NEURAL CIRCUITS AND NEUROENDOCRINE MECHANISMS OF MAJOR DEPRESSIVE DISORDER AND PREMENSTRUAL DYSPHORIC DISORDER: TOWARDS PRECISE TARGETS FOR TRANSLATIONAL MEDICINE AND DRUG DEVELOPMENT

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Editorial: Neural circuits and neuroendocrine mechanisms of major depressive disorder and premenstrual dysphoric disorder: Toward precise targets for translational medicine and drug development

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Editorial on the Research Topic
Editorial: Neural circuits and neuroendocrine mechanisms of major depressive disorder and premenstrual dysphoric disorder: Toward precise targets for translational medicine and drug development

With the intensified social competition and increased psychological pressure in modern society, the impact of emotions on people' health has attracted increasing attention from around the world. Major depressive disorder (MDD) and premenstrual dysphoric disorder (PMDD) are the two common types of depressive disorders described in The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (1). Depressive disorder, represented by PMDD and MDD, is the most common mental illness in modern society, and has a chronic and recurrent course (2). With the development of social economy and the influence of factors such as unemployment as well as changes in life rhythm, depressive disorder has become one of the most serious diseases threatening human health. According to a survey conducted by the World Psychiatric Association, the incidence rate of depressive disorder worldwide is currently 4.2%, while that in China is 6.9%, with an annual growth rate of 113%. According to data from the Global Burden of Disease Organization, mental/neurological diseases occupy the number-one spot in terms of the burden of disease, of which depressive disorder is first among mental/neurological diseases (3).

Although the pathogenesis of depressive disorder has not yet been fully elucidated, there are several clues that neural circuits and neuroendocrine pathways are involved in pathogenesis and drug intervention mechanisms (4–7). Substantial evidence exists for significant alterations in the interactions of relevant brain regions and their neural circuits in MDD (6, 7). Functional Magnetic Resonance Imaging (fMRI) methods have been widely used in clinical research on the mechanism of MDD neural circuits, most of which focus on related brain regions involved in emotion regulation and cognitive function, such as the amygdala, cingulate cortex, prefrontal cortex, striatum, and insular cortex (8, 9). In terms of animal experiments, the synaptic plasticity (such as synaptic density and synaptic protein density) in the prefrontal cortex, nucleus accumbens, amygdala, and hippocampus of MDD model animals was significantly altered (10, 11), while the incidence of PMDD is more closely related to neuroendocrine factors. The premenstrual period is a period of rapid fluctuations in the levels of female reproductive hormones. During the premenstrual phase, the concentration of estrogens, such as estradiol and progesterone, in the body increases significantly, reaching its highest level in the middle and late luteal phase. Get used to it gradually. After menstruation, estrogens show a rapid "withdrawal" phenomenon, returning to the normal range. Some researchers have proposed that this "withdrawal" phenomenon is the most critical reason for premenstrual dysphoric disorder, an idea that has been summarized as the "ovarian-steroid-withdrawal hypothesis" (12, 13). Animal experiments have shown that rapid withdrawal of progesterone can induce PMDD-like behavior in animals, an effect that can also be mimicked by blocking progesterone metabolism (reducing allopregnanolonein [ALLO] levels) (14, 15). As a positive allosteric regulator of γ-aminobutyric acid receptors (GABARs), the sudden drop in ALLO after menstruation leads to abnormal regulation of the function of GABARs, which plays an important role in the pathogenesis of PMDD (16, 17). In clinical terms, the risk of PMDD can be reduced by supplementing ALLO levels, which can be achieved *via* certain antidepressant treatments (18, 19).

The regulation of emotions by the brain is specific to certain brain regions and cells and involves complex changes in neural circuits and neuroendocrine levels. However, the lack of clarity regarding the drug target and mechanism greatly limit translational medicine and drug development. The current treatment drugs are mainly selective serotonin reuptake inhibitors (SSRIs). Overall, 30–40% of patients with MDD or PMDD are insensitive to drug treatment and experience substantial psychiatric side effects and slow onset of action. This can also produce drug resistance, with obvious time lag and inefficiency (20). Therefore, further research into the neural circuits and neural endocrine mechanisms of MDD and PMDD as well as treatment moving toward translational medicine and drug development are keys to solving the above problems. Meta-analysis and animal experimental evidence have shown the high potential of complementary and alternative therapies in the treatment of PMDD and MDD (21, 22). Unlike single-target chemical drugs, Chinese medicine therapy can regulate specific neural circuits and neuroendocrine functions with multiple targets and pathways to treat these diseases, avoiding the side effects of chemotherapy and representing a promising therapeutic direction.

In consideration of the aforementioned realization, we organized this special issue to advance our understanding of the pathogenesis of MDD and PMDD, particularly regarding neural circuits and neuroendocrine mechanisms. This information will provide a basis and possible clues for clinical treatments and drug development. For this Research Topic, we invited recent studies that focus on the neural circuits and neuroendocrine mechanisms of PMDD and MDD and received 11 submissions. After a half year of critical peer review, nine papers have been accepted.

In the experimental report titled "*Decreased Plasma Hydrogen Sulfide Level Is Associated With the Severity of Depression in Patients With Depressive Disorder*," Yang et al. recruited 47 depressed patients and 51 healthy individuals and found that decreased H_2S is involved in the pathophysiology of depression as well as that plasma H_2S may be a potential indicator for depression severity.

In the paper titled "*Antidepressant Treatment-Induced State-Dependent Reconfiguration of Emotion Regulation Networks in Major Depressive Disorder,*" Zhao et al. collected data from 70 MDD patients and 43 sex- and age-matched healthy controls and found that four dFC states were identified in the emotion networks. Their alterations of state-related occurrence proportion were found in MDD and subsequently normalized following 12-week antidepressant treatment. Baseline strong dFC predicted the reduction rate of Hamilton Depression Rating Scale (HAMD) scores.

In Yu et al.'s paper, titled "*Serum Lipid Concentrations Are Associated With Negative Mental Health Outcomes in Healthy Women Aged 35-49 Years*," the authors recruited 319 healthy participants and found that there was a significant association between K10 scores and metabolic parameters, including Body Mass Index (BMI), total and LDL cholesterol, and triglycerides.

In the paper titled "*Sleep Disturbances and Depression Are Co-morbid Conditions: Insights From Animal Models, Especially Non-human Primate Model*," Li et al. evaluated the prevalence, clinical features, phenotypic analysis, and pathophysiological brain mechanisms of depression-related sleep disturbances and emphasized the current situation, significance, and insights from animal models of depression.

In Chang et al.'s paper "*Depression Assessment Method: An EEG Emotion Recognition Framework Based on Spatiotemporal Neural Network,*" the authors proposed a novel EEG emotion recognition framework for depression detection, which provides a robust algorithm for real-time clinical depression detection based on EEG.

In the paper titled "Brain Activation during Processing of Depression Emotion in College Students with Premenstrual Syndrome in China: Preliminary Findings," Gao et al. investigated 13 PMS patients and 15 healthy controls and found that abnormal functional regulation of brain regions such as the occipital lobe and cerebellum leads to abnormal changes in emotional regulation, cognitive ability, and attention distribution in PMS patients, implying significant central pathogenesis.

In the paper "*An End-to-End Depression Recognition Method Based on EEGNet*," Liu et al. proposed an end-to-end deep learning framework for MDD diagnosis based on EEG signals and found that the method is highly accurate for the diagnosis of MDD and can be used to develop an automatic plug-and-play EEG-based system for diagnosing depression.

In another study titled "*Does Childhood Adversity Lead to Drug Addiction in Adulthood? A Study of Serial Mediators Based on Resilience and Depression*," He et al. conducted a thorough investigation of the mental status from 937 participants and found that depression led to drug addiction, while resilience weakened the effect of adverse childhood experiences on depression and drug addiction.

In Gu et al.'s paper, "*The Relationship Between 5-Hydroxytryptamine and Its Metabolite Changes With Post-stroke Depression*," the authors reviewed the relationship of post-stroke depression with three monoamines and emotions. Moreover, they summarized the advantages of psychological therapy in recent years and posted some suggestions for the pharmacology and psychotherapy of post-stroke depression.

Collectively, these studies have thoroughly investigated the neural circuits and neuroendocrine mechanisms of MDD and PMDD as well as some diagnostics and interventions for these emotional diseases. Because neural circuits and neuroendocrine mechanisms are heavily involved in the pathogenesis of MDD and PMDD and the mechanism of drug intervention, multi-faceted exploration in this field will further reveal the underlying neurobiological mechanisms, thereby promoting translational medicine and drug development.

Author contributions

SW, FW, JL, and YW wrote 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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BRIEF RESEARCH REPORT
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Serum Lipid Concentrations Are Associated With Negative Mental Health Outcomes in Healthy Women Aged 35–49 Years

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Background: Although the relevant underlying biological mechanisms are still lacking, mental disorders have been closely associated with several metabolic abnormalities including high rates of obesity and metabolic syndrome especially in vulnerable populations. Therefore, the current study aims to examine how metabolic parameters increase the risk for developing mood disorders in individuals stratified by gender and age.

Methods: In a routine physical examination, 319 healthy participants were recruited and assigned to six different groups according to age (young adults: 25–34 Y, middle age: 35–49 Y, and older age: 50–65 Y) in both males and females. A linear regression and bivariate correlation analysis were used to analyze the relationship between mood health outcomes measured by the Kessler 10 Psychological Distress Scale (K10) and the metabolic function.

Results: The results demonstrated that there was a significant association between K10 scores and metabolic parameters, including Body Mass Index (BMI), total-, LDL-cholesterol, and triglyceride. Furthermore, poor mental health (higher K10 scores) was observed in individuals with increased BMI, total-, LDL-cholesterol, and triglyceride levels particularly in middle-aged women relative to other groups.

Limitations: This is a cross-sectional study with a small sample size and lacks longitudinal follow-up evidence and preventive interventions and therefore could not provide the causal inference of metabolic pathophysiology on the increased sensitivity to mental disorders.

Conclusions: The potential association suggests that targeting of the metabolic parameters might give us a better understanding of the underlying mechanisms of psychiatric diseases and provide preventive strategies and potential treatment for those with metabolic disturbances especially in middle-aged females.

Keywords: mood disorders, psychosocial stress, obesity, body mass index—BMI, total-cholesterol, LDL-cholesterol, triglyceride, middle-aged women

INTRODUCTION

A growing body of evidence have demonstrated that metabolic syndrome including obesity, changes in cholesterol, triglycerides, lipoproteins, and blood glucose increase the risk of developing mental disorders such as major depressive disorder and anxiety, although the relevant underlying biological mechanisms are still lacking. Psychosocial stress leads to the development and maintenance of both metabolic dysfunctions and psychiatric disorders. There are several biomarkers to illustrate the stressful status such as hair cortisol concentrations are increased in chronically stressed populations due to the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (1). Psychological stress also induces chronic neuroendocrine dysregulation leading to metabolic changes that define the metabolic syndrome. Furthermore, chronic stress altered plasma lipids parameters levels including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, and reduced the number of peripheral lymphocytes and subsequently induced immune dysfunction, which is involved in emotional disorders (2). However, evidence showed that not all people with psychiatric disorders display metabolic impairments due to age and gender are the most significant factors influencing the relationship between metabolism and mental disorder. For instance, metabolic conditions (abdominal obesity, high triglyceride, and glucose levels) are associated with an increased risk of a future depressive episode in middle-aged adults (3). Moreover, therapeutic targeting of metabolic parameters might provide new insights into the beneficial effects in depressed patients with high Body Mass Index (BMI) (4). Accordingly, the present study aimed at demonstrating the association between mental health and metabolic measures (i.e., total-, LDL-, and HDL-cholesterol, triglycerides, glucose, and lymphocytes) among heathy young, middle-aged and older individuals and to offer personalized interventions early in the course of the disorder. We hypothesized that abnormal metabolic functions may predict increased mood disorders in vulnerable populations.

METHODS

Data for the current study were collected by a routine physical examination conducted in 319 individuals aged from 25 to 65 years old between January and December 2019. The enrolled subjects were from different job types, such as university staff, doctors in hospital, electrical engineers, office workers, estate agents, and skilled workers. Participants completed a demographic questionnaire including age, gender, relationship status, education, BMI, smoking history, and alcohol consumption. The mental health was assessed by the Chinese version of the Kessler 10 Psychological Distress Scale (K10), which is a 10-item questionnaire developed by Kessler et al. in 2002 and is administered to evaluate distress symptoms in community samples. This scale has brevity, reliability, good precision and strong psychometric properties covering major sociodemographic cases, making it being widely administered in clinical studies as well as in general-purpose health surveys including the annual government health surveys and WHO World Mental Health Surveys (5). The Chinese K10 was administered with a minor modification from the original English version, in which each of the 10 questions relates to an emotional state, and each response has a five-level scale, "1" being "none of the time," "2" "a little of the time" "3," "some of the time," "4" "most of the time," and "5" "all of the time." Total scores are ranging from 10 to 50. Hence, a higher score suggests a greater level of psychological distress especially during the past 4 weeks. Considering the sensitivity to determine the risk of samples developing psychiatric disorders, the involvement of K10 assessment in the routine physical examination would fill the gap between community and clinical epidemiology of emotional disorders. Height and weight were measured to calculate BMI [=weight (kg)/height $(m)^2$]. The fasting venous blood samples were collected in the morning from all subjects after starved for at least 12 h. Metabolic measures, including total-, HDL-, LDL-cholesterol (mmol/L), triglyceride (mmol/L), fasting glucose (mmol/L), and lymphocytes were measured from the plasma samples of participants using routine standardized laboratorial methods. Considering the various prevalence of stress-related mood disorders in different age populations, we divided the subjects into six groups according to the age and gender: young adults (25–34 Y), middle age (35–49 Y), old age (50–65 Y) in both males and females. The participants with chronic diseases such as diabetes, hypertension, cardiovascular diseases, and other somatic disorders that would affect the metabolism as well as severe nicotine and alcohol abusers were excluded from the data analysis. In addition, the mental health of the subjects was evaluated by an experienced psychiatrist, anyone with psychiatric concern was not included in the data collection. A linear regression model and correlation analysis by Pearson were used to evaluate the possible link between K10 scores and BMI and the lipid concentrations measured. The level of statistical significance was set at $p < 0.05$. Ethical approval was received from the Ethics Committee of Tianjin Union Medical Center (No. 2021B15).

RESULTS

In the whole cohort, the average of K10 scores is 11.69 ± 3.13, suggesting they are in a health psychosocial state. Results of the sociodemographic data, BMI, metabolic characteristics and K10 scores of the sample are summarized in **Table 1**. The differences in sociodemographic data, physiological and psychological characteristics were assessed by the one-way analysis of variance (ANOVA) and the chi-square test. Bivariate correlation analysis demonstrated that there was a significant association between K10 scores and BMI, total-, LDL-cholesterol, and triglyceride particularly in middle-aged women. We observed that BMI in middle-aged women was positively correlated with psychological distress (r^2: 0.116; 95% CI, 0.075–0.561, $p = 0.013$), followed by an increase of total-cholesterol (r^2: 0.0796; 95% CI, 0.009–0.515, $p = 0.043$), a high level of triglyceride (r^2: 0.1002; 95% CI, 0.048–0.543, $p = 0.022$), and having a high LDL-cholesterol level (r^2: 0.0828; 95% CI, 0.016–0.519, $p = 0.039$) (**Figure 1**). In female young adults, psychological distress was negatively associated with fasting glucose (r^2: −0.1037; 95% CI,−0.549–0.051 $p = 0.021$). While we did not observe a correlation between fasting glucose and mental health outcome in female middle-aged

TABLE 1 | Sociodemographic data, BMI, metabolic characteristics, and K10 scores of the sample.

