in an outpatient setting. This makes it necessary to adapt the BFB to this special patient clientele.

But how can BFB treatment be implemented in existing daily clinical regimes? Before scheduling BFB treatment, personnel resources should be planned in advance and be available accordingly to minimize the increase of the workload and thus avoid resistance and frustration among the team. Although in this study, the BFB was mainly performed by nursing staff, other patient-related occupational groups could also perform and offer the BFB after appropriate training. The personnel requirements depend on the individual structures of the respective clinic as well as on the number of patients to be treated with BFB. In order to offer adequate BFB training, a time of 1.5 h per patient per week should be calculated, which results from

two training sessions of 30 min each as well as 15 min each for preparation and follow-up of the session as well as discussion with the patient. However, an increase in staff is often not feasible due to a shortage of skilled staff nurses and tight budgets. Finding a solution to how BFB treatment can be firmly established in the inpatient setting despite the difficulties and how BFB treatment can be provided permanently, would provide many patients a therapy offer which they could not make use of otherwise, since BFB is mainly offered in the outpatient setting and is considered a self-pay service in most cases. A BFB offer in the psychosomatic-psychotherapeutic inpatient setting now allows access to this type of treatment for a broad patient clientele. In order to ensure a high quality of BFB treatment even though different BFB practitioners perform the sessions, the BFB treatment should be manualized. A standardization and manualization of the sessions would thus facilitate workflows among BFB practitioners. Moreover, an intensive preparation of the BFB treatment and an ongoing support of the BFB practitioners should be ensured. For this purpose, detailed manuals and guidelines should be developed as well as regular training and supervisions should be offered. In addition, a contact person should be available on site and be able to quickly help with both content-related and technical problems. The results of this study also show that appointment management should be discussed with all parties involved before the start of BFB treatment. This would prevent scheduling conflicts and make appointments more reliable.

Due to the challenges identified in this study, we consider a manual based realization and standardization of the BFB treatment for psychosomatic inpatients to be necessary. This would facilitate BFB implementation and BFB practitioners' workflows, create clear routines, and ensure high quality BFB treatment. Furthermore, this would create the basis for a comparable and effective BFB training in a heterogeneous group of patients. However, a manual based and standardized BFB treatment should not be a substitute for individualized BFB but should be designed specifically for this therapy modality.

4.1. Study limitations

Although the results of the present study are promising, some limitations must be considered. First, the selection of patients for the BFB treatment did not follow a structured approach. Since resources and time capacities were limited, it was not possible to offer BFB treatment to all inpatient treated patients. We rather included those patients, who explained interest and had suitable time slots in their therapy schedules. Moreover, four patients discontinued the therapy because they did not like this type of therapy, which leads to a bias in the results. In addition, patient data was lost because some patients were spontaneously discharged from the clinic and were therefore no longer able to complete a questionnaire. Another limitation might be the need for exclusion of patient data due to incomplete questionnaires. Furthermore, the present study did not investigate the effectiveness of BFB treatment. In addition, the treatment success compared to the TAU has not been investigated. It is therefore necessary to conduct appropriate trials in the future.

4.2. Clinical implications

The organizational and structural challenges encountered in the inpatient context make clear planning of BFB necessary before the implementation. Not only should space be provided and personnel resources available, but also different areas of responsibility among the BFB practitioners should be clarified. An analysis of the actual situation and the target situation carried out in advance might create a good starting position for determining the feasible scope of BFB treatment.

5. Conclusion

The present study shows that BFB as an additional treatment in a psychosomatic-psychotherapeutic inpatient unit is an accepted treatment offer both by patients and BFB practitioners. Even though patient satisfaction and BFB practitioners' motivation were high, the implementation of BFB treatment in an inpatient context requires special actions to be taken. Therefore, personnel resources should be planned and be available in advance. Moreover, conducting BFB treatment should be standardized to guarantee high quality of the treatment and to simplify workflows for the BFB practitioners. Consequently, the introduction of a standardized and manualized BFB treatment should be considered. Nevertheless, more research needs to be done about suitable BFB protocols for this particular patient clientele.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the University Duisburg-Essen. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KS undertook project management, designed the study, actively participated in acquisition of data, performed statistical analysis, interpretation of data, and prepared the manuscript. DB-D made substantial contributions to data acquisition, recruiting of patients, and editing of the manuscript. AK supervised BFB treatment and edited the manuscript. PT, CP, AR, and ND actively participated in implementing the BFB treatment in our wards and contributed to editing the manuscript. E-MS and AB made major contributions to the study's conception and edited the manuscript. MF actively participated in project management and study design, made major contributions to statistical analysis and interpretation of data, and supervised the preparation of the manuscript and edited it. MT made major contributions to the study's conception and design, actively participated in the interpretation of data, and revised the manuscript critically for important subject-specific content. All authors contributed to the article and approved the final version of the manuscript.

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Conflict of interest

AK is employed by NeuroFit GmbH.

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1140880/full#supplementary-material

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Neural basis of the attention bias during addiction stroop task in methamphetamine-dependent patients with and without a history of psychosis: an ERP study

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Background: Attentional bias plays an important role in sustaining various types of drug addiction. No prior studies examined methamphetamine (MA)-associated psychosis (MAP) relationships between ERP time course and performance on an addiction Stroop task in MA abusers. The aim of the present study was to determine whether MA abusers with (MAP+) or without (MAP-) psychosis exhibit alterations of the ERP during the addiction Stroop task.

Methods: Thirty-one healthy controls (CTRL), 14 MAP-, and 24 MAP+ participants were recruited and completed the addiction Stroop task during EEG recording using 32 electrodes. Group variations were compared on measures of behavioral task performance and event-related potentials (ERP) of performance monitoring (N200, P300, N450). The Barratt impulsiveness scores were analyzed to investigate correlations with ERP changes.

Results: MA-related word stimulus elicited a more negative N200 amplitude over left-anterior electrodes in MAP- abusers; furthermore, a positive association between the N200 amplitude and Barratt attentional scores and non-planning scores was observed, while no such differences were found in MAP+ abusers. There were no significant differences in reaction time (RT) and error rate between each group.

Conclusion: This is the first study to examine psychosis relationships between ERP time course and performance on an addiction Stroop task in MA abusers with or without psychosis. These findings support the association between attentional bias measured by the MA addiction Stroop task and N200 component as well as indicate the possibility of using this cognitive task in combination with ERP technology to detect psychosis factors among abstinent MA abusers.

KEYWORDS

methamphetamine, methamphetamine-associated psychosis, addiction stroop task, attention bias, EEG

Introduction

Methamphetamine is a psychomotor stimulant with high liability for abuse, and MA abuse has become a public health concern across the globe. MA abuse has been of particular concern for a number of reasons including its association with the psychotic and cognitive symptoms that are similar to those observed in schizophrenia (Hsieh et al., 2014). Methamphetamine-associated psychosis is commonly referred to psychiatric services, displaying signs of positive symptoms such as delusions, paranoia and persecutory ideation and hallucinations (Sommers et al., 2006; Yang et al., 2020). Research has found that MAP is present in up to half of those with chronic methamphetamine dependence, leading to a heavier burden on drug treatment services (Grant, 2012). Further detection is needed to understand the underlying mechanism between MA abusers with (MAP+) or without (MAP-) psychosis.

The involvement of cognitive control modifications in addictive behaviors is evident through the presence of attentional bias, impaired decision-making, deficient response inhibition, and compulsive maladaptive behaviors (Goldstein and Volkow, 2011; Zilverstand et al., 2018). Furthermore, the cognitive processing of addiction-related stimuli is a key factor in substance cue reactivity; thus, it is essential to consider when exploring the neural basis of cognitive processing of exposures to substance cues on drug-seeking, craving, and relapse. The Stroop task (MacLeod, 1991) necessitates cognitive control as successful execution of the task demands individuals to react to one aspect of a stimulus while disregarding another contradictory element. More specifically, participants are directed to identify the ink color of a sequence of color words, consequently inhibiting the instinctive inclination to read the semantic meaning of the words. Previous research has demonstrated the association of color-naming Stroop performance in substance abuse, and MA-dependent subjects have made more errors and responded more slowly than controls in the color-naming Stroop task (Nestor et al., 2011). A related task is the addiction Stroop task (Cox et al., 2006), an analogous task of the classic color-naming Stroop task, where matched neutral and addiction-related words are used. Previous research using an addiction Stroop task has determined that the interference effects, such as an extended reaction time and increased error rate, are indicative of an attentional bias toward substance-related cues (Cox et al., 2006). Attentional bias in drug-word Stroop tests is thought to be a factor in the maintenance of drug-taking behavior and has been shown to be a reliable predictor of relapse elapse (Cox et al., 2002; Waters et al., 2003; Poireau et al., 2022). Attention bias assessed using the MA addiction Stroop task in MA abusers showed impairment in terms of a higher error rate of MA-related words relative to the CTRL participants (Chen et al., 2020). However, there is a scarcity of understanding regarding attention bias impairment in MAP+ abusers.

Event-related potentials (ERPs), high temporal resolution measures of human brain processing, have revealed the temporal sequence of the sub-processes involved in the Stroop interference and conflict resolution (Zhao et al., 2020). Previous research has suggested that a fronto-central negative-polarity effect in the 200 to 350 latency range, often referred to as the N200 (Folstein and Van Petten, 2008), can be elicited by conflict in a Stroop task (Boenke et al., 2009), and later, an N450-latency effect can also be observed (Larson et al., 2014). However, no difference was found in P300 latency or amplitude between the congruent and incongruent stimuli (Rosenfeld and Skogsberg, 2006). Electroencephalography (EEG) has been proposed as a neurophysiological biomarker to delineate psychotic disorders, expanding our understanding of the underlying neural mechanisms (Cao et al., 2022; Han et al., 2022a,b; Wang Q. et al., 2022). There has been limited research investigating patterns of the EEG that characterize MA abusers to detect electrophysiological abnormalities of their cortical networks and their associations with behavioral factors, including reduced working memory performance (Newton et al., 2003). A power spectrum analysis revealed an apparent EEG slowing in MA abusers (Newton et al., 2004). An ERP study of MA addiction Stroop task showed that attentional ERP components such as P300 were reduced with decreased craving within the first 3 abstinent months, and increased P300 amplitudes elicited by MA-related words were observed over left-anterior electrode sites (Haifeng et al., 2015). In addition, disruptions to resting EEG microstates were observed in MA abusers, leading to alterations in the microstate topographies over time, and these variations were associated with attention bias and a history of drug use (Chen et al., 2020). Recent research suggests that the left frontal electrode plays a distinct role in MAP. During resting eyes closed, MAP+ showed a higher delta/alpha frequency activity globally, while during resting eyes open, MAP+ displayed a higher delta/alpha frequency activity in all electrodes except the left frontal, when compared to the CTRL. Additionally, during the cognitive task, MAP+ exhibited a higher delta/alpha frequency activity in all electrodes except the left frontal (Howells et al., 2018). An EEG delta/alpha frequency activity assessment can help to identify the neurophysiological mechanisms associated with MAP disorder. However, the electrophysiological effects of MAP+ abusers remain largely unexplored, despite its growing prevalence.