Characteristics	Total (*N*)	Young adults		Middle age		Old age		*P*
		Male	Female	Male	Female	Male	Female	
Overall	319	51	51	50	52	51	64	
Age (years)	43.97 ± 12.48	30.78 ± 2.35	29.50 ± 3.06	41.58 ± 4.66	39.75 ± 4.81	58.16 ± 3.89	58.88 ± 4.15	<0.0001
Education (years, Mean ± SD)	16.73 ± 6.01	17.94 ± 4.89	17.87 ± 5.40	17.67 ± 8.05	16.5 ± 7.02	14.42 ± 4.51	11.52 ± 4.31	<0.0001
Marital status								
Married	273 (85.6%)	33 (64.7%)	31 (60.8%)	48 (96%)	49 (94.2%)	51 (100%)	61 (95.3%)	<0.0001
Widowed	3 (0.9%)	0	0	1 (2%)	0	0	2 (3.1%)	
Single	43 (13.5%)	18 (35.3%)	20 (39.2%)	1 (2%)	3 (5.8%)	0	1 (1.6%)	
Working status								
Employed	272 (85.3%)	51 (100%)	51 (100%)	50 (100%)	51 (98.1%)	40 (78.4%)	29 (45.3%)	<0.0001
Unemployed	0	0	0	0	0	0	0	
Retired	47 (14.7%)	0	0	0	1 (1.9%)	11 (21.6%)	35 (54.7%)	
Smoking	47 (14.7%)	10 (19.6%)	0	12 (24%)	0 (0%)	23 (45.1%)	2 (3.1%)	<0.0001
Drinking	67 (21%)	17 (33.3%)	0	22 (44%)	3 (5.8%)	23 (45.1%)	2 (3.1%)	<0.0001
BMI (Mean ± SD)	24.14 ± 3.33	25.38 ± 3.01	21.01 ± 2.92	25.02 ± 3.18	23.97 ± 3.06	26.46 ± 2.89	23.93 ± 2.23	<0.0001
Total cholesterol (SEM ± SD)	5.15 ± 1.02	4.87 ± 0.73	4.52 ± 0.74	5.08 ± 0.86	4.68 ± 0.93	5.24 ± 0.93	5.90 ± 1.19	<0.0001
Triglyceride (Mean ± SD)	1.46 ± 0.84	1.62 ± 0.82	0.84 ± 0.34	1.94 ± 1.03	1.32 ± 0.66	1.54 ± 0.75	1.61 ± 0.83	<0.0001
HDL-cholesterol (Mean ± SD)	1.44 ± 0.26	1.32 ± 0.25	1.55 ± 0.23	1.32 ± 0.20	1.52 ± 0.24	1.31 ± 0.23	1.54 ± 0.27	<0.0001
LDL-cholesterol (Mean ± SD)	2.74 ± 0.63	2.57 ± 0.45	2.34 ± 0.46	2.73 ± 0.59	2.41 ± 0.61	2.82 ± 0.57	3.18 ± 0.71	<0.0001
Fasting glucose (Mean ± SD)	5.54 ± 1.45	5.19 ± 0.44	4.96 ± 0.29	5.52 ± 1.02	5.16 ± 1.62	6.44 ± 2.54	5.79 ± 1.06	<0.0001
Lymphocytes (Mean ± SD)	0.35 ± 0.077	0.36 ± 0.075	0.36 ± 0.076	0.36 ± 0.070	0.37 ± 0.083	0.33 ± 0.063	0.36 ± 0.080	0.1648
K10 scores (Mean ± SD)	11.71 ± 3.13	12.29 ± 2.99	12.20 ± 3.60	11.42 ± 2.29	14.75 ± 2.78	10.31 ± 0.84	11.52 ± 4.31	0.0033

adults, which is consistent with recent meta-analytic evidence that glucose metabolism was not altered in depressed patients (6). In male older group, the higher scores in K10 and increased total-cholesterol (r^2: 0.1018; 95% CI, 0.0481–0.547, $p = 0.022$), and LDL-cholesterol levels were noted (r^2: 0.0924; 95% CI, 0.031–0.535, $p = 0.030$), showing a significant relationship between total- and LDL-cholesterol and psychological distress. For further information, see **Table 2**.

DISCUSSION

In current study, we investigated the impact of metabolic functions on the associations of mental health outcomes by assessment of psychosocial stress in healthy subjects. To our knowledge, our study is the first one to explore the potential relationship between metabolic measures and mental state in health subjects stratified by age and gender. Our results demonstrated that poor mental health was significant associated with increased BMI, total-, LDL-cholesterol, and triglyceride levels in healthy middle-aged women but not in young or older adults. These findings support the notion that women are more vulnerable to mental health disorders than men, and specifically, middle-aged women are likely to have an increased risk of obesity and poor mental health due to reaching the menopause, changing marital or socioeconomic status, and unhealthy lifestyle habits (7). The negative and reciprocal impact of metabolic syndrome (i.e., triglycerides, fasting glucose, and obesity) in middle-aged females on the physical, psychological, emotional, and behavioral responses toward a stressful event has been evidenced (8), emphasizing the notion that susceptibility to stress exposure and metabolic dysregulations and their consequences are responsible for the elevated risk of psychiatric disorders. Particularly, female participants experiencing high stress showed higher low-density lipoprotein levels compared to the low stress group (9), suggesting that a higher level of blood lipids and lipoprotein is correlated with psychological stress associated with high prevalence of emotional disorders.

The bidirectional associations between mental health and metabolic disturbances have been intensively evidenced although it still remains unclear whether the risk factors are cause or consequence. Nevertheless, the association between higher BMI and greater serum cholesterols levels and increased risk of

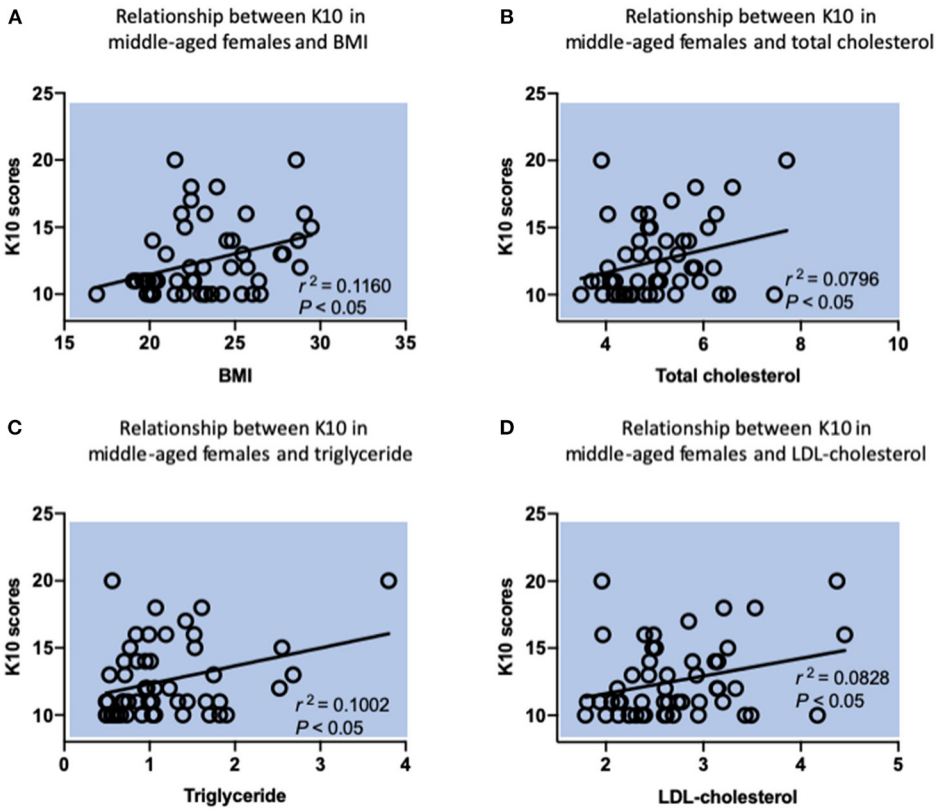

FIGURE 1 | Relationship between K10 scores and metabolic parameters in middle-aged females by Pearson correlation analysis. **(A)** A positive relationship between K10 scores and BMI. $r^2 = 0.116$, $P = 0.0135$. **(B)** A positive relationship between K10 scores and total cholesterol. $r^2 = 0.0796$, $P = 0.0427$. **(C)** A positive relationship between K10 scores and triglyceride. $r^2 = 0.1002$, $P = 0.0222$. **(D)** A positive relationship between K10 scores and LDL-cholesterol. $r^2 = 0.0828$, $P = 0.0385$. $n = 52$ individuals for this group.

mental disorders, e.g., being overweight is positively associated with increased risk to depression has been confirmed by several community-based cross-sectional studies particularly in women but not in men (10, 11). Since the detailed insight into the biological mechanisms linking depression and metabolic impairment is not fully clarified, the longitudinal studies are indispensable in producing more evidence on the bidirectional association.

Given the numerous studies reporting increased lipid metabolism levels involved in psychiatric disease, the association between low levels of serum cholesterol and mental illnesses, such as depression and other stress-related mental illnesses, could not be dismissed. For example, it has been proposed that cholesterol levels were reduced in patients with major depressive disorder possibly *via* disruption the availability of serotonergic receptors, which are major targets implicated in depression pathophysiology and in the mechanism of antidepressant action (12, 13). Further evidence supporting the complex relationship between lipid metabolism and mood disorders and the exact regulation is required.

Our data did not show an association between the immune marker lymphocytes and the mental health among different age groups, indicating that peripheral immune system is not a central process to induce the development of mood and metabolic alterations in the current cohort. Notably, neutrophil to lymphocyte ratio, but not absolute lymphocytes counts, was used to explore the biological mechanisms underlying psychiatric disorders (14, 15). The specific relationship between blood immune markers and mental status needs further examination. According to the current data, the metabolic parameters (total and LDL-cholesterol) also correlated with the K10 scores in male older participants. There may be multiple factors rather than metabolic signal contributing to this association in this subgroup. It is worth noting that the psychosocial stress from retirement and subsequent alterations in social connection, economic status, and environmental opportunities may increase the negative consequences of mental health in male old adults (16). However, women also exhibit better psychological resilience than men following retirement (17). So we did not observe this association between retirement and the mental health in older female group.

Given the evidence of altered lipid metabolism in vulnerable populations, lifestyle factors such as diet, exercise, and physical complications influencing metabolic process have also been ascertained in the development, progression and treatment of mental health disorders. For example, depressive symptoms are also positively associated with the high consumption of fast food

TABLE 2 | Multivariate general linear regression, stratified by age and sex.

Mood outcome	Biological measures	Whole cohort (*N* = 319)	Yong adults (25–34 Y)		Middle age (35–49 Y)		Old age (50–65 Y)	
			M (*N* = 51)	F (*N* = 51)	M (*N* = 50)	F (*N* = 52)	M (*N* = 51)	F (*N* = 64)
K10 scores	BMI	(0.175) [−0.184, 0.034]	(0.573) [−0.369, 0.207]	(0.105) [−0.413, 0.040]	(0.927) [−0.420, 0.384]	(**0.013**) [0.075, 0.561]	(0.366) [−1.43, 0.537]	(0.955) [−0.135, 0.127]
	Total cholesterol	(0.115) [−0.064, 0.007]	(0.378) [−0.100, 0.039]	(0.436) [−0.082, 0.036]	(0.214) [−0.174, 0.040]	(**0.043**) [0.003 to 0.185]	(**0.022**) [0.053, 0.656]	(0.219) [−0.112, 0.026]
	Triglyceride	(0.505) [−0.039, 0.019]	(0.566) [−0.056, 0.101]	(0.439) [−0.037, 0.016]	(0.276) [−0.199, 0.058]	(**0.022**) [0.011, 0.139]	(0.069) [−0.019, 0.476]	(0.579) [−0.062, 0.035]
	HDL-cholesterol	(0.712) [−0.008, 0.011]	(0.379) [−0.034, 0.013]	(0.794) [−0.021, 0.016]	(0.841) [−0.028, 0.023]	(0.99) [−0.025, 0.025]	(0.452) [−0.048, 0.106]	(0.749) [−0.018, 0.013]
	LDL-cholesterol	(0.141) [−0.039, 0.0056]	(0.505) [−0.057, 0.028]	(0.505) [−0.048, 0.024]	(0.261) [−0.116, 0.032]	(**0.039**) [0.016, 0.519]	(**0.030**) [0.021, 0.391]	(0.197) [−0.068, 0.014]
	Fasting glucose	(0.259) [−0.080, 0.022]	(0.422) [−0.059, 0.025]	(**0.021**) [−0.048, −0.004]	(0.912) [−0.122, 0.136]	(0.287) [−0.077, 0.253]	(0.845) [−0.956, 0.786]	(0.932) [−0.059, 0.065]
	Lymphocytes	(0.537) [−0.002, 0.004]	(0.367) [−0.004, 0.010]	(0.681) [−0.007, 0.005]	(0.171) [−0.003, 0.015]	(0.964) [−0.009, 0.008]	(0.137) [−0.005, 0.037]	(0.779) [−0.006, 0.004]
	Marital status	(0.018) [−0.027, −0.0026]	(0.720) [−0.038, 0.055]	(0.870) [−0.036, 0.043]	(0.568) [−0.032, 0.0178]	(0.580) [−0.0307, 0.0174]		(0.729) [−0.015, 0.010]
	Education	(0.246) [−0.127, 0.033]	(0.922) [−0.059, 0.054]	(0.589) [−0.047, 0.082]	(0.167) [−0.073, 0.412]	(0.738) [−0.117, 0.164]	(0.799) [−1.202, 0.930]	(0.421) [−0.076, 0.179]
	Smoking	(0.829) [−0.061, 0.049]	(0.320) [−0.522, 0.174]		(0.195) [−0.089, 0.0186]		(0.943) [−0.179, 0.166]	(0.618) [−0.013, 0.008]
	Drinking	(0.490) [−0.020, 0.009]	(0.104) [−0.009, 0.096]		(0.341) [−0.033, 0.093]	(0.474) [−0.015, 0.033]	(0.877) [−0.159, 0.186]	(0.618) [−0.013, 0.008]

The multivariate general linear model in lipid concentrations and mood outcomes; stratified by age groups (25–34, 35–49, 50–65 years old) and sex. Expressed by p-values are in parentheses and 95% confidence intervals are in square brackets. The bold values mean significant results. M, male; F, female; K10, Kessler 10 Psychological Distress Scale.

(18), low levels of physical activity (especially in women and those aged 40 years and older) (19), and reduced sleep quality (20) through regulation of several physiological pathways involved in mood disorders. Therefore, future mental health interventions targeting these lifestyle factors would enhance the outcome of interventions associated with psychosocial stress symptoms and metabolic dysfunction.

Concerning the limitations, the current study shows the potential correlation based on observational data from routine physical examination and inevitably results in an underestimate or overestimate of the causal inference due to confounding, selection and measurement biases. Applications of statistical and design-based methods are required to minimize potential bias and establish an improved estimation of the causal inference. In addition, this is a cross-sectional study with a small sample size and lacks longitudinal follow-up evidence and preventive interventions and therefore could not provide the causal inference of metabolic pathophysiology on the increased sensitivity to mental disorders. Future studies aiming at determining the relationship between metabolic indicators and mood outcomes in a large sample size with intervention and follow-up design are needed to provide an early prediction and treatment in vulnerable individuals such as middle-aged women. Moreover, the fact that the high education level of the recruited participants (average is more than 16 years) lack of the representative of all respondents with psychological distress makes it difficult to extend the current findings to general population and reduces the generalizability of our results.

In conclusion, we found that metabolic risk factors affect psychosocial stress in middle-aged female adults and reciprocally changing the coping style to psychological distress may reduce the development of the metabolic syndrome in women. Our findings reveal that metabolic conditions may play an important role in predicting outcomes for middle-age female patients with high risk for mood disorders, raising the possibility that metabolic functions should be seriously taken into consideration not only for improving psychosocial stress response such as health lifestyle, diminished stress, physical activity, and weight-loss interventions in an early stage but also for providing precise interventions for mood disorders in vulnerable middle-aged women.

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 author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Tianjin Union Medical Center (No. 2021B15). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JY, WZ, CL, JZ, and ZD initiated the study. JY obtained ethics approval. CL, JZ, ZZ, and ZD analyzed the data. JY, ZZ, and WZ wrote a first draft of the study protocol. WZ, ZZ, and QW obtained funding for the study and critically revised the manuscript. WZ and QW supervised the project and provided substantial contributions to the paper. All authors participated in the conception of the study and approved the final manuscript.

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Decreased Plasma Hydrogen Sulfide Level Is Associated With the Severity of Depression in Patients With Depressive Disorder

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Accumulating evidence has suggested a dysfunction of synaptic plasticity in the pathophysiology of depression. Hydrogen sulfide (H_2S), an endogenous gasotransmitter that regulates synaptic plasticity, has been demonstrated to contribute to depressive-like behaviors in rodents. The current study investigated the relationship between plasma H_2S levels and the depressive symptoms in patients with depression. Forty-seven depressed patients and 51 healthy individuals were recruited in this study. The 17-item Hamilton Depression Rating Scale (HAMD-17) was used to evaluate depressive symptoms for all subjects and the reversed-phase high-performance liquid chromatography (RP-HPLC) was used to measure plasmaH_2S levels. We found that plasma H_2S levels were significantly lower in patients with depression relative to healthy individuals ($P < 0.001$). Compared with healthy controls (1.02 ± 0.34 μmol/L), the plasma H_2S level significantly decreased in patients with mild depression (0.84 ± 0.28 μmol/L), with moderate depression (0.62 ± 0.21μmol/L), and with severe depression (0.38 ± 0.18 μmol/L). Correlation analysis revealed that plasma H_2S levels were significantly negatively correlated with the HAMD-17 scores in patients ($r = -0.484$, $P = 0.001$). Multivariate linear regression analysis showed that plasma H_2S was an independent contributor to the HAMD-17 score in patients ($B = -0.360$, $t = -2.550$, $P = 0.015$). Collectively, these results suggest that decreased H_2S is involved in the pathophysiology of depression, and plasma H_2S might be a potential indicator for depression severity.