Magnetic resonance imaging (MRI) has become an essential tool in the study of mental illness, which helps clinicians and researchers better understand the patterns of brain activity and structures that are associated with different disorders, such as depression (Wang J. et al., 2022), Alzheimer's disease (Gao et al., 2022a), schizophrenia (Gao et al., 2022b). Few imaging studies, however, have characterized brain dysfunction associated with MAP (Yang et al., 2021; Jia et al., 2022) nor investigated EEG differences in brain dysfunction of MAP. Therefore, neurological dysfunctions related to cognitive performance and psychosis in MA abusers need to be elucidated. The present study aimed to investigate the neurological functions using EEG measurement during addiction Stroop task in MA abusers with or without psychosis compared with age-matched normal participants.

Materials and methods

Participants

All participants were recruited from Shenzhen Kangning Hospital and local communities to take part in a set of neuropsychological tests, a psychiatric interview (see Table 1), and electrophysiological recordings. Participants were enrolled

TABLE 1 The demographic data of abstinent methamphetamine users with and without psychosis and healthy control subjects.

	MAP- (n=13)	MAP+ (n=24)	CTRL (n=31)	χ2 /F/t (p-value)
Demographic variables				
Age, years	38.18 (9.05)	34.19 (5.64)	35.49 (9.26)	1.02 (0.37)
Range	20-53	23-47	20-56	
Female subjects	2	3	5	0.15 (0.93)
Education, years	12.38 (3.57)	11.00 (3.31)	11.97 (3.08)	0.95 (0.39)
Clinical Variables				
Methamphetamine use				
Duration, years	2.85 (2.08)	3.83 (2.37)	-	0.25 (0.22)
Range	1-7	1-10	-	
Months abstinent	31.67 (12.79)	33.73 (20.62)	-	5.68 (0.75)
Range	8-54	2-68	-	
Age of first use, years	31.15 (8.76)	27.00 (6.04)	-	1.23 (0.10)
Mean daily use (grams)	0.59 (0.47)	0.60 (0.38)	-	0.26 (0.96)
Barratt impulsiveness scale				
Motor	22.31 (6.90)	22.67 (6.458)	-	0.24 (0.88)
Non-planning	27.62 (6.29)	29.54 (8.59)	-	0.90 (0.48)
Attention	26.08 (5.77)	27.62 (6.29)	-	1.68 (0.49)
Total	76.00 (14.42)	80.13 (18.05)	-	1.91 (0.50)

The value represents mean ± SD. MAP- and MAP+ = Methamphetamine without and with psychosis, and CTRL = healthy control, respectively.
p value for the statistical tests: Chi-Square test for gender distribution (across 3 groups), one-way ANOVA for age and education (across 3 groups) and Student two sample t-test (unequal variance assumed) for the drug use measures and Barratt scale (MAP- vs MAP).

into three subgroups: 24 patients with MA-associated psychosis (MAP+, 5 female), 14 MA users without psychosis (MAP-, 2 female), and 31 healthy controls (CTRL, 5 female) with matched age, gender, and education. All participants were required to have normal or corrected-to-normal vision, normal hearing, be aged between 18 and 59 years, and belong to the Chinese Han ethnicity. The MAP+ met a lifetime diagnosis of MA-associated psychosis, while the course of symptoms could be longer than 6 months. The inclusion criteria for the MAP group were 2-fold: (1) Patients had to meet the diagnostic criteria for MA dependence, and they had to exhibit at least three instances of hallucinations and/or delusions; (2) patients were required to have abstained from MA use for a minimum of 15 days to ensure that any observed effects were not due to acute drug use or withdrawal. The MAP- received a diagnosis of MA dependence or abuse, without current or past psychotic symptoms. Subjects were excluded if they had any severe neurological disease, including head trauma, cardiovascular disease, and physical illness. Those with other psychiatric disorders in the DSM-IV axis I, or abuse of other substances, except for tobacco, coffee, and alcohol drinking without alcoholism, were also excluded. Ethical approval for this study was issued by the Research Ethics Committee of Shenzhen Kangning Hospital (2019-k003-01), and written informed consent in accordance with the Declaration of Helsinki was obtained from all the participants after receiving a full explanation of the study. As a token of appreciation for their time spent on the study, each participant was given 200 yuan after completion of the study.

Measures

MA-use patients (including the MAP- and the MAP+) completed the UCLA Natural History Interview (NHI) to provide detailed drug use information, and the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) was used to measure impulsiveness, which consists of 30 items for three domains of impulsivity (attention, motor, and non-planning).

Addiction stroop task

The addiction Stroop task was constructed and performed on E-Prime 2.0 software (Psychology Software Tools, Inc.). Reaction times and responses for the participant's key presses were recorded. Four stickers were placed on the Q, R, U, and P keys on the keyboard, each representing one of the four colors the participant used to select a response in the Stroop task (red, yellow, blue, and green, respectively). Each word remained on the screen for 1,500 ms or was ended by the

reaction button, and each of the 16 words [8 MA-related words and 8 matched control words, which were used in previous research (Haifeng et al., 2015)] were shown in the four colors consequently creating 64 trials for each block, 4 blocks in total. These 256 trials were randomized across participants, and the same category of the words was set not to appear three times consecutively. Before the first block, a practice block would be performed to avoid unfamiliarity with task operations. The fixation cross and the following word were presented on a black background 75 cm away from the eyes. All evaluations were performed following the standardized instructions by trained researchers.

EEG acquisition and processing

While participants performed the Stroop task, EEG data were recorded from 32 Ag/AgCl scalp electrodes (BrainCap, GmbH, Germany) according to the international 10–20 system. The placement of the recording reference was at Cz, while the ground was positioned at approximately AFz. The impedances were kept below 10 kΩ with the sampling frequency at 1,000 Hz.

Utilizing MATLAB (MathWorks, Natick, MA, United States) and the EEGLAB toolbox (Delorme and Makeig, 2004), we processed the continuous EEG data with in-house scripts. An offline digital band-pass filter (0.1–30 Hz) was applied. Epochs were extracted from −200 to 1,000 ms relative to the onset of the word stimulus and baseline corrected using the prestimulus interval (−200 to 0 ms). Independent component analysis (ICA) was used to correct eye movement, muscle artifacts, and heartbeat artifacts. All EEG epochs were processed for artifact detection by visual inspection and EEGLAB, and detection of obvious eye blinks and epochs with amplitude values exceeding ±100 mV at any electrode were rejected and later re-referenced to the average reference (Tafuro et al., 2019; Overbye et al., 2021). To guarantee the quality of data, patients with >20% of bad epochs for each condition and/or five bad channels were removed from the analysis, and one MAP- participant with more than 20% of bad epochs was excluded.

ERPs

ERP analyses mainly focused on the components of N200, P300, and N450. Time course of the average of left-anterior frontal channels was used to obtain the amplitude and latency of N200, P300, and N450. The time windows for evaluating ERP peaks were determined by inspecting the grand-averaged waveforms; the time windows are as follows: 200 to 300 ms for N200; 250 to 450 ms for P300; and 400 to 650 ms for N450. The mean amplitude and latency (FDR corrected) of these components in MA-related word trials were measured on left-anterior electrodes (F3, F7, FC5 electrodes), and a 50% fractional area technique (Kiesel et al., 2008) was applied to measure the latency of components.

Statistics

For demographic and clinical characteristics, the groups were compared with Student's *t*-test or one-way ANOVAs (analysis of variance) followed by Tukey's *post-hoc* test, and a chi-square test was conducted for categorical variable comparisons (Table 1). For the Stroop effect, error rate and mean reaction time (RT) were analyzed using a 3 × 2 mixed-design ANOVA with the groups (MAP- vs. MAP+ vs. HCs) as a between-subjects factor and stimulus type (MA word vs. neutral word) as a within-subject factor. In addition, only MA word trials were considered in the EEG data analysis; a one-way analysis of covariance (ANCOVA) followed by Tukey's *post-hoc* test was used to analyze the amplitude and latency of the groups in outcome measures, with the groups as the between-subject factor. The entire statistical analysis was conducted using IBM SPSS Statistics version 26 (IBM Corp., Armonk, N.Y., USA).

Results

Participant characteristics and behavior

The outcomes (mean values) of all dependent variables (CTRL, n =31; MAP-, n = 13; MAP+, n = 24) are presented in Table 1. There was no significant difference in the mean age and education between groups. MAP+ and MAP- show no difference in methamphetamine use variables and Barratt impulsiveness scores.

The descriptive behavioral data for both groups, including mean RTs (ms) and error rate (%) for each condition, are shown in Figure 1. The two-way ANOVAs were conducted on the mean RTs and the error rates. For the analysis of the RTs, all incorrect trials were excluded. Figure 1A illustrates the procedure of the MA addiction Stroop task. A 3×2 ANOVA on the RTs showed no significant main effect for group or condition (MA-related words and neutral words), respectively (Figure 1B, group: F (2, 128) = 1.270, $p = 0.284$; condition: F (1, 128) = 0.008, $p = 0.930$), and the group×condition interaction was also not significant (Figure 1B, F (2, 128) = 0.007, $p = 0.993$). There were no significant differences between the groups in the error rate of each condition (Figure 1C, group: F (2, 128) = 0.311, $p = 0.733$; condition: F (1, 128) = 0.008, $p = 0.930$; group×condition: F (2, 128) = 0.031, $p = 0.970$).