Keywords: depression, hydrogen sulfide (H_2S), plasma, severity, correlation

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INTRODUCTION

Depression is a common illness with more than 264 million people affected in the worldwide (1). Person with depressive disorder experiences depressed mood, loss of interest and enjoyment, and reduced energy leading to diminished activity for at least 2 weeks. Depression results from a complex interaction of social, psychological and biological factors (2). Although the neurobiological mechanisms underlying depression have not been recognized completely, emerging evidence suggests a dysfunction of synaptic plasticity in the pathophysiology of depression (3–5). For

example, exposure to chronic stress was shown to induce dendritic atrophy and spine loss in the hippocampus and prefrontal cortex (6–8). Impaired long-term potentiation (LTP) was observed in the hippocampus of the chronic stress mice model of depression (9). Restoration of stress-induced changes in synaptic plasticity within the corticoaccumbal glutamate circuit prevented the behavioral vulnerability of mice to chronic stress (10).

Synaptic plasticity is an experience-dependent change in synaptic strength at preexisting synapses, in which one type of ionotropic glutamate receptors, N-methyl-D-aspartate receptor (NMDAR), plays a key role (11). Numerous studies have reported that there are abnormal gene expression and function in NMDARs in the hippocampus of depressed patients (12–14). Chronic stress could reduce the expression of NMDARs in the hippocampus in rodents (15–17). Preclinical studies indicate that both acute and chronic stress can perturb the normal balance between synaptic potentiation and depression in hippocampal pyramidal neurons (18–20). Furthermore, a number of experimental and clinical studies have demonstrated that improving actions of antidepressants are associated with restoration of maladaptive brain plasticity (21–23).

Hydrogen sulfide (H_2S) is a member of the gasotransmitter family that is associated with the maintenance of neuronal plasticity, excitability, and homeostatic functions (24). It is mainly produced by the enzyme cystathionine-β-synthase (CBS) in the brain and the enzyme cystathionine-γ-lyase (CSE) in the peripheral tissues (25). Abe and Kimura first demonstrated the influences of H_2S on synaptic plasticity. They showed that physiological concentrations of H_2S facilitated the induction of hippocampal LTP by increasing the activity of NMDARs (26). Inhibition of H_2S generation would lead to a reduction in NMDAR-mediated synaptic response and cause an impairment of LTP in the amygdala (27). Gas can freely diffuse across cell membranes and blood-brain barrier. Previous studies have demonstrated that intraperitoneal injection of NaHS (an H_2S donor) or inhalation of H_2S can increase brain H_2S content and promote amygdalar LTP and emotional memory in rats (28), and systemic administration of NaHS could elevate hippocampal H_2S level and dramatically reversed the cognitive and synaptic plasticity deficits in APP/PS1 transgenic mice (29).

Since H_2S has an important regulatory role in synaptic plasticity, some studies have explored its role in depression. Chen et al. reported that chronic intraperitoneal treatment with NaHS produced a specific antidepressant-like effect in non-stressed mice and rats (30). Administration of NaHS significantly alleviated the depressive-like behaviors in streptozotocin-induced diabetic rats (31). Moreover, a recent study showed that decreased level of endogenous H_2S in the hippocampus was responsible for the abnormal behaviors induced by chronic unpredictable mild stress, and the depressive-like behavior of rats could be alleviated within a few hours by increasing H_2S level in the hippocampus through giving H_2S donor or inhaling H_2S (32). However, whether plasma H_2S levels are changed in patients with depression and its association with the severity of depression remains unknown. In this study, we further explored the role of H_2S signaling in the pathophysiology of depression by investigating whether (1) plasma H_2S level was altered in patients with depression and (2) there were any relationships between H_2S levels and depressive symptoms in these patients.

METHOD

Subjects

Forty-seven inpatients with acute depressive episode (male/female = 20/27) were recruited from Jiangxi Mental Hospital. Two psychiatrists have confirmed the diagnosis of depression based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). The exclusion criteria included any other axis I or axis II DSM-IV diagnoses, including schizophrenia, bipolar disorder, substance abuse, anxiety disorder and so on. Fifty-one healthy controls (male/female = 28/23), matched with the patients by gender, age, education years, and body mass index (BMI), were recruited from the local community. Subject with a personal or family history of mental illness was excluded from control group. The exclusion criteria for all participants also included current pregnancy, autoimmune, allergic and neoplastic diseases, as well as other physical diseases that had occurred in the past 3 months, including hypertension, diabetes, heart or brain infarction.

The 17-item Hamilton Depression Rating Scale (HAMD-17) was used to evaluate depressive symptoms for all subjects (**Supplementary Table 1**) (33). The severity of depression was ranked on a HAMD-17 score: mild depression (8–17), moderate depression (18–24), and severe depression (>24) (34). To investigate whether antidepressants affected plasma H_2S level, the depressed patients were divided into an antidepressant-treatment subgroup ($n = 31$) and an antidepressant-naive subgroup ($n = 16$). Subjects who were free of any antidepressant treatment for at least 1 month were defined as antidepressant-naive patients.

The research was approved by the Institutional Review Board at Jiangxi Mental Hospital and carried out in accordance with the Declaration of Helsinki. A written informed consent was provided from each subject, or his or her parents/guardians.

Measurement of Plasma H_2S

Whole blood from subjects who fasted overnight was collected into tubes with EDTA. After collection, samples were centrifuged at 3,000 rpm for 5 min at the temperature of 4°C and then the plasma was separated, aliquoted, and stored at−80°C until analysis.

The concentration of H_2S in plasma was measured using a monobromobimane method coupled with reversed-phase high-performance liquid chromatography (RP-HPLC) (35). Free H_2S in the plasma was analyzed by RP-HPLC after derivatization with excess monobromobimane (MBB) to form stable sulfide dibimane derivative. 30 μL of sample was pipetted and mixed with 70 μL of 100 mM Tris-HCl buffer (pH 9.5, 0.1 mM DTPA), followed by addition of 50 μL of 10 mM MBB. The reaction was terminated by adding 50 μL of 200 mM 5-sulfosalicylic acid at 30 mins later. After centrifugation, the supernatant was determined using an Agilent 1,220 HPLC system (Agilent Technologies,

TABLE 1 | Comparison of demographic and clinical variables in controls and patients.

Variables	Control group ($n = 51$)	Depressive group ($n = 47$)	Statistic value	*P* value	Effect size
Gender (M/F)	28/23	21/26	Chi-squared test, $x^2 = 1.022$	0.312	–
Age (years)	38.02 ± 10.77	35.02 ± 13.98	*t*-test, $t = 1.195$	0.235	Cohen's $d = 0.240$
Education	11.01 ± 2.96	11.57 ± 3.57	U test, $Z = -0.544$	0.586	$r = -0.085$
Illness duration (years)	–	5.13 ± 3.66			
BMI (kg/m^2)	21.30 ± 1.92	21.59 ± 1.96	*t*-test, $t = -0.760$	0.449	Cohen's $d = -0.154$
HAMD-17 score	3.22 ± 2.24	22.15 ± 8.45	*t*-test, $t = -15.423$	<0.001	Cohen's $d = -3.059$
H_2S level (μmol/L)	1.02 ± 0.34	0.59 ± 0.29	*t*-test, $t = 6.697$	<0.001	Cohen's $d = 1.359$

Santa Clara, CA, USA) and an Agilent ZORBAX Eclipse XDB-C18 column. The content of plasma H_2S was calculated based on sulfidedibimane standard curves.

Statistical Analysis

Data were presented as mean ± standard deviation (SD) and analyzed with the Statistical Product and Service Solutions (SPSS) 18.0 software. We compared categorical variables between patients and healthy controls using a chi-squared test. The continuous variables that were distributed normally were compared by Student's *t*-test and the independent variables that did not fit the normal distribution were analyzed by Kolmogorov-Smirnov and Mann-Whitney U tests. The relationships between plasma H_2S and other variables were determined by Pearson correlation analysis and the independent relationships were analyzed by multivariate linear regression analysis. The level of significance was set at $P < 0.05$.

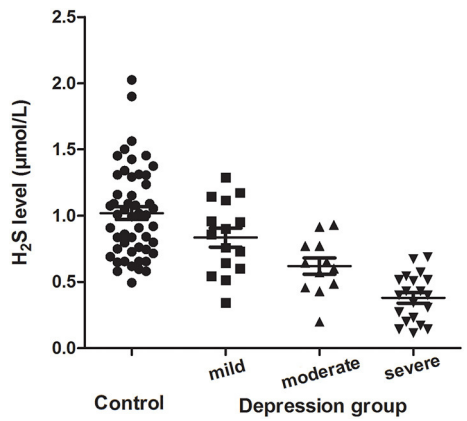

FIGURE 1 | Plasma H_2S levels (mean ± SD) in the controls and the mild, moderate and severe depression group.

RESULTS

Forty-seven inpatients with depression (21 male, 26 female) and 51 healthy controls (28 male, 23 female) was enrolled in this study. **Table 1** shows the demographic variables and the clinical values of control group and depressive group. There was no significant difference between two groups in terms of gender, age and BMI. The mean HAMD-17 score in depressive patients was statistically higher than that in the control group (22.15 ± 8.45 in depressive group *vs.* 3.22 ± 2.24 in control group, $P < 0.001$).

The plasma level of H_2S in the depressive patients was significantly lower than that in healthy controls (patients: 0.59 ± 0.29 μmol/L, controls: 1.02 ± 0.34 μmol/L; $t = 6.697$, $P < 0.001$) (**Table 1**). No significant difference was observed in plasma H_2S level between male and female in both groups (both $P > 0.05$). For depressive patients, the level of plasma H_2S was not different between antidepressant-treatment and antidepressant-naïve subgroup ($t = 0.218$, $P = 0.828$). A two-way ANOVA for H_2S level in depressive patients showed that there was no significant main effect of gender ($F_{(1,43)} = 2.384$, $P = 0.130$), no significant main effect of antidepressant treatment ($F_{(1,43)} = 0.036$, $P = 0.851$) and no main effect of gender × antidepressant treatment ($F_{(1,43)} = 0.731$, $P = 0.397$).

Among 47 depressive patients, 15 patients (31.9%) had mild depression, 12 patients (25.5%) had moderate depression, and 20 patients (42.6%) had severe depression. The level of plasma H_2S in mild, moderate and severe depressive patients was 0.84 ± 0.28, 0.62 ± 0.21 and 0.38 ± 0.18 μmol/L, respectively. One-way ANOVA revealed that there were significant differences among healthy controls, mild depressive, moderate depressive and severe depressive patients ($F_{(3,97)} = 24.984$, $P < 0.001$). Bonferroni *post hoc* multiple tests for depressive subgroups showed that there was a significant decreased trend of the plasma H_2S level among mild depressive patients compared to moderate depressive patients ($P = 0.047$), and moderate depressive patients compared to severe depressive patients ($P = 0.015$) (**Figure 1**).

Within the healthy control subjects, there no significant correlation between plasma H_2S level and any demographic variable including gender, age, and BMI. However, Pearson correlation analysis revealed that the plasma H_2S level was significantly correlated with age ($r = -0.296$, $P = 0.043$; **Supplementary Figure 1**) and HAMD-17 score ($r = -0.484$, $P = 0.001$; **Figure 2**) in patients with depression. Partial correlation analysis showed that the correlation between H_2S levels and theHAMD-17 scores was still significant when controlling for gender, age, education years, BMI, and duration of illness ($r = -0.374$, $P = 0.015$). Finally, we conducted multivariate regression analysis to elucidate independent determinants of

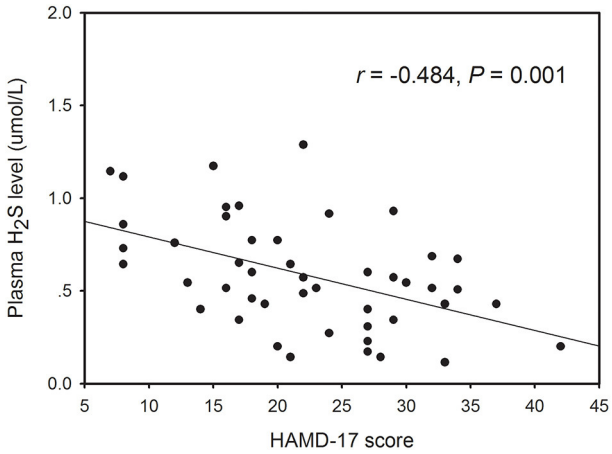

FIGURE 2 | The correlation between plasma H_2S levels and HAMD-17 scores in patients with depression.

TABLE 2 | Correlations between plasma H_2S levels, demographic characteristics and clinical variables in patients with depression.

Variables	HAMD-17 score		
	***B* (95% CI)**	***t***	***P* value**
Gender (M/F)	−0.135 (−0.399, 0.128)	−1.039	0.305
Age (years)	0.210 (−0.091, 0.512)	1.410	0.166
Education	−0.038 (−0.324, 0.247)	−0.271	0.788
Duration of illness (years)	−0.271 (−0.569, 0.027)	−1.841	0.073
BMI (kg/m^2)	0.096 (−0.190, 0.383)	0.680	0.501
Plasma H_2S	−0.360 (−0.646, −0.075)	−2.550	0.015

HAMD-17 scores ($R^2 = 0.586$) and found that plasma H_2S was an independent contributor to the HAMD-17 scores ($B = -0.360$, $t = -2.550$, $P = 0.015$) (**Table 2**).

DISCUSSION

Previous studies have demonstrated that H_2S is implicated in the pathophysiology of depression in rodents (30–32). In this study, the plasma levels of H_2S were determined in Chinese patients with depression. We found a significant decrease in plasma H_2S level in depressive patients compared to healthy controls, and decreased plasma H_2S level was significantly correlated with the severity of depression.

H_2S is an endogenous gasotransmitter with numerous homeostatic functions, such as neurotransmission and neuromodulation (24). A large number of studies have demonstrated that a dysfunction of H_2S signaling takes a part in the pathophysiology of many neuropsychiatric disorders. The H_2S level was decreased in the hippocampus of Alzheimer's disease (AD) mice and treating AD mice with NaHS reversed the impaired hippocampal synaptic plasticity and cognitive function (29, 36). Plasma H_2S level is significantly decreased in both schizophrenia and AD patients, and has a correlation with the severity of cognitive impairments in these patients (35, 37). Hou et al. reported that endogenous H_2S was decreased in the hippocampus of depressive model rats and responsible for the depressive-like behaviors of rats (32). In consistent with these results, we here showed that plasma H_2S levels were significantly decreased in depressed patients and were correlated with the severity of depressive symptoms of patients, providing evidence for the contribution of H_2S signaling to the pathogenesis of depression. It should be noted that change of plasma H_2S in patients might also result from the treatment of antidepressants. However, we enrolled inpatients with acute depressive episode who had HAMD scores >8 in this study. Although some of the patients were taking antidepressants at the time of inclusion, the HAMD score showed that they were still depressed, suggesting that current antidepressants they used were not effective in improving their depressive symptoms. Indeed, meta-analyses of clinical trials have reported that more than 60% of patients fail to obtain significant or sustained remission with any single traditional antidepressant drug, with approximately one third of all depressed individuals failing two or more first-line antidepressant courses of treatment, consistent with the diagnosis of treatment-resistant depression (TRD) (38, 39). Our present study found that the level of plasma H_2S was not different between antidepressant-treatment and antidepressant-naive subgroups in depressive patients, indicating that antidepressants alone do not affect plasma H_2S levels in those patients whose depressive symptoms have not improved significantly. Therefore, in combination with the finding that endogenous H_2S was decreased in the hippocampus of depressive rats (32), we postulate that change of plasma H_2S level in patients is related to the illness *per se*, rather than secondary to antidepressant treatment. However, the mechanisms underlying the reduction of H_2S in depression are still needed further investigations.

The HAMD is the most widely used scale for patient selection and follow-up in depression treatment studies (40, 41). We used HAMD-17 to evaluate the severity of depressive symptoms in the present study. Correlation analysis showed that there was a significantly negative correlation between plasma H_2S levels and the HAMD-17 scores in depressive patients. Partial correlation analysis demonstrated that the correlation between H_2S levels and the HAMD-17 scores was still significant when controlling for gender, age, education years, BMI, and duration of illness. Multivariate linear regression analysis revealed that plasma H_2S level was negatively associated with HAMD-17 score. These results suggest that patients with lower H_2S levels would be more likely to have severer depressive symptoms. Furthermore, the level of plasma H_2S was decreased gradually from mild depression to moderate depression, and from moderate depression to severe depression, also indicating that plasma H_2S is associated with the severity of depression. Therefore, the plasma H_2S level may be served as a biomarker to evaluate the severity of depression.