ERPs

The N200, P300, N450 peaks were observed only in MA-related word condition of each group. The ERP waveforms and topographical distributions of the N200, P300, and N450 components for the analyzed trial types are shown in Figures 2A, E. A significant interaction emerged for N200 amplitude between the groups (Figure 2B, $F_{2.65} = 3$, $p = 0.028$); subsequently, the *post-hoc* analysis showed that compared with the CTRL group, the MAP- group showed a more negative N200 amplitude in the MA-related word condition on left-anterior electrodes ($p = 0.009$), while no significant effects emerged in the mean amplitude of P300 (Figure 2C, F (2.64) = 1.668, $p = 0.196$) and N450 (Figure 2D, F (2.64) = 0.455, $p = 0.636$). With regard to latency, none of the

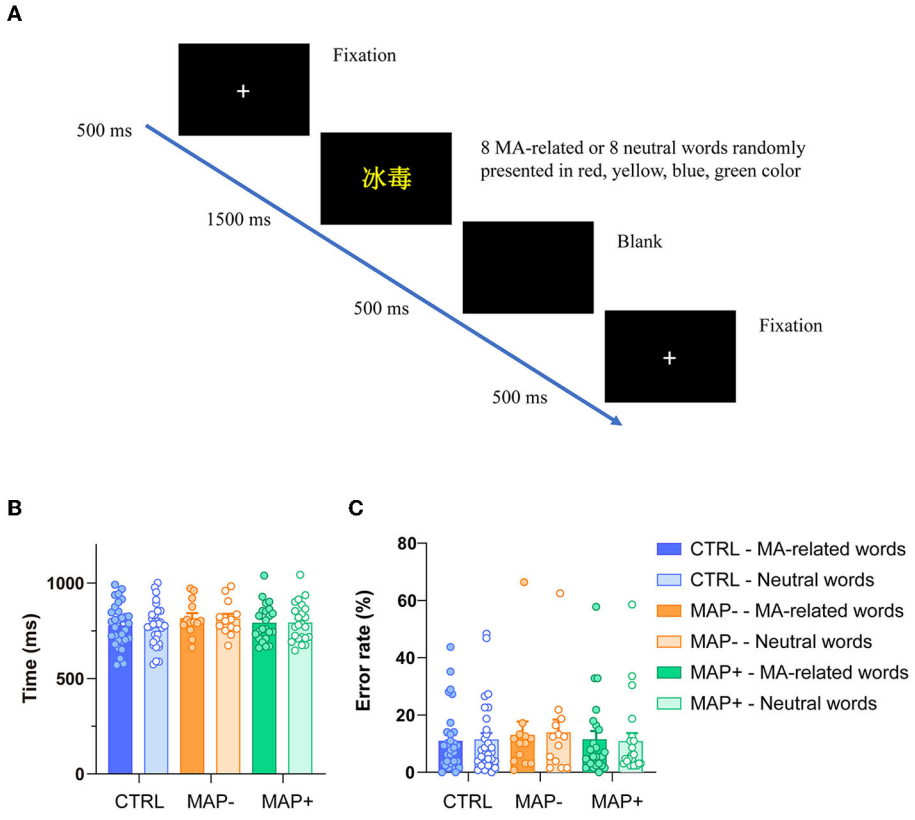

FIGURE 1
Illustration of the experimental procedure and behavioral performance. **(A)** Sequence of trial events in an MA-related words trial. **(B)** RT for correct trial across conditions. **(C)** The error rate committed on each group and each trial type.

changes in the latency of N200, P300, and N450 were statistically significant (please refer to Supplementary Figures 1A–C, N200: F (2.65) = 1.023, $p = 0.365$; P300: F (2.65) = 0.177, $p = 0.838$; N450: F (2.65) = 0.039, $p = 0.962$, respectively).

Correlations with Barratt impulsiveness scores

To further examine the relationship between behavior and electrophysiological signature, we correlated the Barratt total score and sub-domain scores separately with the difference in amplitudes of the N200 on MA-related word trials. Pearson's correlation test was used to assess the correlation between variables (Figures 3A–D). A positive relationship of N200 amplitude with attentional impulsivity score ($p = 0.026$, $r = 0.614$) and non-planning impulsivity score ($p = 0.015$, $r = 0.656$) was observed in MAP- abusers, while this positive correlation was not found in Barratt total score ($p = 0.080$, $r = 0.502$) and motor impulsivity score ($p = 0.788$, $r = 0.083$).

Discussion

This is an initial study to examine the relationships between ERP time course and performance on an addiction Stroop task in MA abusers with or without psychosis history. The current study investigated whether MA abusers with or without a psychosis history are characterized by deficits in ERPs during the addiction Stroop task. We found that MA-related words stimulus elicited a more negative N200 amplitude over left-anterior electrodes in MAP- abusers; furthermore, a positive association between N200 amplitude and Barratt attentional scores and non-planning scores was observed, while no such differences were found in MAP+ abusers.

Attentional bias toward addiction-related cues can impede executive functions that are pivotal in sustaining abstinence from drugs. To measure this attention bias, addiction Stroop tasks, which are similar to the classical Stroop tasks but comprised of both drug-related and neutral words, are used when assessing research participants who use drugs. Despite the lack of any noteworthy disparity in behavioral performance data between groups, high-temporal-resolution ERP technology is more adept at detecting the subtle distinctions in attentional processes, as more negative amplitudes over anterior electrode electrodes elicited by MA-related words that were observed among MAP- abusers and not MAP+ abusers can be attributed to the attentional bias of MAP abusers for MA-related cues. Previous studies (Potvin et al., 2018; Guerin et al., 2019) have shown that those with methamphetamine use disorder have cognitive deficits in many areas compared with controls, with inhibitory control, assessed through the color-word Stroop task, being particularly impaired. Minor addiction Stroop effect can be attributed to certain factors. First, the duration of

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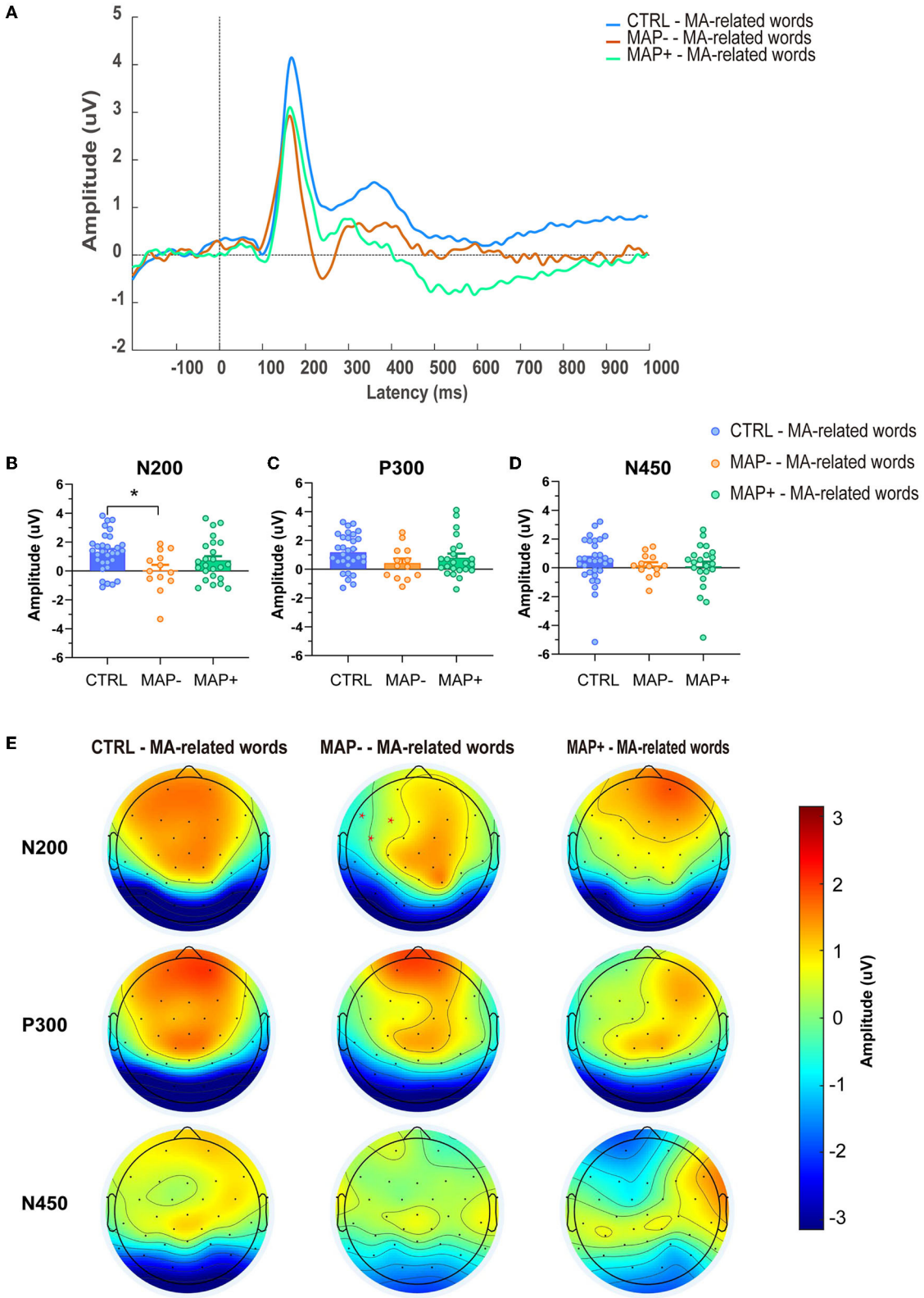

FIGURE 2
Averaged ERP amplitudes and topographical maps. **(A)** Grand mean averages (uV) of ERP waveforms to the MA-related words in the CTRL, MAP-, MAP+ groups across left-anterior electrode sites. **(B–D)** Mean N200, P300, and N450 amplitudes (uV) in each group, averaged across left-anterior electrode sites. Error bars represent SEMs. **(E)** Topographical maps of N200, P30, and N450 across different groups.

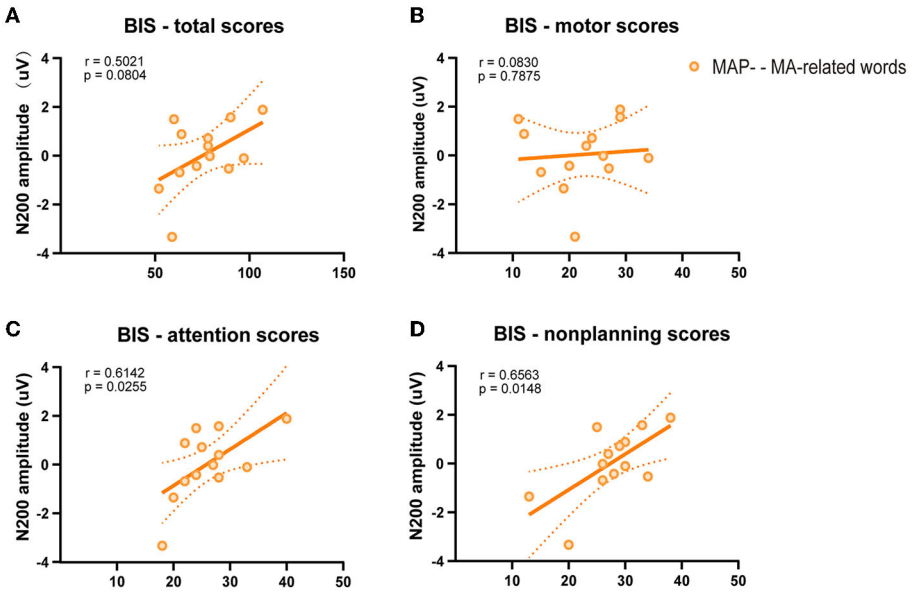

FIGURE 3
Scatterplot of the relation between N200 amplitude and Barratt impulsiveness scores. **(A)** Barratt total scores. **(B)** Barratt motor scores. **(C)** Barratt attentional scores. **(D)** Barratt non-planning scores.

withdrawal time may affect the Stroop effect, as MA abusers in our study were abstinent for a long time ranging from 2 to 68 months. In a recent study, it was observed that individuals who had recently abstained from MA abuse displayed a higher level of Stroop RT interference in comparison with both the control group and those who had been abstinent from MA abuse for a longer period of time. Conversely, no significant difference was observed between the long-term abstinent MA-abusing individuals and the control group (Salo et al., 2009). Second, RTs and error rate are not sensitive indicators of attentional bias from MA abusers in the Stroop task. Previous studies had showed no difference in RTs and error rate, however, there was evidence of intraindividual variability (IIV) and excessively long RTs (tau) in MA abusers who were abstinent for 2 to 60 months (Fassbender et al., 2015). Finally, quiet investigations of the addiction Stroop task did not detect any behavioral performance between drug abusers and participants, with quick response and high accuracy (Fehr et al., 2006; Haifeng et al., 2015; Chen et al., 2021), which might refer to the ceiling effect of this task, so a task of low difficulty would not be able to distinguish between drug users and the general population in terms of behavior.