There are some limitations in this study. First, the sample size was relatively small and all subjects were recruited from a single hospital. Replication in larger and multicenter samples is required to validate this conclusion. Second, H_2S levels were

measured in plasma, but not in the brain. Whether H_2S level in the brain changes parallel with the level in plasma in patients is still unclear. Third, this was across-sectional study. Future studies are needed to elucidate the role of plasma H_2S in the progression of depression. Additionally, although an association of decreased plasma H_2S and the severity of depressive symptoms in patients with depression was found in this study, the mechanisms through which H_2S affects depressive behaviors are needed to be investigated.

CONCLUSION

Our present study shows that patients with depression have lower plasma H_2S levels than healthy controls, and decreased H_2S was associated with the severity of depressive symptoms inpatients. These results demonstrate an important role of H_2S signaling in the pathophysiology of depression, suggesting that plasma H_2S level may be a potential biomarker for the severity of depression.

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 Institutional Review Board at Jiangxi Mental Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

Y-JY, C-NC, J-QZ, Q-SL, YL, and S-ZJ participated in clinical data collection and lab data analysis. Y-JY and BW designed the study, analyzed the data, and prepared the manuscript. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.765664/full#supplementary-material

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Antidepressant Treatment-Induced State-Dependent Reconfiguration of Emotion Regulation Networks in Major Depressive Disorder

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Deficits in emotion regulation are the main clinical features, common risk factors, and treatment-related targets for major depressive disorder (MDD). The neural bases of emotion regulation are moving beyond specific functions and emphasizing instead the integrative functions of spatially distributed brain areas that work together as large-scale brain networks, but it is still unclear whether the dynamic interactions among these emotion networks would be the target of clinical intervention for MDD. Data were collected from 70 MDD patients and 43 sex- and age-matched healthy controls. The dynamic functional connectivity (dFC) between emotion regions was estimated via a sliding-window method based on resting-state functional magnetic resonance imaging (R-fMRI). A k-means clustering method was applied to classify all time windows across all participants into several dFC states reflecting recurring functional interaction patterns among emotion regions over time. The results showed that four dFC states were identified in the emotion networks. Their alterations of state-related occurrence proportion were found in MDD and subsequently normalized following 12-week antidepressant treatment. Baseline strong dFC could predict the reduction rate of Hamilton Depression Rating Scale (HAMD) scores. These findings highlighted the state-dependent reconfiguration of emotion regulation networks in MDD patients owing to antidepressant treatment.

Keywords: major depressive disorder, recurring functional interaction patterns, emotion regulation, antidepressants, dynamic functional connectivity

INTRODUCTION

Major depressive disorder (MDD) is characterized by persistent low mood and loss of interest (1). As a disorder that involves extensive affective aberrations, MDD must be elucidated by its brain mechanisms of emotion dysregulation (2). Human health and well-being benefit from appropriate emotion regulation that allows one to adaptively control the intensities, durations, and types of emotional experiences and behavioral responses evoked by external or internal stimuli

(3, 4). Therefore, emotion regulation in healthy individuals and dysregulation in MDD have very important research significance (5). Previous studies have been trying to uncover how the brain generates and manages emotion, especially which depends largely on the knowledge about its large-scale organization (6). Functional magnetic resonance imaging (fMRI) has become a dominant tool for understanding emotion regulation and some specific brain loci that engage in the generation and regulation of emotion have been revealed (7). The fact that individual brain regions usually contribute to more than one specific emotion and that one emotional task can activate multiple brain regions simultaneously point out the promise of network-level representation for emotion (8). The characterization of large-scale brain networks (LBNs) and their functional interactions is becoming an increasingly common gateway to uncover how emotions are organized in the brain (9). Applying a meta-analytic k-means clustering approach on 385 experiments from 107 published papers, a recent study identified four LBNs based on convergent brain activation patterns during emotion regulation (10). Each LBN represents an activation pattern that occurs in multiple emotion regulation experiments. These four data-driven LBNs underwent also functional decoding to validate their differences in functional characterization. Especially, the first network mainly consisted of the lateral dorsal prefrontal cortex, which was associated with working memory, explicit memory, reasoning, and inhibition. The second network exhibited convergent activation in a lateralized ventral prefrontal network, which was primarily linked to language processes. The third network was based on convergent activation in the insula, precuneus, and posterior cingulate cortex, which was associated with the action, perception, and interoception domain. The last network consisted of subcortical regions such as the bilateral amygdala, left parahippocampus, and bilateral fusiform gyrus. This network indicated a focus on the emotion and memory domains. This progress provided relatively complete emotion regulation networks to enable further research on emotion dysfunction in MDD based on the functional interactions among hierarchical neural systems.

Despite the amount of effort to develop antidepressant treatments, treatment effectiveness has not been increased sufficiently in recent decades (11). This is partly because of the obscure knowledge with respect to the neural bases of MDD and its effective treatment (12). Emotion regulation is a key predictor for the course of MDD (13), and the strategy required to regulate the emotion of MDD patients varies with their severity of depressive symptoms (14). Adaptive emotion regulation could enhance the therapeutic effect on MDD and hence enable itself to be a promising target in clinical intervention for MDD (15, 16). Furthermore, numerous previous studies using resting-state functional magnetic resonance imaging (R-fMRI) have supplied clues about the association between the therapeutic outcomes of antidepressants and areas known to be involved in emotion generation or regulation. For example, effective antidepressant treatment for MDD patients was relevant with lower functional connectivity (FC) between the subcallosal cingulate cortex and ventromedial prefrontal cortex (17). Hyperconnectivity of the amygdala in MDD patients was reduced following 8-week antidepressant treatment (18). The FC between the medial prefrontal cortex and posterior cingulate cortex at baseline was predictive of the remission status of antidepressant treatment (19). However, most of these studies relied on the assumption of temporal stationarity during the entire R-fMRI scan. Time-averaged or static functional connectivity (sFC) may limit the detection of time-varying functional interaction patterns.

Emotion regulation itself conveys the adaptive nature of emotion from one aspect that demands one to reorganize his/her mind or behavior to deal with the changing environment for the purpose of achieving and maintaining well-being (20, 21), which obviously needs to be instantiated by different functional interaction patterns among LBNs. Emotion dysfunction usually occurs when one's emotion regulation dynamics fail to achieve short- or long-term goals (4). Therefore, investigating the mental illness labeled emotion dysfunction from the view of emotion regulation dynamics will deepen our comprehension of MDD pathology. Characterizing the dynamic functional interactions among LBNs that represent emotion regulation may help to elucidate how emotions are controlled or become out of control in the course of the emotion process. A dynamic functional connectivity (dFC) analysis approach has been proposed to capture the course of dynamic interactions among LBNs (22). After characterizing several recurring functional interaction patterns over R-fMRI scan time, high-level summaries would be obtained based on the temporal configurations of them (23), which were thought to load important physiological significance (24, 25). The human brain organizes and integrates various neural systems across multiple spatiotemporal scales constantly to achieve personal adaptability to internal or external environments (26). It makes this method significant when examining the neural mechanisms underlying kinds of disorders including schizophrenia (27), MDD (28), chronic pain (29), and attention deficit hyperactivity disorder (30). However, it is still unclear whether this method could be utilized to delineate the dynamic interactions among the LBNs serving for emotion regulation, and more importantly, whether the temporal configuration of the recurring functional interaction patterns would be a target of clinical intervention for MDD.

In the present study, we explored the recurring functional interaction patterns among four LBNs enrolled in emotion regulation. We hypothesized that there would be several recurring functional interaction patterns over time during the R-fMRI scans and that MDD would be associated with the abnormalities in such patterns. Furthermore, the abnormal characteristics of these patterns would be reconfigured in MDD patients by the administration of antidepressants. Additionally, we constructed multivariate linear regression models to investigate which patterns had the potential to predict the outcome of antidepressant treatment in MDD.

MATERIALS AND METHODS

Participants

Seventy patients with MDD (49 females/21 males) were enrolled from the Department of Psychiatry of Hangzhou Seventh People's Hospital and the Department of Psychiatry

at the Affiliated Hospital of Hangzhou Normal University. The course of interview and diagnosis for all MDD patients were accomplished by certified psychiatrists using the Mini-Neuropsychiatric International Interview (MINI) based on the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) criteria. Forty-three healthy controls (HC, 27 women/16 men) matched in age and sex were enrolled from the local community. The 24-item Hamilton Depression Rating Scale (HAMD) was used to evaluate the depression severity of all participants. Individuals who had a neurological or medical illness, were pregnant or breastfeeding, showed severe suicidal tendencies, or displayed substance dependence were not included in the present study. Those who had excessive head motion were also excluded. All study procedures were performed in accordance with the Declaration of Helsinki on Ethical Principles and approved by the local Institutional Review Boards (IRB No.20150729) of Hangzhou Normal University. All subjects provided written informed IRB-approved consent before participating in study procedures.

Treatment Outcomes

After medical and psychiatric assessments, participants who met the inclusion criteria completed both magnetic resonance imaging (MRI) scans at baseline. MDD patients then began to receive antidepressant treatment with typical selective serotonin reuptake inhibitors (SSRIs). The medication doses were prescribed and adjusted by the treating clinicians according to routine clinical practice and followed the recommended dose ranges. During 12-week antidepressant treatment, 19 patients were administered with atypical antipsychotics and benzodiazepines to improve quality of life. After 12 weeks of antidepressant treatment, 37 MDD patients underwent a repeated MRI scan and clinical assessment. These MDD patients were divided into responsive depression group (RDG) and non-responsive depression group (N-RDG) according to whether the reduction rate of the HAMD scores at the end of 12 weeks was >50% or not. HC did not undergo a repeated MRI scan after 3 months.

Image Acquisition and Preprocessing

All MRI data were collected using a 3.0T GE scanner (General Electric, Waukesha, WI, USA) at the Center for Cognition and Brain Disorders of Hangzhou Normal University. The participants were asked to stay relaxed with their eyes closed, and not to fall asleep in particular, and their heads were fixed using a tight cushion. Functional images were obtained in an interleaved order using a T2*-weighted gradient-echo echo-planar-imaging (EPI) sequence (TR/TE = 2,000/22, flip angle = 77°, field of view = 240 × 240 mm^2, matrix = 96 × 96, 2.5 mm isotropic spatial resolution with 42 slices and 240 volumes). A high-resolution T1-weighted anatomical image in sagittal orientation using Fast Spoiled Gradient echo sequence (3D FSPGR, TR/TE = 9/3.66, flip angle = 13°, field of view = 240 × 240 mm^2, matrix = 300 × 300, 0.8 mm isotropic voxels, 176 slices without interslice gap) was obtained for visualization and localization of the functional data.

TABLE 1 | The MNI coordinates of the ROIs within four large-scale brain networks enrolled in emotion regulation.

ID	Regions of interest	X	Y	Z
	LBN 1			
1	Superior Frontal Gyrus (L)	0	24	50
2	Middle Frontal Gyrus (R)	40	24	42
3	Inferior Parietal Lobule (R)	58	−52	38
4	Inferior Parietal Lobule (L)	−58	−50	44
5	Middle Frontal Gyrus (L)	−36	52	−2
6	Middle Frontal Gyrus (L)	−42	14	48
7	Middle Frontal Gyrus (R)	42	46	−8
8	Insula (R)	36	16	6
9	Cingulate Gyrus (R)	2	−22	30
10	Precuneus (R)	10	−64	36
	LBN 2			
11	Inferior Frontal Gyrus (L)	−46	24	−8
12	Superior Frontal Gyrus (L)	−4	10	62
13	Inferior Frontal Gyrus (R)	50	28	−8
14	Superior Temporal Gyrus (L)	−46	−52	28
15	Middle Temporal Gyrus (L)	−54	−34	−2
16	Middle Frontal Gyrus (L)	−44	6	50
17	Superior Frontal Gyrus (L)	−30	48	26
18	Caudate (L)	−16	10	12
19	Tuber (R)	36	−60	−30
	LBN 3			
20	Amygdala (L)	−22	−4	−16
21	Amygdala (R)	24	−4	−18
22	Fusiform Gyrus (R)	40	−46	−18
23	Thalamus (R)	6	−26	0
24	Fusiform Gyrus (L)	−38	−54	−14
25	Parahippocampal Gyrus (L)	−22	−28	−4
26	Medial Frontal Gyrus (B)	0	54	−10
27	Inferior Occipital Gyrus (L)	−42	−76	−6
	LBN 4			
28	Postcentral Gyrus (L)	−58	−22	32
29	Insula (L)	−44	−4	10
30	Superior Parietal Lobule (L)	−28	−52	56
31	Postcentral Gyrus (R)	62	−22	30
32	Cuneus (L)	−10	−76	22
33	Middle Occipital Gyrus (L)	−48	−74	2
34	Thalamus (R)	10	−26	−4
35	Precuneus (R)	28	−60	38
36	Posterior Cingulate (R)	16	−56	16

B, bilateral; L, left; R, right; LBN, large-scale brain network.

The MRI data were processed using the DPARSF toolbox (http://www.rfmri.org/), SPM (http://www.fil.ion.ucl.ac.uk/spm/), and custom code written in MATLAB. The first 10 functional volumes were discarded to allow for signal equilibration and environmental adaptation. The remaining images were corrected for the time shifts among different acquisitions within each volume by sink interpolating volume slices. The participants who had a maximum displacement of

higher than 2.5 mm in the x-, y-, or z-axes and an angular motion of higher than 2.5° during the entire scan were excluded from the study (31, 32). The mean framewise displacement (FD) for each participant was recorded and participants with mean FD exceeding 0.5 mm were excluded (33). The corrected images were then spatially normalized into the standard stereotactic space of the Montreal Neurological Institute (MNI) with a resampled voxel size of $3 \times 3 \times 3$ mm^3. Nuisance covariates including the white matter and cerebrospinal fluid (CSF) signal and Friston-24 motion parameters were regressed out from the time course of each voxel. Then, the images were smoothed with a 6-mm full-width at a half-maximum Gaussian kernel. The linear trends were removed by detrending the signals of each voxel. Temporal bandpass filtering was performed at a frequency range of 0.01–0.10 Hz. Finally, scrubbing was performed to reduce the noise derived from head motion (33). The signal at the "bad" time points was interpolated using a cubic spline with an FD threshold of 0.5 mm (34).

Sliding-Window dFC Analysis

We performed dFC analysis for four brain networks or LBNs enrolled in emotion regulation that was revealed by a previous study (10). The four LBNs included 36 brain areas with distinct spatial distributions and functional profiles. As shown in **Table 1**, their spherical regions of interest (ROIs) with a 5 mm radius were obtained based on the MNI coordinates of the peak voxels in the corresponding areas and used for the following analysis.

As shown in **Figure 1**, the dFC was measured via the sliding-window approach. The window size was set to 22 TRs (44 s) and data in each window were convolved with a Gaussian ($\sigma = 3$ TRs) (35). For each subject, 209 consecutive windows were obtained by setting the shift step as 1 TR (2 s). The covariance matrix was estimated using the graphical LASSO (Least absolute shrinkage and selection operator) method on the windowed data (36). For each subject, the L1-regularization penalty was set using five-fold cross-validation with 50 repetitions. Finally, FC matrices were Fisher z-transformed to improve statistical normality.

To capture the recurring functional interaction patterns characterized as connectivity matrix over time, we applied a k-means clustering method based on dFC values to classify all windows across all participants into several distinct states. The correlation distance function was used to measure the distances between each window and cluster centroids. The optimal number of states was determined by using the elbow criterion ranging from 2 to 9. To avoid locally optimal solutions, the clustering procedure was repeated 100 times. At baseline, the between-regional interaction pattern at each state was obtained by averaging connectivity matrices of all windows within that state. In an iterative process, one individual's connectivity matrix was selected from all time windows at the post-treatment and compared against the connectivity matrix of each state at baseline to find the matrix that was maximally similar, and then the window at the post-treatment was assigned to the state with their maximum correlation coefficients.

Dynamic indices were assessed for each participant, including (1) occurrence proportion, measured as the proportion of time window number in a particular state to the total number of time windows during the scan (209 windows in the present study); (2) state-dependent alterations in FC; and (3) state-dependent alterations in graph-theory measure. We calculated the FC in each state separately and named it dFC strength. For each subject, the dFC strength in a state was acquired by averaging all the windows assigned to that state. Mean local efficiency was investigated to demonstrate the efficiency of information transfer in each functional interaction pattern. The local efficiency of each node was calculated using the GRETNA software (http://www.nitrc.org/projects/gretna) with the non-negative value of the weighted FC matrix as input (37). The sFC was also calculated to test whether state-dependent alterations could be detected in static functional interaction patterns.