ERPs, a highly informative and dynamic method of tracking brain activity with a high temporal resolution, are characterized by a series of positive and negative components. N200, P300, N450, and conflict slow potential (SP) latency and amplitude on the variable Stroop test were usually measured to differ between conditions (Ergen et al., 2014; Sahinoglu and Dogan, 2016; Fang et al., 2022). According to a prior investigation, smoking-associated images elicited a relatively negative response at frontal and central electrode locations during the 200–250 ms timeframe, as well as left frontal negativity between 400 and 500 ms at the F7 site, as compared to neutral images in the context of the addiction Stroop test (Fehr et al., 2007). Although we found relative negativity at left-anterior electrode sites between 200 and 300 ms, N450 did not reach a significant level. The functional implications of N450 have been extensively studied in order to differentiate between conflict resolution and response selection processes. This has been achieved by analyzing the ERP data obtained from various versions of the Stroop test. The results indicate that N450 exhibits greater negativity in response to incongruent trials as compared to congruent trials (Chuderski et al., 2016; Guo et al., 2018). Further inquiry into the part that N450 plays in addiction is needed in the future. Additionally, an ERP study of the addiction Stroop task revealed that abstinence from MA resulted in a decrease in left-anterior P300 to MA-related words at 3 and 6 months, and this decrease was associated with a decrease in craving (Haifeng et al., 2015). Despite the lack of P300 alteration in MA abusers in the present study, it is reasonable to assume that the period of abstinence is a crucial factor in MA-related words related to P300. It is apparent that further EEG investigations on the addiction Stroop task necessitate validation in subsequent research.

Correlations between ERPs and measured results provided useful information and may further multiply the results of the present research. Pearson's correlation analysis between the Barratt scores and the N200 amplitude was conducted to determine the relationship between subjective traits and N200 amplitude elicited by MA-related cues. A positive association between N200 amplitude and Barratt attentional scores and non-planning scores was observed in MAP-abusers. It may be concluded that those people who scored high in the Barratt attentional score and non-planning score showed a higher N200 amplitude in MA-related word condition.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee of Shenzhen Kangning Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MY and XJ were instrumental in the conception and design of the work. FL and ZK were involved in the acquisition of the data. YL, YZ, and GY were involved in the investigation and formal analysis. GH, CH, and JY were responsible for analyzing and interpreting the data and as well as writing the article. In the course of a rigorous review process, GH, IJ, and CJ collaborated to scrutinize the article and have committed to being answerable for all elements of the project. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1173711/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Averaged ERP latencies. **(A–C)** Mean N200, P300, and N450 amplitudes (uV) in each group, averaged across left-anterior electrode sites, respectively. Error bars represent SEMs.

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Psychometric evaluation and validation of Urdu Social Rank Scale for women with infertility in Pakistan

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Background: Infertility negatively affects nearly all aspects of women's life and is a source of demotion in the rank/status of women that they have achieved after marriage. This social rank/status demotion due to infertility may result in depression and several other psychopathologies. No extant instrument is available to measure the phenomenon of social rank in women with infertility in Pakistan.

Objective: The aim of the current study was to evaluate the psychometric properties and validate the Social Rank Scale for women experiencing infertility in Pakistan.

Methodology: This study was conducted in four phases. The data were collected from women with primary infertility who visited hospitals all over Pakistan from 2016 to 2018. Social Rank Scale for Women with Infertility (SRS-WI) comprising of two scales, the Social Comparison Scale for Women with Infertility (SCS-WI) and the Submissive Behavior Scale for Women with Infertility (SBS-WI), was developed.

Results: The factor structure of 37 items of SCS-WI and of 21 items of SBS-WI was determined through exploratory factor analysis (EFA) on a sample of 215 women with primary infertility with an age range of 20–45years (M_{age}=31.03; SD=6.18). Principal component analysis with varimax rotation method yielded a three-factor solution for SCS-WI, and 32 items were retained for SCS-WI that accounted for 62.38% variance. For SBS-WI, a uni-factor solution was obtained, and 20 items were retained for SBS-WI, which collectively accounted for 42.01% variance. The factor structure for both scales was confirmed via confirmatory factor analysis among a sample of 210 participants with good model fit indices.

Conclusion: The study provides acceptable psychometric properties of the SRS-WI in Pakistan. Testing of psychometric properties in different groups of samples would justify the generalized use of the instrument.

KEYWORDS

social rank, infertility, social comparison, submissive behavior, psychometric evaluation

Introduction

Social rank is directly associated with reproductive ability amongst married people in Pakistani society (1). Psychological repercussions of infertility include stigmatization, seclusion, depression, anxiety, and guilt (2, 3). Pakistani women face persistent pressure to bear a son for the sake of the continuation of lineage (4). Failure to do so imposes labels such as "barren and

cursed" on them (5). Women perceive an insurmountable portion of psychological distress compared to men (6).

Cross-cultural differences in the perception of infertility are rather prominent, as in Eastern societies deficient social support results in high levels of psychopathological outcomes (7). A feeling of inferiority and consequential loss of social rank lead to depressive symptoms owing to hopelessness and worthlessness (8). Pakistani women with primary infertility are subjected to systematic and progressive devaluation, as child-bearing is a prerequisite for strengthening their foothold in the in-laws' house (9). For this reason, it is imperative to assess this phenomenon. Social rank is measured by social comparison and submissive behavior variables. Social comparison is comprised of perceptions of personal superiority or inferiority (10, 11), and submissive behavior consists of inhibition in situations of challenge or conflict (12–14).

Keeping in view the significance of the phenomenon of social rank and its variables in relation to the detrimental effects caused by a medical condition like primary infertility, there is a strong need to assess this phenomenon in women. In the West, scales such as the Scale of Social Comparison Submissive (15), Submissive Behavior Scale (16) and INCOM by Gibons and Bunk (17) are available with their local norms, but no such scale is available in Pakistan to assess the variable of social rank, i.e., social comparison and submissive behavior, especially with respect to infertility. Although two self-report scales of social rank, i.e., Social Comparison Scale (SCS) and Submissive Behavior Scales (SBS) were developed in the English language for the student population language in the West and are available, there are certain reservations to using them directly in the Pakistani population, as firstly, they are developed in Western culture according to their norms, and the Pakistani culture has different norms and values. Secondly, both scales are in English, and in all the provinces of Pakistan, the most commonly used and comprehendible language is Urdu. Therefore, we need self-report scales that are easier to understand by most Pakistani women who can read or understand the Urdu language. Thirdly, the available scale of social rank variables, i.e., SCS (15) and SBS (16), are generic tools and cannot give us a true picture of the perception of social rank variables with special reference to primary infertility in women of Pakistan. So, it was felt that a self-report infertility-specific scale of social rank in the context of Pakistani culture needed to be developed.

Materials and methods

The study was conducted in four phases.

Phase I: generation of an item pool

An initial item pool in the Urdu language was generated using both inductive (semi-structured interviews) and deductive approaches. The item pool was then presented to a committee comprised of five judges (three assistant professors and two lecturers from the Department of Psychology) to determine content validity. After consensus, 37 items were retained for the SCS for Women with Infertility, and 21 items were reserved for the SBS for Women with Infertility based on a strict selection criterion: construct reliability, the perception, the precision of statement, comprehensibility, clarity, and redundancy. The arrangement of the items was shuffled by arranging the items from general to more defined and specified content.

The format of the response by the participants for the 37 items in the SCS-WI (18) was categorized to be a Likert type 5-point scale (0 = strongly disagree, 1 = disagree, 2 = indecisive, 3 = strongly agree, 4 = strongly agree). The response format of the 21 items SBS-WI (19) was also decided to be 5-point Likert type scale (0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Mostly, 4 = Always).

Phase II: pilot study

The pilot study was conducted for the psychometric scrutiny of the items (removing the ambiguous, repeatedly occurring and redundant items) and to test the initial scale to ensure lucidity and comprehensibility of the items' statements.

The study was carried out by recruiting 30 women with primary infertility from Rawalpindi city by using purposive sampling strategy. The age range of the participants was 20 to 45 years (M_{age} = 31.37, SD = 5.18).

The participants were thus informed about the purpose of the current investigation and the procedure of affirmative consent. Respondents were asked to answer the questions of the survey on the spot, and their queries were catered to accordingly.

The integral purpose of this preliminary study was to grasp the comprehensibility and clarity of the content of the scale and consequently finalize the items for the exploratory factor analysis for phase III of this study. In order to determine the normality of the data, the Shapiro–Wilk test was incorporated, and values W (30) = 0.94, $p > 0.05$ of SCS-WI and values W (30) = 0.96, $p > 0.05$ indicated that there was normal distribution of data within the group. Some of the items were modified after getting feedback from the participants. For example, item number 1 was re-phrased to "I feel physically inferior as equated to child bearing mothers" from "I feel inferior as compared to child bearing mothers." Item 9 was rephrased from "I understand that I am given less importance in the family in comparison to child bearing mothers" to "I understand that as compared to child bearing mothers, I do not have that much influence in the family." Item 11 was rephrased from "I understand that I am not as likeable as child bearing mothers are." Item 28 was rephrased to "I understand that I am not as likeable in the family as compared to child bearing mothers" from "Due to infertility, I feel more helpless and cry." In Item 30, the word people were replaced by "family." However, there was no deletion done for any single one of the items. For SBS-WI, item 1 was rephrased to "I feel inferior due to infertility" from simply "I feel inferior." It was the judges' mutual consent to add "due to infertility" in all item statements.

Ultimately, 37 items for Social Comparison Scale for Women with Infertility (SCS-WI) with reverse scoring for items 6 and 7 and maximum score of 148 were finalized. Further, 21 items for the Submissive Behavior Scale for Women with Infertility (SBS-WI) with a maximum score of 84 were finalized.

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Phase III: dimensionality and internal consistency

This phase was conducted for finding the factorial validity of SCS-WI and SBS-WI. Both the scales were analyzed in order to finalize the statements that could be retained after assuring the appropriate structure. Cronbach's alpha, item-total scale correlation, and item subscale correlation were computed to conclude the reliability and internal consistency of the overall scale.