Predicting the Reduction Rate of HAMD Scores

In the present study, we constructed multivariate linear regression models to determine whether and which recurring functional interaction pattern could predict the reduction rate (RR) of HAMD scores. According to previous studies (31, 38), we employed a leave-one-out cross-validation (LOOCV) strategy to evaluate the performance of the regression models. For each iteration of LOOCV, the state-dependent FC of an MDD patient at baseline was applied to predict his/her RR of HAMD scores based on the regression model trained by remaining patients. Finally, Pearson's correlation coefficient between the observed and predicted RR of HAMD scores was calculated to evaluate the performance of the predictive model. An additional multivariate linear regression model was also constructed to examine the predictive ability of static functional interaction patterns for the treatment effect of antidepressants.

Statistical Analysis

Statistical comparisons between MDD and HC at baseline were performed on dynamic measures via the general linear model (GLM), with age, sex, and mean FD as covariates. The paired-sample *t*-test was utilized to evaluate the longitudinal alterations of depression severity and abnormal dynamic measures in RDG and N-RDG following antidepressant treatment. The threshold of statistical significance was set at 0.05. The correction for multiple comparisons was performed using the false discovery rate ($p < 0.05$, FDR corrected). The one-sample *t*-test was utilized to examine the main FC of each state in the MDD and HC groups, respectively. The one-sample *t*-test results of the two groups were combined as a conjunction mask for subsequent between-group comparisons.

The statistical significance of the prediction results was assessed using permutation tests (39). Firstly, the observed RR of HAMD scores were randomly permuted beforehand across participants. Then, the aforementioned prediction processes were performed on the permuted dataset. This procedure was repeated 10,000 times. The performance of a regression model was assumed to be reliable if the result obtained by the regression model trained on the true dataset was higher than the 95% confidence interval of the regression model trained on a randomly permuted dataset.

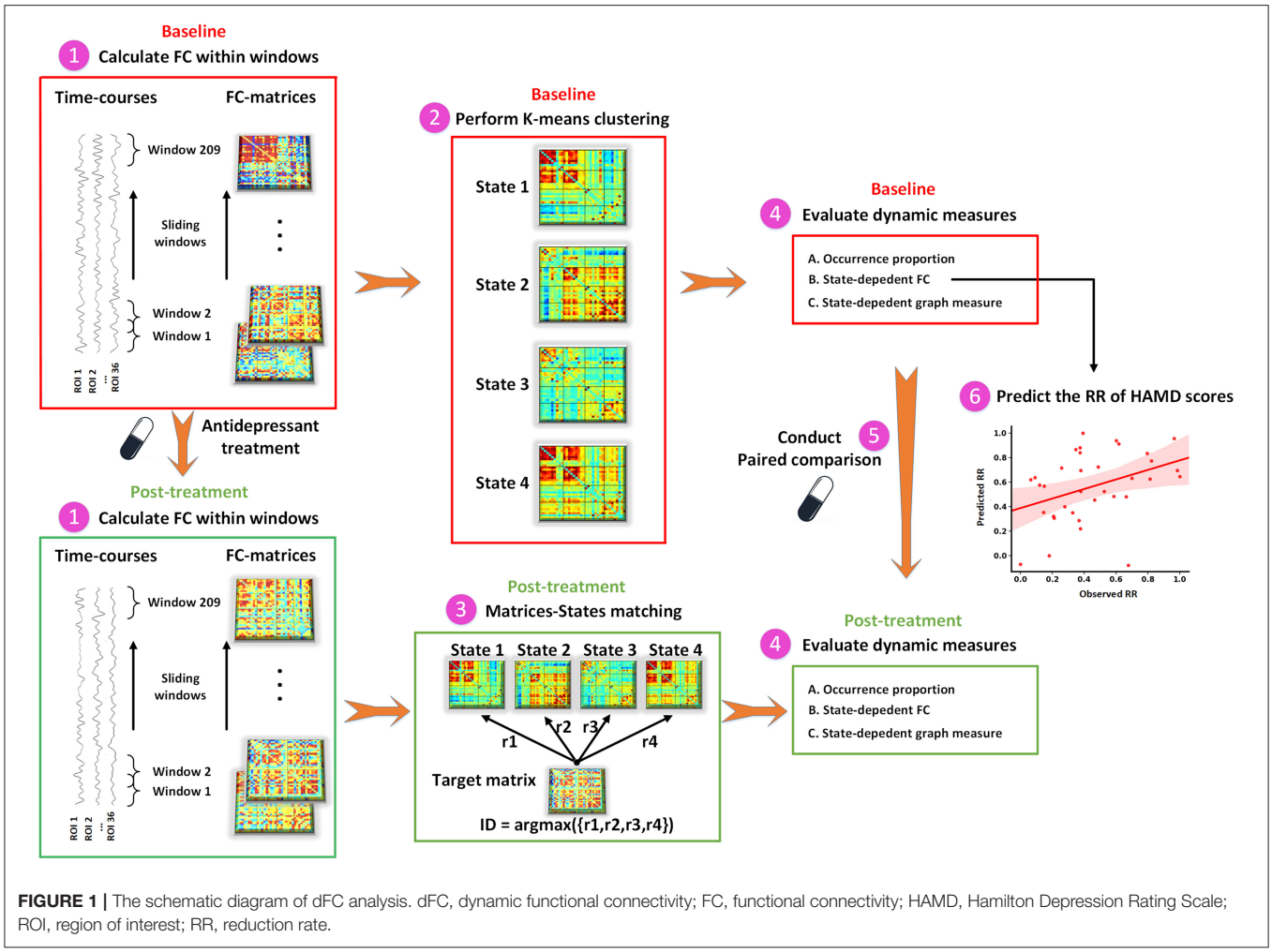

FIGURE 1 | The schematic diagram of dFC analysis. dFC, dynamic functional connectivity; FC, functional connectivity; HAMD, Hamilton Depression Rating Scale; ROI, region of interest; RR, reduction rate.

RESULTS

Demographic and Clinical Data

The demographic and clinical characteristics of the participants were summarized in **Table 2**. MDD patients were matched with HC on gender ($t = 0.629$, $p = 0.428$), age ($t = -1.217$, $p = 0.226$), and mean FD ($t = -1.041$, $p = 0.300$). Following 12-week antidepressant treatment, a total of 37 of 70 MDD patients completed a repeated MRI scan and HAMD assessment. A significant reduction on depression severity was found (paired t-tests, $t = -9.479$, $p < 0.001$). Twenty-three (62.16%) MDD patients achieved the responsive criteria and were then grouped into RDG. The remaining 14 sMDD (37.84%) patients were placed into N-RDG.

Between-Group and Follow-Up Comparisons of Dynamic Measures

To identify the recurring inter-regional functional interaction patterns over R-fMRI scan time, all window slices were automatically divided into four distinct states by a k-means clustering method in the baseline phase. **Figure 2A** displays the recurring functional interaction patterns among four LBNs. State 1 exhibited strong FC between LBN 1 and LBN 2. In state 2, LBN 2, LBN 3, and LBN 4 were interconnected strongly. There was relatively sparse FC in state 3. Similar to state 1, state 4 had a strong FC between LBN 1 and LBN 2. Furthermore, stronger FC of LBN 4 with LBN 1 and LBN 2 was found in state 4 relative to state 1. Compared with state 1 and state 3, state 2 and state 4 exhibited significantly higher average local efficiency ($p < 0.05$, **Figure 3**).

The between-group differences of the time to occurrence proportion of each state and average local network efficiency at baseline were shown in **Figure 2**. Compared with HC, MDD patients had a significantly more occurrence proportion in state 1 ($t = 2.177$, $p = 0.032$) and state 3 ($t = 2.123$, $p = 0.036$), but less occurrence proportion in state 2 ($t = -2.627$, $p = 0.010$). We observed that MDD patients showed significantly lower average local efficiency than HC in state 1 ($t = -2.689$, $p = 0.008$), state 3 ($t = -2.969$, $p = 0.004$) and state 4 ($t = -2.313$, $p = 0.023$). In state 2, MDD patients at baseline had significantly decreased dFC strength between the left amygdala and left cuneus ($t = -4.070$, $p < 0.001$) compared with HC (**Figure 4**). In sFC analysis, MDD patients at baseline did not show any significant alteration compared to HC ($p > 0.05$).

TABLE 2 | Demographic and clinical data.

Characteristics	MDD	HC	*p*-value	t/χ^2 value
Sex (male/female)	70 (21/49)	43 (16/27)	0.428[a]	0.629
Age (years)	26.93 ± 9.14	29.42 ± 12.55	0.226[b]	−1.217
Mean FD	0.11 ± 0.05	0.12 ± 0.06	0.300[b]	−1.041
HAMD	28.06 ± 6.67	1.35 ± 1.38	<0.001[b]	25.647
Duration of illness (months)	7.37 ± 12.60			
Episodes				
First	43			
Recurrence	27			
Medication history	29			

The data were presented as the mean ± standard deviation. HC, healthy controls; MDD, major depressive disorder; HAMD, Hamilton Depression Rating Scale; FD, framewise-displacement.

[a] *The p-value was obtained by a chi-square test.*

[b] *The p-value was obtained by a two-tailed two-sample t-test.*

After 12 weeks of antidepressant treatment, MDD patients in RDG exhibited significant alterations in dynamic measures compared to those at baseline (**Figure 2B**). Specifically, patients in RDG showed increased occurrence proportion in state 2 ($t = 2.505$, $p = 0.020$) but decreased occurrence proportion in state 1 ($t = -2.463$, $p = 0.022$) and state 3 ($t = -2.214$, $p = 0.037$). No significant alteration was found in dFC strength and average local efficiency in each state ($p > 0.05$). Patients in N-RDG did not show significant alteration after treatment ($p > 0.05$).

The Predicted RR of HAMD Scores

As shown in **Figure 5**, the baseline dFC strength in state 2 of MDD patients significantly predicted their RR of HAMD scores following treatment ($r = 0.440$, $p = 0.008$). In the prediction model, the medial frontal gyrus (MFG) exhibited the highest prediction weight among all ROIs. In addition, the sFC did not predict the RR of HAMD scores significantly ($r = -0.057$, $p = 0.585$, **Figure 5**).

DISCUSSION

The present study investigated the recurring functional interaction patterns among four LBNs enrolled in emotion regulation. Four recurring functional interaction patterns over time were identified. Patients with MDD exhibited abnormal dynamic measures at baseline, including state occurrence proportion, state-dependent FC, and state-dependent average local efficiency. Administrated with antidepressants, the abnormal state occurrence proportion of patients in RDG was reconfigured toward a direction of healthy controls. The FC in state 2 at baseline predicted the RR of HAMD scores significantly wherein the connectivity of the MFG contributed the most to prediction.

Recurring Functional Interaction Patterns

In the present study, four states represented distinct functional interaction patterns among four LBNs implicated in emotion regulation. State 1, which accounted for more than 30% of time windows, exhibited a strong interaction between LBN 1 and LBN 2. LBN 1, consisting mainly of the frontoparietal network including the dorsolateral prefrontal cortex (dlPFC), is implicated in working memory and response inhibition (10, 40). LBN 2 covers mainly the lateral ventral prefrontal network and is functionally associated with the cognition domain, especially language-related cognitive processing (10, 41). Approximately 90% of the experiments contributing to LBN 1 and LBN 2 were involved in the regulation phase of the emotion process (10). Most of these experiments implemented reappraisal as a regulation strategy. Though exerting strong interactions with each other, these two networks showed sparse connectivity with LBN 3 and LBN 4. Sparser connectivity could be found in state 3, of which relatively strong connectivity was concentrated between LBN 3 and LBN 4. The functional interaction patterns represented by state 1 and state 3 presented functional separation between the prefrontal cortex and subcortical regions.

State 2 had strong functional couplings between LBN 2, LBN 3, and LBN 4. As a network implicated in the cognitive regulation of emotion, LBN 1 did not show strong coordination with other LBNs. This could be interpreted by functional differences between the two regulatory networks along a dorsal (LBN 1)—ventral gradient (LBN 2) (42, 43). Previous studies have suggested that dorsal prefrontal regions play an important role in maintaining the goals of reappraisal in working memory during emotion regulation (42, 44) but are no longer required to maintain the monitoring of representations in working memory after finally selecting one from multiple representations of stimulus-appropriate reinterpretations which is mainly supported by ventral prefrontal regions (43, 45). Strong connectivity between the ventral and dorsal prefrontal regions is more likely to be found in the selection phase of goal-appropriate reappraisals where multiple reappraisals need to be represented in working memory (43). Therefore, the functional interaction pattern represented by state 2 might be related to the execution of cognitive reappraisals of emotion. LBN 3 consists of subcortical regions including the amygdala and is primarily involved in reactivity and generation of emotion. LBN 4 is composed of the areas relevant to emotion perception and interoception such as the insula, precuneus, and posterior cingulate cortex. It serves as

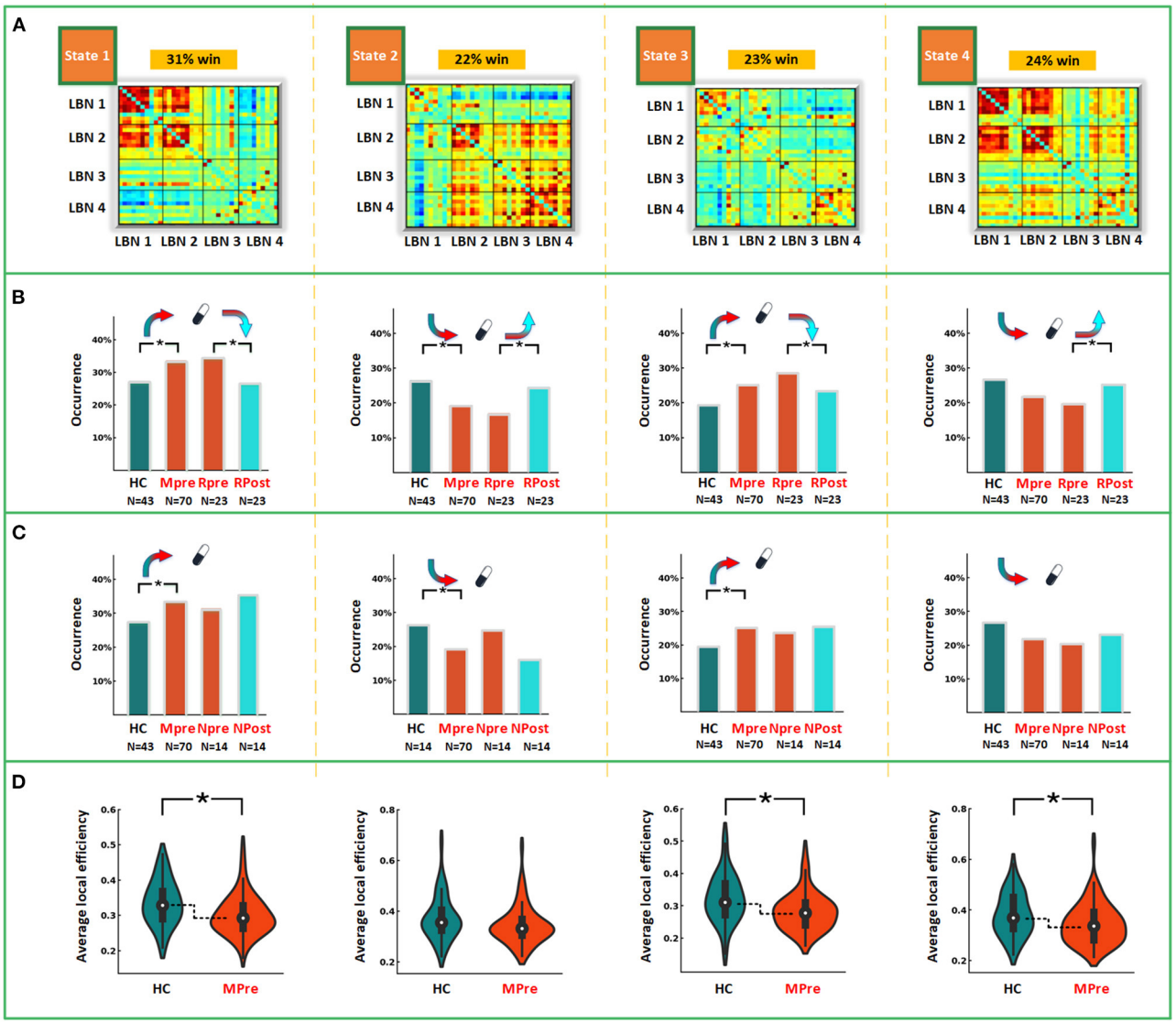

FIGURE 2 | Intra- and between-group comparisons in dynamic measures. **(A)** Functional interaction patterns are represented by four states. The mean occurrence proportion of each state across all subjects was listed above each matrix. **(B)** The differences of occurrence proportion between MDD and HC, and between post-treatment and paired baseline responsive depression group. **(C)** The differences of occurrence proportion between MDD and HC, and between post-treatment and paired baseline non-responsive depression group. **(D)** The differences of average local efficiency between MDD and HC. LBN, large-scale brain network; win, window; HC, healthy controls; Mpre, major depressive disorder patients at baseline; Rpre, responsive depression group at baseline; Rpost, responsive depression group after treatment. Npre, non-responsive depression group at baseline; Npost, non-responsive depression group after treatment. $^{*}p < 0.05$ after FDR corrected.

a hub that plays an intermediary role in integrating information from the prefrontal cortex (LBN 1 and LBN 2) and subcortical regions (LBN 3). Functional synchronization between LBN 2 and LBN 3 might be associated with the reinterpretations for emotion reactivity, and LBN 4 maintained and coordinated information communication courses between them (46).