The sample of the current study was recruited through a purposive sampling, and 230 women with primary infertility were selected from all major cities of different provinces of Pakistan. Participants of the study fall in the age range of 20–45 years ($M_{age} = 31.03$; $SD = 6.18$). The mean duration of infertility period was approximately 8 to 9 years ($M = 8.88$; $SD = 6.52$). The average number of treatments sought by the women in this study was six ($M = 5.76$; $SD = 6.35$). Participants of the study had formal educational levels from primary to post-masters level and belonged to a variety of socioeconomic classes. On the whole, the participants were quite cooperative; however, eight participants dropped out of the study for personal reasons while six respondents were unable to return the survey, so their data was excluded from the study. The final sample consisted of 215 women with infertility. Overall response rate of the participants was 93.4%.

Instruments used in study were demographic sheet, 37-item Social Comparison Scale for Women with Infertility (SCS-WI), with a response format of a 5-point Likert scale and 21 item Submissive Behavior Scale for Women with Infertility (SBS-WI). Participants were encouraged to fill out all the questionnaires during the current investigation, and their queries related to survey forms were acknowledged and answered then and there for their satisfaction.

Before officially carrying out Exploratory Factor Analysis, the assumptions and rules of Factor Analysis were empirically tested for checking the data to be factor analyzed and were found satisfactory for both SCS-WI and SBS-WI. The sample adequacy for SCS-WI (37-item) was tested with Kayser-Myer sample of adequacy measure (KMO, Kaiser, 1960). The KMO value was 0.95, and it was excellent $\chi^2(496) = 5606.98$, $p < 0.001$. Moreover, significant Bartlett's test also assured the factorability.

For SBS-WI, the sampling adequacy was 0.93 for The Kaiser-Meyer-Olkin measure which was depicted as excellent for structure detection, while the Bartlett's Test of Sphericity was highly significant $\chi^2(210) = 2390.33$, $p < 0.001$ with a prominent indication that factor analysis had been proved appropriate for the current data. Hence, the study proceeded forward. The normality of the SCS-WI and SBS-WI items was checked by computing the skewness and kurtosis, as factor analysis is robust to the assumptions of normality. It was found that all the items were in the range of acceptable levels for SCS-WI and SBS-WI. It was assured that before running the factor analysis, no potential missing values were present in the data; for furthering our study, this assumption was found to be satisfactory. The computed item correlation matrix of SCS-WI and SBS- WI indicated that all the items were suitable for structure detection. All the communality values of SCS-WI and SBS-WI were within the acceptable range. There were no outliers found in the data of SCS-WI and SBS-WI revealed by the box plot.

Results of factor analysis in Table 1 yielded a three-factor solution through principal component analysis and a fixed factor solution followed by orthogonal rotation (varimax method) with Eigen values greater than 1.0. Out of 37 items, 32 items showed factor loadings on three factors. On the basis of scree plot, factor loadings greater than 0.40 in each subscale and theoretical relevance, three were well defined, interpretable, clear accurate factors were retained. These factors labeled as Social Distress (F1: factor 1), Emotional Burden (F2: factor 2) and Personal Incapacity (F3: factor 3). The Eigen value for factor 1 is 16.35, explaining 51.11% of variance; factor 2 is 2.46, explaining 8.24% of variance, and factor 3 is 1.41, explaining 4.41% of variance, and totally they accounted for 63.76% of the total variance.

TABLE 1 Factor loadings, mean and standard deviation (N=215) of social comparison scale for women with infertility SCS-WI.

Old item no./New item no.	Factors			*M*	*SD*
	1	2	3		
SCS-WI 21/ SCS-WI 18	**0.87**	0.27	0.12	2.20	1.56
SCS-WI 20/ SCS-WI 17	**0.87**	0.21	0.20	2.07	1.56
SCS-WI 25/ SCS-WI 22	**0.85**	0.19	0.19	2.03	1.63
SCS-WI 19/ SCS-WI 16	**0.79**	0.27	0.26	2.20	1.53
SCS-WI 22 /SCS-WI 19	**0.77**	0.26	0.25	2.23	1.55
SCS-WI 26/SCS-WI 23	**0.75**	0.23	0.25	2.38	1.54
SCS-WI 35/SCS-WI 30	**0.71**	0.32	0.20	2.47	1.51
SCS-WI 18/SCS-WI 15	**0.67**	0.22	0.45	2.49	1.45
SCS-WI 24/SCS-WI 21	**0.67**	0.45	0.17	2.56	1.56
SCS-WI 23/SCS-WI 20	**0.64**	0.46	0.23	2.07	1.56
SCS-WI 30/SCS-WI 32	**0.59**	0.20	0.34	2.05	1.50
SCS-WI 9/ SC S-WI 6	**0.57**	−0.13	0.28	2.20	1.53
SCS-WI 11/SCS-WI 8	**0.53**	0.30	0.51	2.50	1.41
SCS-WI 27/SCS-WI 24	**0.43**	−0.31	−0.14	1.65	1.71
SCS-WI 15/SCS-WI 12	**0.42**	−0.08	−0.34	1.59	1.61
SCS-WI 33/SCS-WI 28	0.15	**0.78**	0.13	3.33	1.08
SCS-WI 32/SCS-WI 26	0.23	**0.76**	0.11	3.27	1.07
SCS-WI 28/SCS-WI 27	0.32	**0.65**	0.36	3.01	1.30
SCS-WI 2/SCS-WI 2	0.07	**0.65**	0.42	2.46	1.45
SCS-WI 5/SCS-WI 5	0.33	**0.61**	0.17	1.59	1.61
SCS-WI 3/SCS-WI 3	0.26	**0.60**	0.45	2.30	1.50
SCS-WI 34/SCS-WI 29	0.28	**0.55**	0.52	2.91	1.29
SCS-WI 37/SCS-WI 31	0.33	**0.53**	0.41	2.99	1.24
SCS-WI 12/SCS-WI 9	0.33	0.17	**0.72**	2.46	1.45
SCS-WI 10/SCS-WI 7	0.33	0.19	**0.72**	2.31	1.51
SCS-WI 13/SCS-WI 10	0.42	0.17	**0.71**	2.30	1.50
SCS-WI 14/SCS-WI 11	0.35	0.30	**0.71**	2.54	1.49
SCS-WI 1/SCS-WI 1	0.01	0.44	**0.62**	2.50	1.41
SCS-WI 4/SCS-WI 4	0.26	0.48	**0.59**	2.54	1.49
SCS-WI 16/SCS-WI 13	0.17	0.47	**0.54**	3.28	1.02
SCS-WI 17/SCS-WI 14	0.34	0.45	**0.50**	3.05	1.20
SCS-WI 29/SCS-WI 25	0.41	0.44	**0.45**	2.03	1.63
Eigen values	16.35	2.64	1.41		
% of variance	51.11	8.24	4.41		

Communality > 0.40 (Field, 2005).

Out of 37 items, 5 items (items no. 6, 7, 8, 31, and 36) were deleted that had factor loading less than 0.40 with Eigen value <1.0 (item 6 "I am affable"; item 7 "I feel more attractive as compared to child bearing mothers." Item 8 "I feel more helpless as compared to child bearing mothers" has same content as item 28 "I cry over my helplessness more than child bearing mothers" which was rephrased and retained. Item 31 "Due to infertility my husband does not give importance to me" because the content was nearly the same as item 22 "My husband does not cooperate with me due to infertility/childlessness." Item 36 "I avoid social gatherings as compared to other women"). No item required reverse coding, as negatively phrased items were reported as confusing by the women in pilot study. High score on SCS-WI indicates higher negative and unfavorable social comparison.

Factor 1 (Social Distress). Items 6, 8, 12, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 30, and 32 had independent loading on factor 3, and it represents social distress (social factors that have an impact on women with infertility such as social comparison, diminished social status, diminished respect and importance in family, social stigmatization, negative and critical attitude of people, reduced liking in family especially in-laws, rejection by family, blaming by family, reduction in love and attention by husband, left out by husband, cold attitude of husband, uncooperative husband towards treatment, threats of being expelled from husband's home, threats of second marriage by husband and in-laws, distant relations with husband, gap in communication with husband, in-laws thinking of women with infertility as useless and take her for granted in all household chores and other tasks, social isolation, avoiding social gathering, etc.). It explained 51.11% of variance. *Factor 2 (Emotional Burden)*. Items 2, 3, 5, 26, 27, 28, 29, and 31 had independent loading on factor 2, and Emotional Burden subscale of emotional factors is related to diminished social status of women with infertility, such as feelings of sadness, sorrow, worthlessness, loneliness, helplessness, hopelessness, negative feelings, depression, anger, anxiety, aggression, frustration, irritability, distress, grief, loss of happiness, reduced interest in daily activities, envy, jealousy, insecurity shame, humiliation, etc. It explained 8.24% of variance. *Factor 3 (Personal Incapacity)*. Items 1, 4, 7, 9, 10, 11, 13, 14, 25 had independent loading on factor 1. The items indicate various forms of social comparison of women with primary infertility, such as feelings of inferiority, self-blaming, fatigue, lack of resourcefulness, low self-esteem, low confidence, reduced eye contact, feelings of physical and mental illness and weakness, meaningless life, feeling incomplete, feelings of being left out, negative future apprehensions, reduced attraction, decreased sexual attraction, negligence of personal care and hygiene, etc. It explained 4.41% of variance. The factorial validity of the scale was demonstrated on empirical and theoretical grounds. The final scale came up with 32 items and three well delineated factors, i.e., Social Distress (15 items), Emotional Burden (8 items), and Personal Incapacity (9 items) (Table 1).

Item-total correlation of SCS-WI was run to see the internal consistency of the scale. Results indicated that each item of Social Comparison Scale for Women with Infertility correlated (r ranging from 0.44 to 0.78) with the sum of total items. Moreover, mean inter-item correlation was 0.50. Thus, all items are considered valid and reliable indicators of Social Comparison scale for Women with Infertility. Cronbach's alpha for SCS-WI with infertility (α ranging from 0.89 to 0.94), which is good along with the potential range and actual range of the SCS-WI. Furthermore, if we compare the mean of the sample with the potential range of the score on the relevant scale, it appears that on SCS-WI, the mean score is 81.85 and the maximum potential range is 0–128, which indicates that average score of the sample lies on the higher direction showing higher social comparison in women with primary infertility. As far as factor 1, i.e., Social Distress, is concerned, the mean score is 30.10 and the maximum potential range is 0–60, indicating that the score of the sample lies on the average side, whereas a mean score of 21.06 on factor 2, i.e., Emotional Burden, with potential range of 0–36, indicates that the sample mean lies on higher side on this factor. Lastly, the sample mean on factor 3, i.e., Personal Incapacity, is 24.76 with potential range of 0–32, indicating sample mean on higher side in this factor as well. The reliability of this scale (Cronbach's alpha) was $\alpha = 0.92$ (Table 2).