Reconfiguration for Abnormal Dynamic Measures

MDD patients exhibited a lower occurrence proportion in state 2 but a higher occurrence proportion in state 1 and state 3. A lower occurrence proportion in state 2 seemly signified the difficulty of MDD patients to enter the functional interaction pattern in which the meaning of their emotional reactivity could be reinterpreted. By contrast, the functional separation between prefrontal and subcortical regions which appeared more frequently in temporal co-evolution of LBNs might be associated with less tendency or greater difficulties for MDD patients to regulate their emotions by using cognitive reappraisal. Cognitive reappraisal is an infrequently used adaptive emotion regulation strategy in MDD (2). Conversely, patients with MDD preferentially performed maladaptive emotion regulation

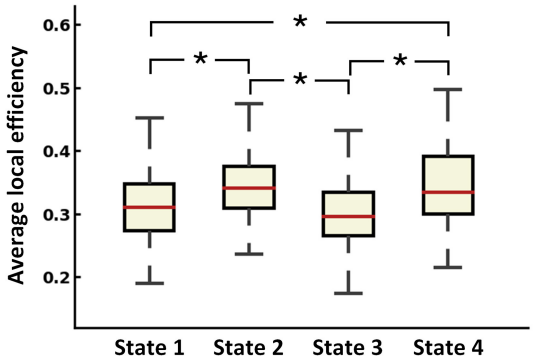

FIGURE 3 | Average local efficiency of dFC states across all subjects. $^{*}p <$ 0.05 after FDR corrected.

strategies, for instance, rumination (47). Most of the regions in LBN 3 and LBN 4 are implicated in self-referential processing and have been reported to engage in rumination (48, 49). Superfluous immersions in relatively strong connectivity between these regions might be the neural basis for excessive rumination in MDD.

Decreased FC between the amygdala and cuneus was only found in state 2. The amygdala, a core region of the limbic system known to control emotion processing, plays a major role in the generation and regulation of emotion (50). Convergent evidence suggests that the amygdala is responsible for crucial functions related to depression including the processing of visual information elicited by emotional stimuli (51). The cuneus is located in the occipital lobe and is mainly involved in the processing of visual information (52). We speculated that decreased FC between the amygdala and cuneus in state 2 might reflect bias evaluation to emotion stimuli of MDD patients when performing cognitive reappraisal. We observed that four states had significantly different network efficiency. The functional interaction patterns represented by state 1 and state 3 presented lower efficiency of information transfer than state 2 and state 4. In addition, MDD patients had lower efficiency of information transfer in low-efficiency states (i.e., state 1 and state 3). Taken together, these state-dependent alterations indicated that the disruption of functional interaction patterns was not constant but intermittent.

After 12 weeks of antidepressant treatment, normalization for abnormal occurrence proportion was observed in MDD patients who responded to treatment. However, state-dependent alterations in FC and graph-theory measures were not modified by antidepressant treatment. This indicated that antidepressants might promote remission of MDD by modulating the dynamic interaction process between LBNs related to emotion regulation. Specifically, the prefrontal cortex displayed more frequent functional communication with subcortical networks compared to baseline in RDG. Such an effect was potentially relevant to more frequent employment of adaptive emotion regulation strategies (e.g., reappraisal) in MDD patients after antidepressant medication (53). However, reconfiguration for abnormal occurrence proportion was not found in those who did not respond to treatment. Similar to previous studies (54), our results, from the dynamic interaction process among LBNs, supported the view that adaptive emotion regulation is a key therapeutic target for effective treatment for MDD (55, 56).

The Dynamic Interaction Pattern With Predictive Power

The static functional interaction pattern at baseline failed to predict the RR of HAMD scores after 12 weeks of treatment. Interestingly, the functional interaction pattern of state 2 at baseline significantly predicted the RR of HAMD scores in MDD patients. Although previous studies have underlined the classifying and predictive ability of dFC (57, 58), most of them focused on its temporal variation instead of recurring functional interaction patterns. Our findings highlighted the potential of state-based dFC analysis in developing biomarkers for clinical applications. In addition, the FC of the MFG contributed the most to the prediction. The MFG, a midline frontal region, is typically implicated in emotion regulation (42). It was thought to facilitate the generation of purposeful and adaptive behavior (59). Functional impairments in this area were reported and related to negatively biased attention in MDD patients (60). More importantly, a previous study demonstrated that structural alteration of the MFG was correlated with the improvement of depressive symptoms following cognitive-behavioral therapy (61). Our results provide further evidence that the MFG plays an important role in the effective treatment of depression.

Limitations

Several limitations need to be considered in the present study. First, the sample size of MDD patients administrated with antidepressants was relatively small, which might reduce the generalizability of the work. Future studies with a larger sample size are imperative to assess the reproducibility of our findings. Second, the acquisition time of R-fMRI was 8 min. More time points might help to discover more subtle functional interaction patterns with a low occurrence proportion. Third, some patients withdrew from the study after baseline and did not undergo a repeated MRI scan, which may weaken the statistical power of a longitudinal study. More samples are warranted to offset this effect in future studies. Finally, our efforts were mainly concentrated on dFC. It is worth mentioning that emerging evidence demonstrates the co-evolutionary relationship between FC and local brain activity (23). Future studies could further explore co-evolutionary patterns between FC and local brain activity of LBNs enrolled in emotion regulation.

CONCLUSIONS

Given the adaptive nature and network-level representation in the brain of emotion, exploring time-varying functional interactions is important to characterize emotion dysregulation in MDD. The present study identified several recurring functional interaction patterns among LBNs enrolled in emotion regulation and further investigated their abnormal temporal configuration as well as reconfiguration following antidepressant

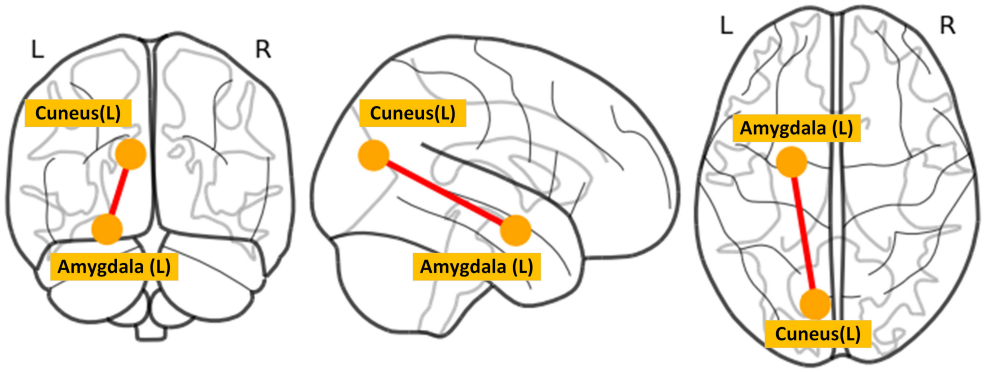

FIGURE 4 | The between-group difference of dFC strength in state 2. L, left; R, right.

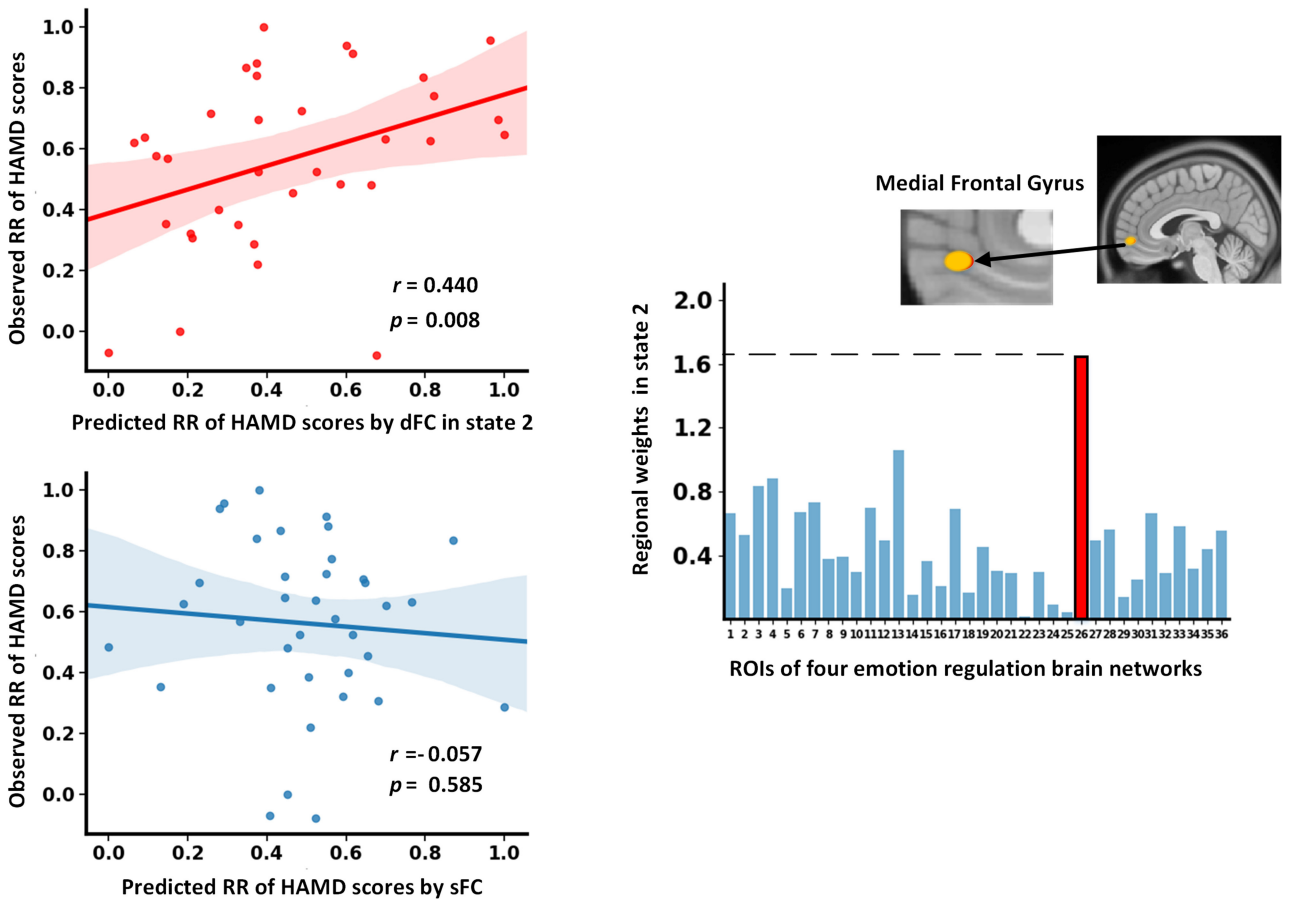

FIGURE 5 | The results of dFC strength and sFC as features to predict the RR of HAMD scores. dFC, dynamic functional connectivity; HAMD, Hamilton Depression Rating Scale; RR, reduction rate; sFC, static functional connectivity.

treatment in MDD. Furthermore, we found that predictive biomarkers of effective antidepressant treatment were embedded in the dynamic interactions among LBNs. These findings demonstrate that the dynamic interactions among LBNs serving for emotion regulation have the potential to be the target of clinical intervention for 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 Local Institutional Review Boards (IRB) of Hangzhou Normal University. 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

S-WX, LZ, DW, and ZT: concept and design. LZ, S-WX, and ZL: drafting of the manuscript. LZ, S-WX, ZL, and YX: critical revision of the manuscript for important intellectual content. LZ, CK, HLi, and CP: statistical analysis. DW, S-WX, and HLu: obtained the funding. LZ, XH, SF, and YW: administrative, technical, and material support. S-WX and DW: supervision. All authors: acquisition, analysis, and interpretation of data.

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REVIEW
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Sleep Disturbances and Depression Are Co-morbid Conditions: Insights From Animal Models, Especially Non-human Primate Model

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The incidence rates of depression are increasing year by year. As one of the main clinical manifestations of depression, sleep disorder is often the first complication. This complication may increase the severity of depression and lead to poor prognosis in patients. In the past decades, there have been many methods used to evaluate sleep disorders, such as polysomnography and electroencephalogram, actigraphy, and videography. A large number of rodents and non-human primate models have reproduced the symptoms of depression, which also show sleep disorders. The purpose of this review is to examine and discuss the relationship between sleep disorders and depression. To this end, we evaluated the prevalence, clinical features, phenotypic analysis, and pathophysiological brain mechanisms of depression-related sleep disturbances. We also emphasized the current situation, significance, and insights from animal models of depression, which would provide a better understanding for the pathophysiological mechanisms between sleep disturbance and depression.

Keywords: depression, sleep, non-human primate, brain development, animal model

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INTRODUCTION

Sleep is an essential physiological requirement for human and most animals. A mechanistic link is evident between sleep and depression at the molecular and neurophysiological level. The periodic regulation of awake and sleep requires the participation of many neurotransmitters, including excitatory neurotransmitters (such as acetylcholine) and inhibitory neurotransmitters (such as gamma aminobutyric acid, GABA). Abnormalities of these neurotransmitter systems not only lead to sleep-wake rhythm disorders, but also can contribute to developing depression. Depression and sleep disturbances are common co-morbid conditions (1, 2). More than 90% percent of patients with major depressive disorder will suffer from sleep disorders, which changed the patients' sleep structure. A further demonstration of the link between depression and sleep is that sleep can be improved by most clinically effective antidepressant drugs. Compared with lower mammals, the sleep of non-human primates (NHPs) is better comparable with that of humans. Recently, significant progress has been made in the study of using NHPs to establish depression models. Monitoring the sleep status of animals during modeling will help us further understand the role of sleep in the development of depression, and provide an objective biomarker for the early diagnosis, treatment, and efficacy evaluation.

SLEEP STRUCTURE AND RELATED NEUROTRANSMITTERS

Sleep is vital for human beings and most animals, and control mechanisms are embodied in all levels of biological organizations, from genes and intracellular mechanisms to cell population networks, and then to all central nervous systems, including systems that control movement, arousal, autonomic function, behavior, and cognition. Mammalian sleep is characterized by the periodic alternation of rapid eye movement sleep (REMs) and non-rapid eye movement sleep (NREMs). NREMs includes two stages: slow-wave sleep (SWS) and light sleep. In humans, SWS and REMs, which are the specific modes of potential electric field oscillations and neuromodulator activities, dominate the first half of the night and the latter half of the night, respectively (3).

The mutual transformation between sleep and wakefulness is caused by the excitation or inhibition of many neurotransmitters in the brain, which are released by sleep-promoting neurons in the anterior hypothalamus or sleep-inhibiting neurons in the lateral and posterior hypothalamus activity. These neurons release excitatory or inhibitory neurotransmitters to promote the brainstem to control the mutual transformation of wakefulness and sleep (2, 4).