The 21 items of Submissive Behavior Scale for Women with Infertility (SBS-WI) were factor analyzed. The single factor solution was obtained explaining 42.01% of variance, retaining all the items on the basis of scree plot, and whose factor loading was greater than 0.40 with eigen value >1.0. Only one item, i.e., item number 2 ("I raise voice for my rights"), was discarded, whose factor loading was less than 0.4 with eigen value <1.0. The item-total correlation analysis was performed on 20 items of SBS-WI. The proportion of correlation of each item with the total score of the scale was determined. Results in Table 3 present that each SBS-WI item correlated positively (r ranging from 0.41 to 0.84) and significantly ($p < 0.01$) with the sum of total items; moreover, mean inter item correlation was 0.64. A final 20 items were retained ($M = 51.00$; $SD = 18.52$; response range = 0–4; and skewness = −0.57). Further, if we the compare mean value of the total score of SBS-WI, i.e., 51, with the potential range of 0–80, it appears that it is in higher direction indicating more submissive behavior in women with primary infertility. The item means of almost all the items are also on slightly higher side when compared to potential range, indicating slightly higher submissive behavior in women with primary infertility. Results in Table 3 shows that all items of SBS-WI can be considered valid and reliable indicators of Submissive Behavior Scale in Women with Infertility.

TABLE 2 Final factors, percentage of variance and alpha coefficients of social comparison scale for women with infertility (N=215).

Factor Label	Final (with new item no.) items retained	Final items	Variance	Alpha coefficients
F1 Social Distress	6, 8, 12, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 30, 32	15	51.11%	0.89
F2 Emotional Burden	2, 3, 5, 26, 27, 28, 29, 31	8	8.24%	0.90
F3 Personal Incapacity	1, 4,7, 9, 10, 11, 13, 14, 25	9	4.41%	0.91
SCS-WI	F1, F2, F3	32	63.76%	0.94

Reliability Analysis of SCS-WI.

Inter item correlation of SBS-WI

The item-total correlation analysis was performed on 20 items of SBS-WI. The proportion of correlation of each item with the total score of the scale was determined (Table 4). Results in Table 4 that each SBS-WI item correlated positively (r ranging from 0.41 to 0.84) and significantly ($p < 0.01$) with the sum of total items; moreover, mean inter item correlation was 0.64. A final 20 items were retained ($M = 51.00$; $SD = 18.52$; response range = 0–4; and skewness = −0.57). Further, if we the compare mean value of the total score of SBS-WI, i.e., 51, with the potential range of 0–80, it appears that it is in higher direction indicating more submissive behavior in women with primary infertility. The item means of almost all the items are also on slightly higher side when compared to potential range, indicating slightly higher submissive behavior in women with primary infertility. Results of Table 4 shows that all items of SBS-WI can be considered valid and reliable indicators of Submissive Behavior Scale in Women with Infertility. The reliability of this scale (Cronbach's alpha) was $\alpha = 0.92$ (Table 5).

TABLE 3 Item-total correlations for subscales of 32-item social comparison scale for women with infertility (N=215).

Subscales items	*r*	Subscale items	*r*	subscale items	*r*
Social distress		23	0.74	31	0.69
6	0.44	24	0.50	Personal incapacities	
8	0.77	33	0.66	1	0.56
12	0.48	30	0.72	4	0.70
15	0.79	Emotional burden		7	0.69
17	0.79	2	0.57	9	0.68
17	0.78	3	0.70	10	0.73
18	0.77	5	0.60	11	0.75
19	0.78	27	0.73	13	0.62
20	0.76	26	0.56	14	0.71
21	0.76	38	0.55	25	
22	0.74	29	0.74		

All correlations were $p < 0.01$.

Phase IV: confirmatory factor analysis

To confirm the factor structure and dimensionality of the instruments, the 32 items of Social Comparison Scale for Women with Infertility and 20 items of Submissive Behavior Scale for Women with Infertility were scrutinized through AMOS-21.0. Instruments used were the demographic sheet from the Social Comparison Scale for Women with Infertility (SCS-WI, 32 item). The scale was proven to have good internal reliability with Cronbach's alphas of 0.79 to 0.95. Submissive Behavior Scale for Women with Infertility (SBS-WI), 20

TABLE 4 Factor loadings, item total correlations, mean and standard deviation (N=215).

Old-new item	Factors loading	Item-total correlation (*r*)	Mean	SD	Min	Max
SBS-WI 1–1	**0.48**	0.44	2.24	1.53	0	4
SBS-WI3-2	**0.67**	0.63	2.47	1.43	0	4
SBS-WI4-3	**0.54**	0.50	2.50	1.37	0	4
SBS-WI5-4	**0.44**	0.39	2.71	1.30	0	4
SBS-WI6-5	**0.57**	0.52	2.71	1.26	0	4
SBS-WI7-6	**0.78**	0.75	2.52	1.42	0	4
SBS-WI8-7	**0.56**	0.52	2.39	1.46	0	4
SBS-WI9-8	**0.56**	0.52	2.73	1.33	0	4
SBS-WI10-9	**0.54**	0.50	2.47	1.54	0	4
SBS-WI11-10	**0.64**	0.61	2.33	1.53	0	4
SBS-WI12-11	**0.41**	0.38	2.87	1.31	0	4
SBS-WI13-12	**0.53**	0.50	2.34	1.56	0	4
SBS-WI14-13	**0.59**	0.54	2.21	1.57	0	4
SBS-WI15-14	**0.75**	0.70	2.99	1.18	0	4
SBS-WI16-15	**0.80**	0.74	2.71	1.32	0	4
SBS-WI17-16	**0.83**	0.78	2.62	1.44	0	4
SBS-WI18-17	**0.84**	0.79	2.54	1.49	0	4
SBS-WI19-18	**0.79**	0.73	2.46	1.53	0	4
SBS-WI20-19	**0.78**	0.73	2.66	1.37	0	4
SBS-WI 21–20	**0.77**	0.71	2.54	1.45	0	4
SBS Total	–	–	51.0	18.5	0	80
Eigen value	8.78					
% of variance	42.04					

Bold face Factor loading > 0.40 (Field, 2005).

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item with a Cronbach's alpha of 0.82. Maximum score is 80. Higher scores are indicative of greater feelings of subordination. The study respondents were communicated and informed about the purpose of the current study. Written and affirmative informed consent was taken from all the study participants. It took them approximately 10 to 15 min to complete the questionnaire for the Social Comparison Scale for Women with Infertility and 5 to 10 min to complete the questionnaire for the Submissive Behavior Scale for Women with Infertility. Out of 225 recruited participants, 10 left the study incomplete, and five did not return the questionnaire responses. The final sample consisted of 210 participants.

The current study incorporated numerous indices, standards and criteria to present the best model fit including CFI, TLI, RMSEA, IFI, and GFI, as they have been frequently testified and reported in the recent research (20). The results after confirmatory factor analysis of the Social Comparison Scale for Women with Infertility shows that in the final model, the IFI = 0.91, CFI =0.91 together with χ^2 (317, n = 210) =790.71, p < 0.01, and TLI = 0.90, RMSEA = 0.08. In terms of the overall indices, it is evident that this model was acceptable. In initial model, the values of IFI, TLI, CFI, and RMSEA were not in the acceptable range, and the model was revised through modification indices and also by deleting some of items with correlation less than 0.3. Details of items deleted are: Item 5, "I remain quiet most of the time as compared to child bearing mothers," item 8, "I feel that I am not liked by the family as they do other child bearing mothers," item 15, "I feel that family members reject me due to childlessness," item 18, "My husband love for me has decreased due to childlessness," and item 20, "I feel physically less attractive due to childlessness." A revised model was obtained, which still required further improvement, as the values of IFI = 0.87, TLI = 0.86, CFI = 0.87, RMSEA = 0.10 were still not in acceptable range. In the final model, covariance as suggested by modification indices were entered in the error terms to further improve the model. Lastly, the final obtained model had all the values in acceptable range (Table 6).

TABLE 5 Overall Mean, Standard Deviation, Cronbach's Alpha, Maximum Score, Minimum Score(N = 210).

Scale	K	Final Items retained	M(SD)	α	Min.	Max
SCS-WI	27	1-27	55.17(23.48)	.95	19	103
Social distress	11	5, 10, 13, 14, 15, 16, 17, 18, 19,25, 27	21.28(10.23)	.90	3	44
Emotional burden	7	2, 3, 21 , 22, 23, 24, 26	14.37(6.35)	.85	1	28
Personal Incapacities	9	1, 4,6, 7, 8, 9, 11, 12, 20	17.43(7.99)	.87	2	33
SBS-WI	17	1-17	28.38(15.33)	.95	0	57
SRS-WI	44	----------	81.48(36.70)	.84	19	153

Note. k = no. of items. α = Cronbach's alpha

The results after confirmatory factor analysis of the Submissive Behavior Scale for Women with Infertility (17 items) shows that in the final model, the GFI = 0.90, CFI =0.94 together with χ^2 (107, n = 210) =205.15, p < 0.01, and TLI = 0.92, RMSEA = 0.07. In terms of the overall indices, it is evident that this model is acceptable. The initial model obtained has GFI, CLI, TLI, and RMSEA values that do not fall in the acceptable range of model fit indices, so using modification indices the model was improved further and a revised model was obtained that still had values of GFI = 0.86, TLI = 0.87, CFI = 0.89, RMSEA = 0.10 that were not in the acceptable range, so items no. 13, 14, and 18, with correlation less than 0.3, were deleted, and the final obtained model had all the values in the acceptable range. Details of items deleted are item 13, "I avoid eye contact with people due to infertility," item 14, "I remain quiet when people talk unlikeable things about me," and item 18, "Due to infertility without any hesitation, family makes me do their work without taking my consent." In the final model, some covariance was added in error terms to improve the model as recommended by modification indices (Tables 6–8).

Figures 1–3 indicate that the model supports that Social Rank Scale can be used collectively by including social comparison and submissive behavior independently.

Table 5 indicates the mean, standard deviation, Cronbach's alpha, and minimum and maximum scores. It is found that overall alpha for Social Comparison for Women with Infertility SCS-WI α = 0.95 (α range from 0.87 to 0.90 for subscales) and Submissive Behavior Scale for Women with Infertility SBS-WI α = 0.95. Overall the alpha reliability of Social Rank Scale is 0.84, which is also good.

Convergent and discriminant validity of scales

Convergent validity of SCS-WI was determined by associating it with similarly constructed scales, such as the Social Comparison Scale (15), while convergent validity of SBS-WI was established by correlating it with the Submissive Behavior Scale (16). Taking the research study one step further, the discriminant validity of SCS-WI was determined by correlating it with a theoretically opposing scale, i.e., the Satisfaction with Life Scale (21, 22).Previous studies have shown a negative correlation between social comparison and satisfaction with life, or that low levels of social comparison lead to higher satisfaction with life (23), and discriminant validity of SBS-WI was determined by correlating it with a theoretically opposing scale, i.e., the Self-Assertiveness Scale (24) (previous researchers have shown a negative correlation between submissive behavior and aggressive behavior) (12–14). A purposive sampling technique was employed to recruit a sample of 30 women respondents experiencing primary infertility from different hospitals and clinics in Lahore, Rawalpindi, and Multan city. Instruments used were demographic sheet, the Social Comparison Scale for Women with Infertility (SCS-WI), 27 items, the Submissive Behavior Scale for Women with Infertility, 20 items, and 11 items translated into Urdu from the Social Comparison Scale to assess the internal sense of one's social ranking by determining how one thinks about where one stands in relation to others. The scale has shown good reliability, with Cronbach's alpha of 0.87 and 16-item Submissive Behavior Scale. Higher scores indicate greater feelings of subordination. The scale showed good reliability, with a Cronbach's alpha of 0.78. Furthermore, Urdu translated Satisfaction with Life Scale (5 item) with Cronbach's alpha for the scale ranges from 0.87 and Self-Assertiveness Scale (28 item). It is used to assess self-assertiveness in adults, through a culture-specific measuring device. It consisted of 28 items with a response option on a 5-point Likert-type scale. A higher score on the scale shows more assertiveness while a low score exhibits less self-assertiveness.

Results of convergent validity studies showed that SCS-WI positively correlated with a similar scale SCS (r = 0.37, *p = 0.05),

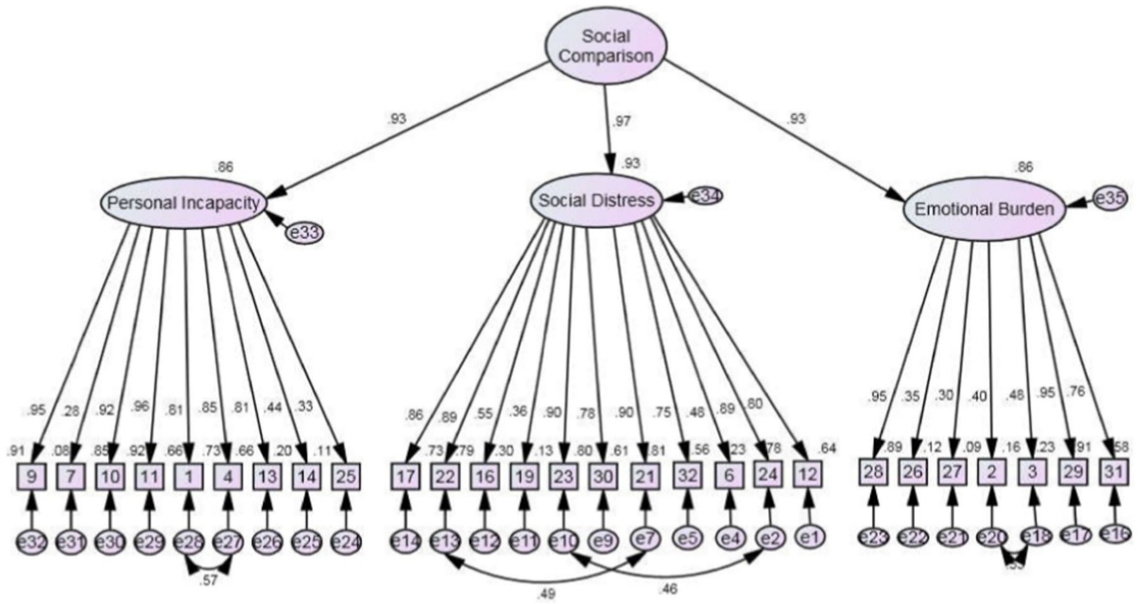

FIGURE 1
Final model SCS-WI 27-item scale (with modification indices).

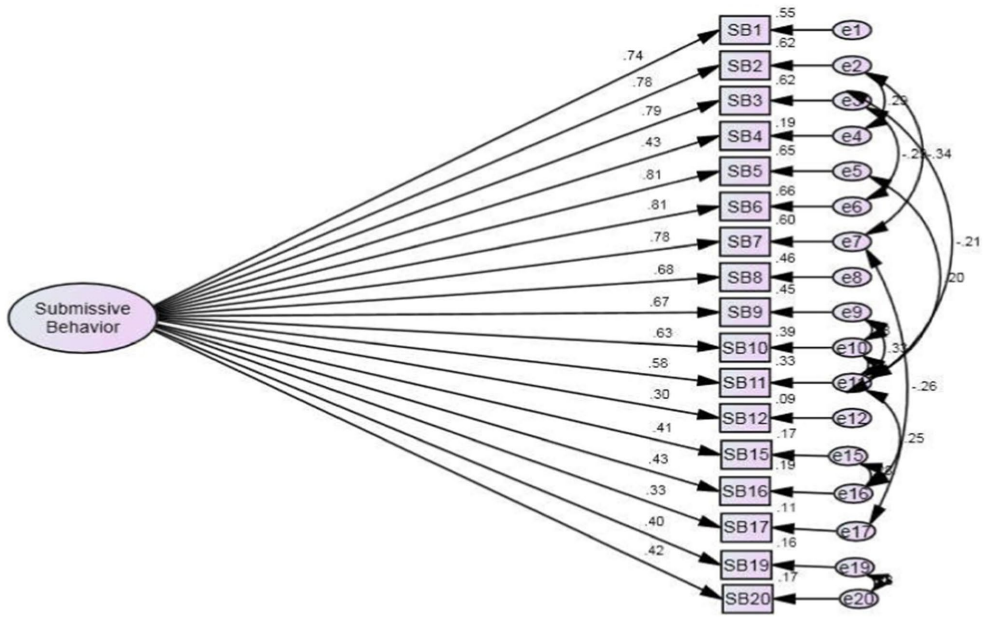

FIGURE 2
Final model SBS-WI complete standardized solution of submissive behavior scale for Women with infertility (N=210).

whereas SCS-WI negatively correlated with SWLS ($r = -0.70$, $^{**}p < 0.01$). The test–retest reliability of SCS-WI after a gap of 1 month on a sample of 30 women with primary infertility was found to be $\alpha = 0.93$. Pearson product moment correlation was also carried out to find the relationship between Submissive Behavior Scale for Women with Infertility (SBS-WI) and Submissive Behavior Scale (SBS), and SBS-WI and Self Assertiveness Scale (SAS). Results suggested that SBS-WI positively correlated with SBS ($r = 0.43$, $^{*}p = 0.05$), whereas it negatively correlated with SAS ($r = -0.57$, $^{**}p < 0.01$). The test re-test reliability of SBS- WI after an interval of 1 month on a sample of 30 women with primary infertility was found to be $\alpha = 0.94$.

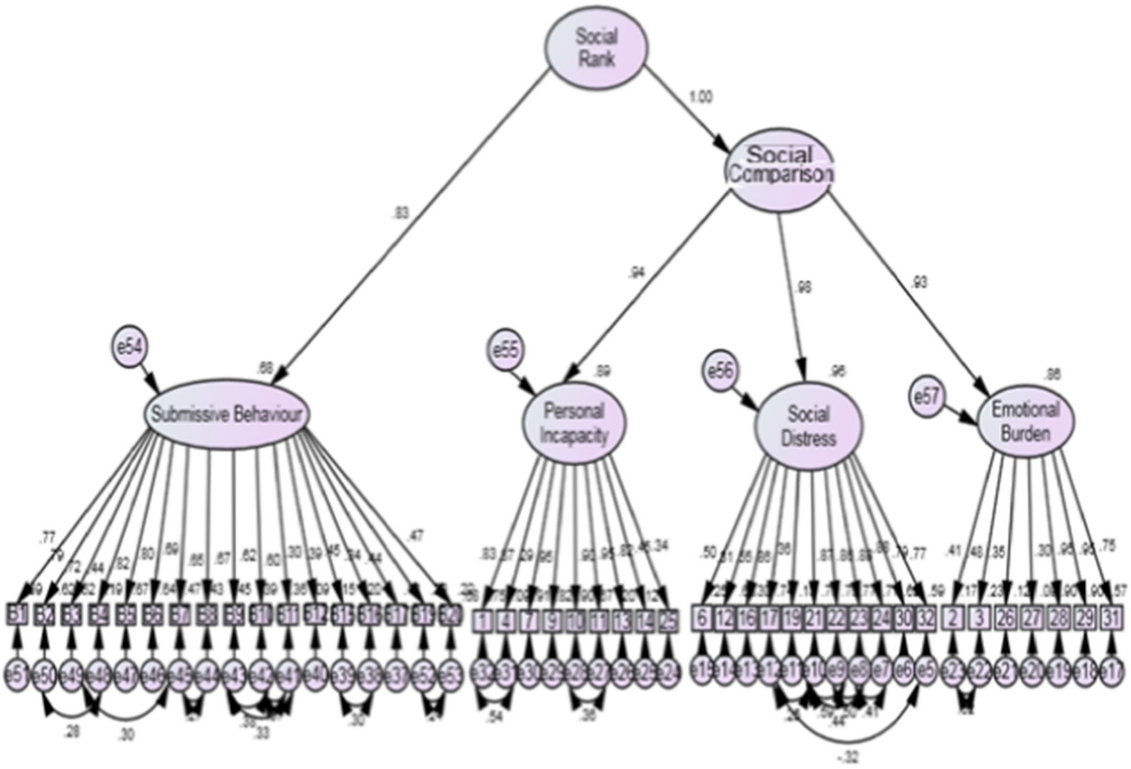

FIGURE 3
Final model of social rank scale for Women with infertility.

TABLE 6 Standardized CFA solution of social comparison scale for women with infertility, *N*=210.

Model	IFI	TLI	CFI	RMSEA	*p*	*df*	χ^2	χ^2/df
Initial Model	0.84	0.83	0.84	0.10	0.000	461	1356.33	2.94
Revised Model	0.87	0.86	0.87	0.10	0.01	321	991.62	3.08
Final Model	0.91	0.90	0.91	0.08	0.01	317	790.71	2.49

IFI, incremental fit index; CFI, comparative fit index; TLI, Tucker Lewis Index Model. Final Model items reduced from 32 to 27 (item nos. 5, 8 15, 18, and 20 deleted).

TABLE 7 Standardized CFA solution of submissive behavior scale for women with infertility (*N*=210).

Model	GFI	CFI	TLI	RMSEA	*df*	*p*	χ^2	$\chi 2/df$
Initial Model	0.80	0.79	0.76	0.10	170	0.000	528.81	3.11
Revised Model	0.86	0.89	0.87	0.10	119	0.000	398.33	3.34
Final Model	0.90	0.94	0.92	0.07	107	0.01	205.15	1.91

GFI, goodness of fit index; CFI, comparative fit index; TLI, Tucker Lewis Index Model. Final Model items reduced from 20 to 17 (item nos. 13, 14, and 18 deleted).