The ascend arousal system mainly comes from a group of explicit cells with definite neurotransmitters. The arousal system actually consists of two channels (5). The ascending pathway to the thalamus is the first branch, which activates the thalamus and is essential to relay neurons for transmitting information to the cerebral cortex. The main sources of input from the upper brainstem to the thalamic-relay nucleus, the thalamic reticular nucleus, the pedunculopontine, and laterodorsally tegmental nucleus (PPT/LDT) are a couple of acetylcholine producing cell populations. The neurons in PPT/LDT discharge fastest during awake and REMs, and are often accompanied by cortical activation, loss of body muscle tone and active dreams. During NREMs, the activity of these cells is much lower. They are important for the input of reticular nucleus, because they are located between thalamic relay nucleus and cerebral cortex. It is very important for arousal that they can block the transmission between thalamic and cerebral cortex, thus acting as a gating mechanism. From the reticular structure and PPT/LDT, monoamine nervous system and parabrachial nucleus in the upper part of the brain stem, have more extensive input to the midline of thalamus and tabular nucleus. The laminar nucleus and midline nucleus are also considered to play a role in cortical arousal (5). Bypassing the thalamus and activating the neuronal pathway of the lateral hypothalamic area, basal forebrain (BF), and the whole cerebral cortex is the second branch of the ascending arousal system. This pathway, which covers noradrenergic locus coeruleus, serotonin dorsal nucleus, and median raphe nucleus, dopaminergic midbrain periaqueductal gray matter ventral and histaminergic nodule papillary neurons, is derived from monoamine neurons in the upper brainstem and caudal hypothalamus. Cortical input is increased by hypothalamic lateral peptidergic neurons (containing melanin concentrating hormone or orexin/retinol) and BF neurons (containing acetylcholine or GABA) (5). Lesions along this path, especially in the left hemisphere and the rostral midbrain, produce the most profound and lasting drowsiness and even coma. The neurons in each monoaminergic nucleus involved in this pathway discharge fastest during waking, slow down during NREMs and completely stop during REMs. It should be noted that all these ascending pathways pass through the regions at the junction of forebrain and brainstem. While, the descending pathways responsible for synchronizing phenomena still remain largely unknown at the brain-stem level.

The pathogenesis of sleep disorder is closely related to sleep-wake homeostasis, but the specific mechanism remains still unclear. During NREMs and REMs, different kinds of neurotransmitters are released in the brain. The interaction between aminergic neurons and cholinergic neurons at the meso-pontine junction leads each other to bring about the Ultradian rhythms alternation of REMs and NREMs. During NREMs, aminergic inhibition is decreased and cholinergic excitation is increased. At the onset of REMs, aminergic inhibition is turned off, cholinergic excitability reaches a peak, and other outputs are inhibited (2). When awake, the pontine aminergic system is tensely activated and the pontine cholinergic system is inhibited. In addition to aminergic and cholinergic neurons, other neurotransmitter systems are also involved in modulating REMs/NREMs alternation and may interact with aminergic and cholinergic systems (2, 6, 7). Extrinsically augmented dopaminergic neurotransmission can influence both REMs and NREMs cycles. Moreover, gamma-amino butyric acid and glutamate also affect the REMs/NREMs cycle (2).

In short, the growth and decline of these neurotransmitters promote the mutual transformation between sleep and wake. If these related neurotransmitters are released abnormally, it will cause sleep problems, such as difficulties in falling asleep and maintaining sleep state, changes of REMs latency, abnormal REMs behavior, and disturbed alternating pattern of REMs/NREMs.

CLINICAL CHARACTERISTICS AND RELATED NEUROTRANSMITTERS OF SLEEP DISORDERS IN DEPRESSION

Depression is the main cause of the burden of mental health-related diseases in the world, and about 300 million people around the world are affected by depression (8). One aspect of efforts to understand depression focuses on its relationship with sleep. In many cases, the onset of depression is announced through sleep disorders, and sleep deterioration occurs before depression and manic episodes (9). There are many forms of sleep disorders reported in patients with depression. It may be only exhibited by the shortening of sleep time, but it also indicates a reduction in sleep efficiency. The latter is defined as the ratio of total sleep time to total time spent in bed over the night. Lack of sleep increases the risk of depressive episodes and depression relapses. Likewise, depression increases the risk of sleep disorders. However, the self-assessment of sleep quality in patients with depression is unreliable. Similarly, there

are differences in the subjective and objective assessment of daytime alertness (10). This leads to bias in the evaluation of sleep efficiency.

Epidemiological investigations confirm that there is a closer relationship between insomnia and the onset of depression. It is reported that most patients often have insomnia and depressive episodes at the same time (11). Approximately 90% of major depressive disorder (MDD) patients have been found to suffer from sleep disorders, including initial insomnia, difficulty in sleep maintenance, non-restorative sleep, and early morning awakenings (12, 13). In reality, the most common subjective sleep complaints reported by depressed patients are insomnia (up to 88%) and hypersomnia (27%) (14). The insomnia and emotional symptoms are bidirectional correlated that poor sleep may precede the onset of depression, and depressive mood may also disrupt sleep patterns. In addition, patients with MDD are three times more likely to suffer from insomnia than those without (15, 16). Furthermore, fatigue, hypersomnia, and sleepiness are closely related to depressive symptoms (14). Many depressed patients complain about non-recovery sleep and excessive daytime sleepiness (16), and about 15% of patients report symptoms of daytime sedation and hypersomnia (17). However, these findings are inconsistent (16). Depression and hypersomnia are two conditions linked in a complex and bidirectional manner. In addition, many patients with depression call their complaints a combination of daytime sleepiness and nighttime anxiety.

Since the 1960s, polysomnography (PSG) sleep studies have repeatedly shown that depression is also associated with disrupted sleep architecture. These abnormalities include increase in RA (REMs activity) and RD (REMs density), as well as a decrease in REMs latency and SWS (18). During REMs, patients with depression often show short latency, prolonged cycle, and increased density (19). Disorders of REMs usually persist throughout the clinical episode, and it is considered to increase the possibility of recurrence, and may reduce the therapeutic effect (19–21). After antidepressant treatment, the number of REMs is decreased and the latency of REMs is increased. Most antidepressants inhibit REMs in patients and healthy volunteers (22).

The increase of serotonin content may be the main reason affecting REMs (23). Antidepressants that increased the contents of serotonin (5-HT) in synapses are effective inhibitors of REMs. 5HT1A agonists can be used as antidepressants and can significantly inhibit REMs (24). However, tryptophan depletion leads to a decrease in serotonin, which has been shown to reverse REMs inhibition caused by antidepressants (25). In addition, trazodone and nefazodone are also used as antidepressants because they have a strong antagonistic effect on serotonergic 5-HT2 receptors, which often promotes sleep and improves sleep continuity (26). The percentage of REMs was most significantly decreased in the early stage of treatment. Additionally, a subsequent study evaluated the changes in sleep structure of 20 patients with unipolar MDD after administration of sustained-release bupropion, and the results showed that 8 weeks of bupropion treatment significantly prolonged REMs latency, increased REMs activity and density in the first REMs period, which led to increased total REM density (27).

Glutamatergic and GABAergic neurons also play a role in the generation of REMs (28). Ketamine is a rapid-acting antidepressant (29), and AMPA-mediated increased neurotransmission is the basis of the antidepressant-like behavioral effects of ketamine (30, 31). The enhancement of AMPA receptor signal is participated in the pathophysiology and the mediation of ketamine-induced rapid antidepressant treatment (32, 33). Importantly, increased levels of ionic AMPA receptor could promote net synaptic strength and induce prolonged waking time in rodents and humans (34).

The REMs density of patients with depression continues to increase, which is regarded as an endophenotype. The reduction of the initial latency and the delta sleep ratio (DSR, the ratio of SWS between the first two NREMs episodes) of the rapid eye movement can be explained by cholinergic-aminergic imbalance (35). The monoaminergic inhibition of PPT/LDT cholinergic cells in patients with depression is weakened and/or the cholinergic-driven effect in pontine reticular formation is enhanced, resulting in an increase in REMs tendency and intensity.

The initiation and maintenance of NREMs also seem to be dependent on the role of monoamine neurotransmitters (26). Sedative antidepressants enhance SWS and prolong sleep duration. For instance, selective serotonin reuptake inhibitors (SSRIs) and non-sedating tricyclic antidepressants (TCA) can result in lighter sleep. In patients with depression, SWS and DSR tends to be low (36, 37). Compared with REMs latency, the measurement of SWS and DSR distribution may be a more reliable predictor of clinical response of antidepressant treatment and recurrence of depressive symptoms. Higher DSR may be more conducive to the treatment of depression (38). Some lines of evidence suggest that ketamine administration significantly increased the intensity of both SWS and DSR in humans and rats (39–41).

In addition, other types of antidepressants can also improve sleep. For example, antidepressants with anti-histaminergic action, such as mirtazapine and ipsapirone, act on their own receptors to support homeostatic maintenance of monoamine levels, block specifically monoamine receptors to enhance serotoninergic neurotransmission. Some patients' sleep can become better even after the first treatment of mirtazapine (42). However, increased levels of noradrenergic and dopaminergic neurotransmission, and raised activation of serotonergic 5-HT2 receptors can worsen the quality of sleep, which are also adverse effects of several antidepressants, such as serotonin and norepinephrine reuptake inhibitors, norepinephrine reuptake inhibitors, monoamine oxidase inhibitors (MAOI), SSRIs, and activated TCA (43). During REMs, monoaminergic neurons reduced significantly their discharge rate or stop their activity, but cholinergic neurons become highly active (44). However, MAOI increases the amounts of monoamine by preventing enzyme degradation and tends to cause the absence of REMs. One possible explanation is the antagonism of three receptors, namely H1 histamine or cholinergic receptor and postsynaptic

TABLE 1 | Comparison of different animal models used to study sleep disturbances and depression.

Animal models	Main application fields	Pros	Cons	References
Zebrafish	Molecular mechanisms of sleep/wake rhythm	Low cost; high gene-editing efficiency and relatively well-defined behavioral phenotypes	Not yet evaluated for depression-related sleep disturbances	(47–57)
Cat	Neuroendocrine mechanisms of sleep and sleep deprivation	Quantitative research of neurotransmitters	Not yet evaluated for depression and depression-related sleep disturbances	(58–60)
Dog	Sleep-wake cycle; narcolepsy; geriatric insomnia; obstructive sleep apnoea; sleep-associated epilepsy; and REMs disorder	Shared risks of many sleep disturbances with humans	More variable and fragmented sleep pattern; not yet evaluated for depression; and depression-related sleep disturbances	(61–67)
Rodents	Depression and sleep homeostasis; sleep structure; sleep-wake cycle; neurotransmitter receptor sensitivity and neuroendocrine stress response; as well as the effects of antidepressants on sleep	Low cost; easy to manipulate and gene-editing	Nocturnal animals; shorter durations of REMs and NREMs cycles	(68–82)
Non-human primates	Sleep-related neurobiology; neuroendocrine; and behavioral pharmacological studies	Highly similar to humans in brain structure, behavior, metabolism, sleep characteristics, and circadian rhythms	Difficult to directly measure mood or thoughts; limited behavioral screening tools; and lack of the effects of antidepressants on sleep	(83–97)

5HT2C receptor (26, 45). Therefore, most antidepressants alleviate depressed symptoms by improving sleep quality.

ANIMAL MODELS USED IN THE STUDY OF SLEEP DISTURBANCES AND DEPRESSION

It is necessary to obtain the best animal model for studying disease in biomedical research. Validity of animal models depends on the extent to which how they can mimic human diseases. Researchers have made exogenous and endogenous animal models to simulate the symptoms of depressed patients and elucidate the mechanisms of antidepressant action, involving acute and chronic stress model, secondary depression model, and genetic model (46). Translation validity of animal models is the key to sleep disorders research. As shown in **Table 1**, zebrafish, mice, rats, cats, dogs, and monkeys are generally useful to develop animal models to study sleep disorders (49, 62, 98–101). Among them, the most used laboratory animals are mice and rats. However, they are quite different from humans as they are nocturnal and adopt a monophasic sleep schedule. While, humans follow a polyphasic sleep pattern and are very flexible in choosing the sleep time (80, 102). Similar to humans, more fragmented and polyphasic sleep patterns are observed in monkeys, and they are generally active during the day and sleep at night (84). In view of this, compared with other animals, the sleep pattern of monkeys is closer to that of humans.

RODENT MODELS

Rodents are more usual choice of preclinical models to develop new pharmacological and non-pharmacological strategies. In the study of sleep deprivation, rodents (i.e., rats, mice) and humans have many similarities in sleep electroencephalogram (EEG) and sleep structure (103). External stressors or risk factors of diseases can affect the number or pattern of REMs (22, 104, 105). In humans, REMs latency is negatively correlated with the severity of depression (37). In rodents, changes in the REMs can precede those of other sleep/wake stages. For example, mice that were applied to water immersion for 2 h and restraint stress exhibited an immediate reduction in REMs (106).

As for the effect of stress on rodents' total sleep time, the primary stressors are immobilization and mild electrical shock. Immobilization increased the time spent in SWS and REMs, while electrical shock resulted in a decrease in total sleep time and total REMs time (107). Similarly, fear conditioning paradigms can also induce a decrease in REMs during both the shock training and cue exposure (104). Chronic unpredictable mild stress can lead to changes in the amplitude of both physiological (i.e., locomotion, temperature) and molecular circadian rhythm, which may cause depressive-like behaviors (108).

Continuous light exposure (LL) increases depressive-like behavior in mice, and light exposure at night (LAN) can lead to depressive-like behavior in diurnal rodents, such as grass rats and hamsters (109–111). This may be because LL brings about the interrupted rhythm of locomotion, temperature, and hormonal release, causing the disruption of circadian rhythm, and increases of NREMs during the rest period and REMs in the active period (112, 113).

For social species such as rats and mice, repeated fighting and/or defeat may be a more natural source of stress. Often, the consequences of chronic social defeat stress (CSDS) can persist until the termination of the stressors, which makes it a particularly attractive method to model stress-related psychiatric illnesses (114). Previous studies have found that CSDS has a direct effect on subsequent sleeping. Specifically, it can increase both the total time of REMs and NREMs, as well as the density of NREMs. However, the number of REMs is significantly decreased in the first few hours after conflict (114, 115). Another

experiment also reported a brief increase in REMs time following 10 days of social conflict, but no changes in SWS were detected (115, 116). Interestingly, there was no difference in NREMs and slow-wave activity between winner and loser, suggesting it is a consequence induced by the conflict process.

NON-HUMAN PRIMATE MODELS

NHPs bridge the gap between rodents and humans (117). Like humans, NHPs have stable sleep at night and some nap during the day. Many kinds of non-human primates, such as baboon, Kenya baboon, South African ape, macaque, cynomolgus monkey, Pada monkey, lemur, and chimpanzee, can be used to study sleep. By comparing the sleep of non-human primates, researchers generally believe that chimpanzee, olive baboon, and rhesus monkey are better model animals. In monkeys, four sleep EEG patterns can be easily identified. Due to its stable and perfect sleep architecture, macaque has become the best model to study the biological characteristics of human sleep (118–121). During the whole night, macaques experienced the alternation of awake, NREMs and REMs, and the total sleep time of rhesus monkey is about 10.5 h per day. It has been found that REMs time accounts for 23%, each of which lasts about 6 min and occurs every 51 min. In the early stage, it is mainly deep sleep, such as SWS. While, it is mainly REMs in the late stage of sleep. These sleep characteristics are very similar to humans that the interval of this cycle is about 90 min. Nevertheless, in rats, the interval is only 13 min. Like humans, obvious theta waves cannot be recorded in the hippocampus during macaques' sleep (122, 123).

EEG is a common method in sleep research, which can provide objective functional indexes for sleep (124). Although EEG can be performed in constrained animals under laboratory conditions, this technique is invasive. Even if it is minimally invasive, it also needs to drill holes in the skull and implant electrodes directly on the brain. PSG plays a cornerstone role in long-term recording of sleep, and has become the gold standard to evaluate sleep disorders. The recorded parameters include the brain activity (EEG), electrooculogram (EOG), expanded EEG montages, and transcutaneous or end-tidal capnography waveform, which are used to comprehensively monitor the normal and abnormal physiological indicators during sleep (125). However, an important limitation of PSG is that it requires electrodes and sensors (126). In addition, expensive and long-term recording intervals may be another limitation. Obviously, these are difficult and impossible to use in freely moving monkeys. A recent study compared videography and actigraphy methods in 10 cynomolgus monkeys during seven nights. It is verified that in the sleep study of NHPs, actigraphy can be regarded as a supplementary technique for routine EEG and/or video analysis to measure the sleep (127).

Researchers have used NHPs to make great efforts in the research of depression. It has been demonstrated for the first time that long-term intracerebroventricular administration of IFN-α (5 days/week for 6 weeks) can induce the monkeys showing considerable depressive-like symptoms with changes in the concentration of monoamine metabolites (128). The relationship between early adversity, chronic stress and depression was also investigated in adolescent monkeys. Eight male rhesus monkeys went through unpredictable chronic stress for 2 months and exhibited significant depression-like behaviors (88). The mechanisms underlying stress-induced depression were also explored in monkeys, and it was found that cortisol hypersecretion interacted with stress to accelerate the development of depressive behaviors (129).