Discussion

The present study was carried out to develop an indigenous scale of social rank for women with infertility in Pakistan with its two subscales, i.e., the Social Comparison Scale and Submissive Behavior Sale for Women with Infertility, by exploring and confirming the factor structure of the scales and establishing the discriminant validity of the scales, and later in the study keeping in mind the significance of assessing social rank variables in our culture specifically, for women with primary infertility. The need for self-reporting scales in the Urdu language was essential for comprehension. The scales developed in these studies are valuable contributions to assess the phenomenon of social rank through social comparison and submissive behavior in women with infertility.

The scales developed in these studies are valuable contributions to assessing the phenomenon of social rank through social comparison and submissive behavior in women with infertility. The scale development process of the Social Comparison Scale for Women with Infertility (SCS-WI) and the Submissive Behavior Scale for Women with Infertility (SBS-WI) was highly intensive, time consuming, and

TABLE 8 Standardized CFA solution of social rank scale (N=210).

Model	IFI	TLI	CFI	*df*	RMSEA	*p*	χ^2	χ^2/ *df*
Initial Model	0.84	0.83	0.84	898	0.08	<0.000	2039.52	2.27
Final Model	0.90	0.90	0.90	881	0.06	<0.01	1576.13	1.78

IFI, incremental fit index; CFI, comparative fit index; TLI, Tucker Lewis Index.

TABLE 9 Convergent and discriminant validity of the SCS-WI and SBS-WI (N=30).

Variables		1	2	3	4	5	6
1	SCS-WI	1	0.37*	−0.70**	0.61**	0.45*	−0.41*
2	SCS		1	−0.30*	0.32*	−0.35*	0.33*
3	SWLS			1	−0.71**	−0.56**	0.37**
4	SBS-WI				1	0.43*	−0.57**
5	SBS					1	−0.36*
6	SAS						1

SCS-WI, Social comparison Scale for Women with Infertility; SBS-WI, Submissive behavior Scale for Women with Infertility; SCS, Social Comparison Scale; SWLS, Satisfaction With Life Scale; SBS, Submissive Behavior Scale; SAS, Self Assertiveness Scale.
*p < 0.05, **p < 0.01.

scientific, and comprised of a mixed method research design. The items for both scales were produced using both inductive and deductive approaches, and the factor structure of the scale was determined through exploratory factor analysis.

The final SCS-WI comprised of 27 items with three well-defined subscales. The first subscale of SCS-WI, i.e., Social Distress, measured the social experiences of women with primary infertility. Participants with high scores on this factor compared themselves unfavorably to childbearing mothers and greatly socially suffered. The items on the scale are based on areas causing social distress. They are related to the status of women with primary infertility in the family, expulsion from home, emotional harassment at home by family members, stigmatization, communal isolation, refusal, fear of rejection, privacy, reduction in love by husband, the uncooperative attitude of husband, and disruption and dissonance in the marital connection due to social and family burden on husband for the need of a second marriage (25). These items are similar to the problems of women with infertility in the Indian subcontinent as well as in Sub-Saharan Africa, and have been highlighted in previous studies (26). Furthermore, women are reported to be engaged in more negative feelings/thoughts in comparison to child bearing mothers, and they also see their lives as meaningless. Continuous social comparison has a strong influence on the emotions of Pakistani women with primary infertility, and the subscale of Emotional Burden would be quite useful to assess this, which was found in previous studies (27). The social suffering of women with primary infertility due to negative social comparisons is in line with the findings of previous research in other countries, especially Asian and developing countries such as Bangladesh, Iran and India (28).

Another prominent factor of the Social Comparison Scale for Women with Infertility was Emotional Burden, as it directly measured the emotional experiences of the women. According to the psychometric properties of the scale, the women with higher scores on this factor had more emotional issues owing to their infertility. The present investigation is very indicative of the significant fact that negative emotions are practiced and experienced by the participants, ranging from crying to feelings of sadness, negative thoughts, low confidence, frustration, sorrow, embarrassment, self-pity, remorse, regret, anger, grief, tension, worry, doubt, shame feelings of rejection, boredom, solitude, depression, helplessness, hopelessness, powerlessness, melancholy, despair, distress, anguish, anxiety, irritability, envy, loss of pleasure/interest in daily activities and reduced sexual interest. Dissatisfaction with life has also been reported, with a strong desire for the child as a source of women's pride. These items are similar to previous studies (25), which also highlighted the negative emotional consequences of infertility.

Subscale 3 of the SCS-WI was Personal Incapacity. A high score on this scale indicated the areas of personal lives of the women in which they were incapacitated due to infertility. For instance, feelings of physical and mental sickness, compact/reduced communication, feelings of inferiority, negligence in personal hygiene and care, fewer capabilities, feelings of physical weakness, fatigue, less resourcefulness, etc. constituted the main content of the items in this sub-scale. A high score on this subscale also shows that women are facing physical illness in the form of headaches, bodily pains, mental illness, and fatigue due to infertility. These findings are in line with previous research, which suggested that Pakistani women with infertility reported greater depression and somatic symptoms than women in the UK with infertility (5). Items of SCS-WI are based on experiences of Pakistani women with primary infertility and the theoretical framework of the social rank theory. Convergent validity of the SCS-WI was determined by correlating it with Social Comparison Scale (9) and was found to be good. Discriminant validity of SCS-WI was determined by correlating it with theoretically opposite scales such as the Satisfaction with Life Scale, and a significant negative correlation was found between both scales. The results coincide with the previous studies that have also shown a negative correlation between social comparison and satisfaction with life (28).

The Submissive Behavior Scale for Women with Infertility (SBS-WI) also appeared as a promising measure with internal consistency and a meaningful pattern of validity. Women with infertility experience all these emotions with more intensity, as previous research reported that women with infertility experience a higher degree of stress and fiery burden due to unfulfilled desire for a child (25). The items included in the scale are somehow similar to the issues reported in previous literature, including depression, acute stress, anxiety, interpersonal problems with friends and family, guilt, loss of self-identity, an increased sense of self-blame, and even in some cases, suicidal ideation (29). Pakistani women with primary infertility are subjected to systematic and progressive devaluation, as childbearing is a pre-requisite for women to strengthen their foothold in their husband's home in the Pakistani culture, norms, philosophy and society (30).

SBS-WI (19) is a uni-dimensional scale, and some of the content of items of the scale appear to be similar to the Submissive Behavior Scale (16), and scale items are based on experiences of Pakistani women with primary infertility. Some of the items were eliminated after confirmatory factor analysis, such as "I avoid making eye contact with people due to infertility", "I remain quiet on displeasing talk of people about me", and "Due to infertility people take me for granted and assign their tasks to me".

Convergent validity of SBS-WI (19) was determined by correlating with a similar construct i.e., the Submissive Behavior Scale (16), and was found to be good. Discriminant validity of SBS-WI was established by correlating it with a theoretically opposite scale such as the Self Assertiveness Scale, and a significant negative correlation was found (See Table 9). The results are in line with the study findings of previous research that showed a negative correlation between submissive behavior and assertive behavior, but at the same time, submissive behavior is not the mirror opposite of assertive behavior (16, 24) (The area of the relationship between assertive and submissive behavior needs to be explored further in the future).

The items of both scales reflect that the loss of one's social rank is often escorted by the experience of one's infertility. Thus, the opinion that most women's ability to reproduce a child is linked to their status as women in every culture and society seems to be related to the findings of previous studies (27), which proposes that the social status of women with infertility can be significant in minimizing the effects of liberalization, with stigmatization and suffering associated with infertility. The study conducted (31) also suggests that negative social inferences about infertility are apparent in women of low status, especially in the emerging and developing world. In short, infertility impacts the overall quality of women's life negatively.

The items of both scales reflect that loss of social rank is often accompanied by the experience of infertility. Thus, the observation that most women's capability to reproduce is linked to their status as women in every culture and society seems to be related to the findings of previous studies (25).

Implications

The newly developed scale seems to have promising reliability and sound convergent and discriminant validities. The scales developed in the study will help psychologists and counselors to assess the phenomenon of social rank demotion in which may contribute to psychopathologies, especially depression, in women with infertility in Pakistani women. The newly developed scales will further open new panoramas of exploration and examination in the domains of social comparison and submissive behavior, and their correlates.

Limitations

Firstly, though the sample of the study was drawn from major cities of four provinces of Pakistan and represented women from various socioeconomic strata, women from rural areas and those who were not seeking treatment from any professionals were not included in this study. Secondly, the items of this newly constructed scale cannot be generalized to women with secondary infertility and men suffering from infertility.

Conclusion

The Social Rank Scale for Women with Infertility with its two components (i.e., the Social Comparison Scale for Women with Infertility, SCS-WI, and the Submissive Behavior Scale for Women with Infertility, SBS-WI) are promising measures of social rank in Pakistani women with primary infertility, with sound psychometric properties, good items homogeneity, high reliability, and significant patterns of validity.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Review Committee of the Department of Psychology, GC University, Lahore Pakistan (Ref: REG-ACAD-ASRB-3/17). The patients/participants provided their written informed consent to participate in this study.

Author contributions

AM: conception and design, data collection, data analysis, writing draft, and revision. SB: critical review, editing, and revision. SA: critical review, editing, and revision. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1150941/full#supplementary-material

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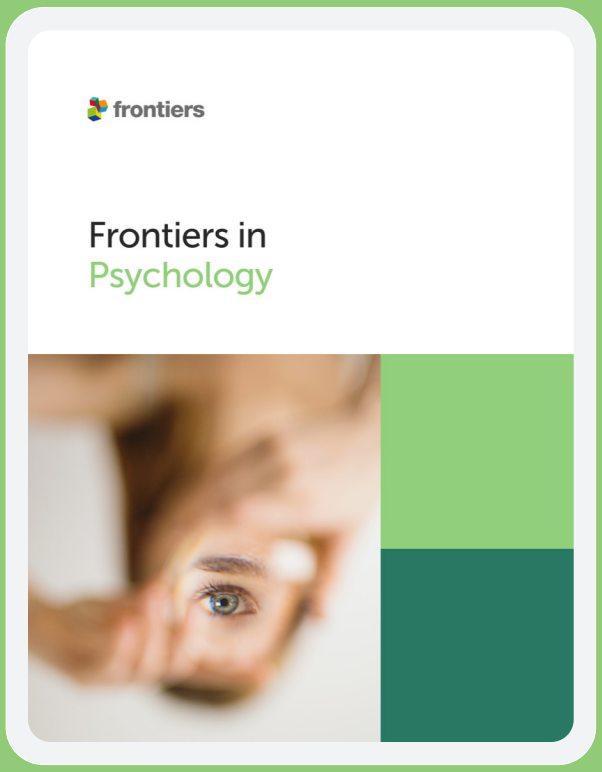

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