In addition, researchers have employed NHPs animal model to make many beneficial explorations on the association between light deprivation and depression. The results showed that monkeys could develop the main symptoms of seasonal affective disorder under short lighting conditions (130). Analogous to depression in humans, sleep disorders have been also reported in spontaneous depressed monkeys (86). Notably, only the hypersomnia subgroup of spontaneously depressed monkeys shows a specific response to acute ketamine administration, characterized as extended wakefulness and shortening of nocturnal sleep. As a matter of fact, these changes are similar to sleep deprivation in depressed patients, suggesting alternation of nocturnal sleep pattern might help improve depressed mood (86, 119, 131).

CONCLUSION AND PERSPECTIVES

There is increasing evidence that sleep plays a causal role in emotional processing and regulation (132). Depression and sleep disturbances are common co-morbid conditions, and almost all depressed patients show some types of sleep disturbances (133, 134). Most antidepressants can change sleep, and the effects appear to be most significant and consistent on REMs (135). Selective REMs deprivation (such as forced awakenings) can produce an antidepressant effect, illustrating the closer association between REMs regulation and mechanisms involved in the development of depression (136). Some neurotransmitter reuptake inhibitors can alleviate depression by suppressing REMs through inhibition of serotonin and norepinephrine reuptake (26). However, many questions remain to be answered in future studies. Firstly, in previous studies, it was found that the effects of antidepressants on sleep initiation and maintenance were inconsistent. Secondly, the mechanism of different effects of antidepressants on sleep continuity is unclear. In rodent experiments, many paradigms of chronic stress have been used to simulate the pathogenesis of human depression, but it is hard to provide a unified description about the impact of chronic stress on sleep patterns. In fact, in addition to the types of stress, the number and persistent time are also important factors for stress responses, which must be carefully considered. NHPs are suitable animal models for experiments related to sleep, however, the study of depression and sleep disorders is far from enough. Although researchers have made continuous efforts and good progress in relevant animal models, it must be recognized that there are deficiencies.

In any way whatever, the research on animal models of sleep disorders provides a good clue and basis for

clinical diagnosis and treatment of depression. NHPs are considered as a further valuable and translational animal model, which is necessary for sleep and related diseases (137, 138). It is also an important entry point for increased efforts dedicated to collaborative translational endeavors.

AUTHOR CONTRIBUTIONS

DQ, LX, XL, and ML designed the structure. ML, JC, BX, YW, CF, and DQ wrote the first draft of the manuscript. DQ, LX, and XL supervised and revised the final version of the manuscript. All authors contributed substantially to the scientific process, writing of the manuscript, and have approved the final version of the manuscript being submitted.

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An End-to-End Depression Recognition Method Based on EEGNet

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Major depressive disorder (MDD) is a common and highly debilitating condition that threatens the health of millions of people. However, current diagnosis of depression relies on questionnaires that are highly correlated with physician experience and hence not completely objective. Electroencephalography (EEG) signals combined with deep learning techniques may be an objective approach to effective diagnosis of MDD. This study proposes an end-to-end deep learning framework for MDD diagnosis based on EEG signals. We used EEG signals from 29 healthy subjects and 24 patients with severe depression to calculate Accuracy, Precision, Recall, F1-Score, and Kappa coefficient, which were 90.98%, 91.27%, 90.59%, and 81.68%, respectively. In addition, we found that these values were highest when happy-neutral face pairs were used as stimuli for detecting depression. Compared with exiting methods for EEG-based MDD classification, ours can maintain stable model performance without re-calibration. The present results suggest that the method is highly accurate for diagnosis of MDD and can be used to develop an automatic plug-and-play EEG-based system for diagnosing depression.

Keywords: depression recognition, electroencephalogram (EEG), convolutional neural network (CNN), end-to-end, EEGNet

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1. INTRODUCTION

Depression is one of the most prevalent mental disorders. Patients with depression experience a severely impaired quality of life and are at increased risk of suicide (1–3). Patients infected with COVID-19 experience sleep disorders and are at increased risk of anxiety or depression, all of which are psychological complications (4–7). Yet depression is frequently undiagnosed and untreated because of a lack of effective therapies and inadequate mental-health resources (8). The onset of depression is usually gradual, but can be abrupt, and its progression throughout life varies considerably. Symptoms of depression often occur along with emotional, neurovegetative, and cognitive symptoms, and since they are commonly present in other psychiatric disorders and medical conditions, detection of depressive syndrome is problematic.

Identification of effective biomarkers for major depression is of great importance for improving the diagnosis and effective treatment of this common and debilitating neuropsychiatric disorder. Several different treatments are currently available, including a wide variety of antidepressant drugs (9–11), electroconvulsive therapy (ECT) (12), repetitive transcranial magnetic stimulation (rTMS)

(13), and deep brain stimulation (DBS) (14). However, half of patients with depressive disorder do not respond to current treatments. Therefore, it is necessary to discover new brain activity mechanisms and specific biomarkers for patients who respond to treatment in order to predict the onset and course of the disease, increase the therapeutic response, and enable detection of those patients who are resistant to individual therapies.

In recent years, use of non-invasive sensor-based methods, such as electroencephalography (EEG), has been widely reported in the literature (15, 16). One of the most remarkable research efforts has been in the area of efficient neural network-based approaches to analysis of EEG signals for automatic assessment of mental disorders such as major depressive disorder (MDD) and bipolar disorder (BD). Indeed, EEG is a non-invasive, effective, and powerful tool for recording the brain's electrical activity and diagnosing various mental disorders such as MDD, BD, anxiety (17), schizophrenia (18), and sleep disorders (19). In the case of depression, the body releases signals into the brain that affect neuronal production and communication, which slows or otherwise changes some regions of the brain. Variations in voltage resulting from changes in ionic current within the brain's neurons contribute to EEG signals and might help to diagnose mental disorders like depression. Development of robust approaches to analysis of brain signals is challenging because of their complexity and significant variability related to age and mental state. Moreover, EEG signals are frequently affected by different types of noise due to eye blinking and body motion (20). It is needed a deep learning technique that can effectively learn brain activity patterns from EEG signals.

To achieve the above requirements, we present a novel end-to-end architecture, supervised EEG-based event-related potential (ERP) classification. The EEG database used here is small and does not require complex EEG pre-processing. This method not only successfully extracts information across different subjects for ERP decoding, but also accomplishes three tasks simultaneously.

The remainder of this article is structured as follows: We firstly provide background and introduce the database, then we describe the structure of the proposed method, finally, experimental results are presented and discussed.

2. MATERIALS AND METHODS

This section introduces the EEG depression database, signal pre-processing, evaluation metrics, and details of EEGNet and how it

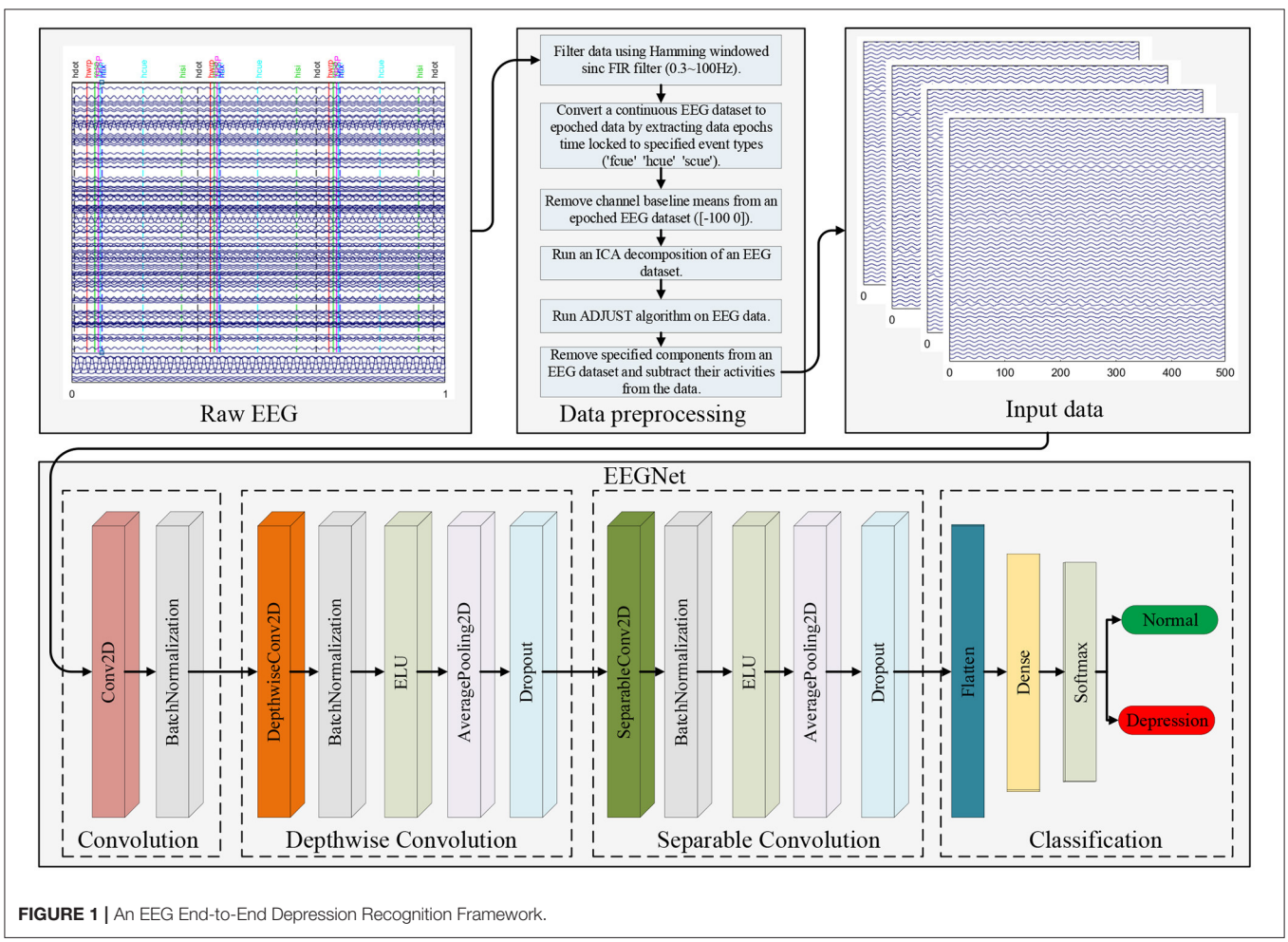

FIGURE 1 | An EEG End-to-End Depression Recognition Framework.

can be used to recognize depression. The end-to-end depression recognition framework is shown in **Figure 1**.

2.1. Depression Database

For depression recognition, we chose the multi-modal open dataset for mental-disorder analysis, i.e., the MODMA dataset. The dataset included 128-channel ERP recordings in **Figure 2**, from 24 subjects with MDD and 29 healthy controls (HCs) in the age range of 16–52 years (21–23). The sampling frequency was 250 Hz. The ERP experiment was a dot-probe task, and its cue stimuli included three kinds of emotional-neutral face pairs, namely happy-neutral (Hcue), sad-neutral (Scue), and fear-neutral (Fcue). In the formal experiment, subjects sat 60 cm in front of a monitor and were asked to focus on the emotion-neutral face pairs randomly presented as targets at the left and right positions. When these face dots appeared, the subjects were asked to press buttons on the reaction box as quickly and accurately as possible; they rested after completing each module. The task consisted of three parts (Hcue, Fcue, and Scue), each with 160 trials. At the beginning of each trial, a fixed white cross appeared on the center of the screen, starting at 300 ms and continuing throughout the experiment. Emotional-neutral pairs of face stimuli were presented on the screen as 500 ms cues, and the faces were arranged in a pseudo-random order. After a short interval (about 100–300 ms), the point probes randomly appeared at the left and right positions of the fixed cross for 150 ms. At the same time, participants were asked to identify the location of the points and to record their responses by pressing a button on the reaction box with their index finger. If the system did not receive responses within 2 s, participants would be directed to a subsequent trial and a black screen was then displayed for 600 ms. This process proceeded gradually until a block was completed. Each block was repeated until the entire task was complete. The entire experimental task was finished in 25 min.

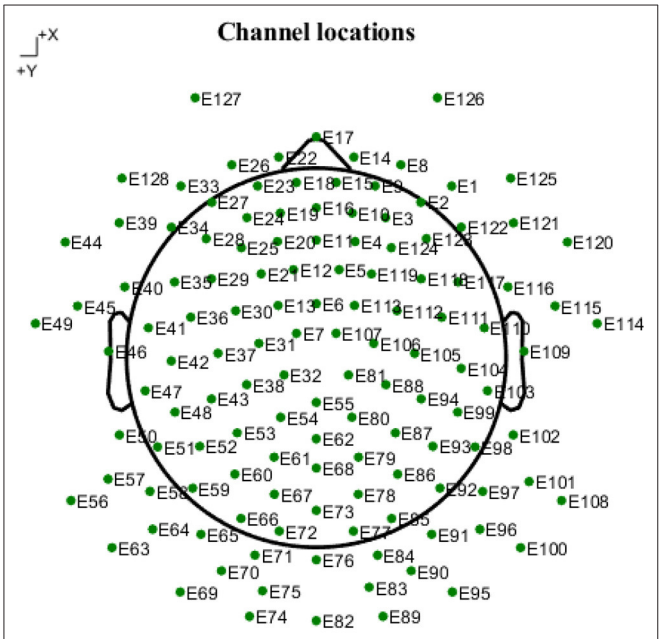

FIGURE 2 | Topological structure map of 128-electrode channels mapped to a two-dimensional picture. The circle represents the electrode, and the label inside is the serial number and name of the electrode.

2.2. Pre-processing Engineering

We used EEGLAB toolbox in MATLAB to preprocess the raw data as follows Brunner et al. (24): (1) an EEG dataset was converted to an average for reference; (2) the data were filtered

TABLE 1 | EEGNet model structure and parameters.

Layer (type)	Size	Output Shape	Param #
input_1 (InputLayer)		(None, 128, 125, 1)	0
conv2d (Conv2D)	8#(1,100)	(None, 128, 125, 8)	800
batch_normalization (BatchNormalization)		(None, 128, 125, 8)	32
depthwise_conv2d (DepthwiseConv2D)	(128,1)	(None, 1, 125, 16)	2048
batch_normalization_1 (BatchNormalization)		(None, 1, 125, 16)	64
activation (Activation)	elu	(None, 1, 125, 16)	0
average_pooling2d (AveragePooling2D)	(1,4)	(None, 1, 31, 16)	0
dropout (Dropout)	0.5	(None, 1, 31, 16)	0
separable_conv2d (SeparableConv2D)	16#(1,16)	(None, 1, 31, 16)	512
batch_normalization_2 (BatchNormalization)		(None, 1, 31, 16)	64
activation_1 (Activation)	elu	(None, 1, 31, 16)	0
average_pooling2d_1 (AveragePooling2D)	(1,8)	(None, 1, 3, 16)	0
dropout_1 (Dropout)	0.5	(None, 1, 3, 16)	0
flatten (Flatten)		(None, 48)	0
dense (Dense)	2	(None, 2)	98
softmax (Activation)		(None, 2)	0

Total params: 3,618

Trainable params: 3,538

Non-trainable params: 80

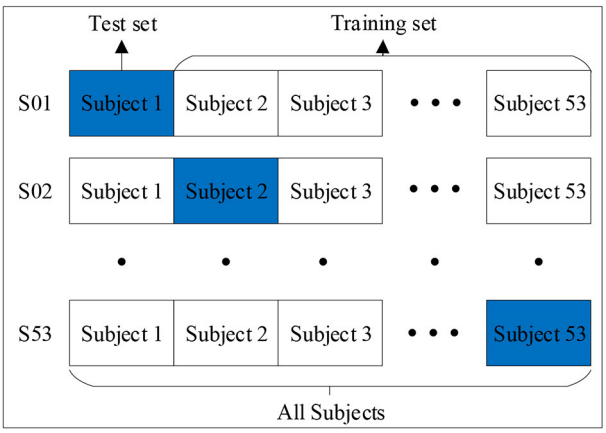

FIGURE 3 | Leave-One-Subject-Out Cross-Validation.

using a Hamming-windowed sinc FIR filter (0.3–100 Hz) to remove the 50 Hz power interference; (3) the continuous EEG dataset was converted to epoched data by extracting data epochs that were time-locked [-100 500]to specified event types (Hcue, Fcue and Scue); (4) channel baseline [-100 0] means were removed from the epoched EEG dataset; (5) an independent component analysis decomposition of the EEG dataset was run and specified components were removed; and (6) their activities were subtracted from the EEG dataset using the Adjust algorithm, as shown in **Figure 1**. The format of the preprocessed data is [*trials*, *channels*, *samples*, *kernels*], where $trials = 480$, $channels = 128$, $samples = 125$, $kernels = 1$.

2.3. EEGNet for Depression Recognition

EEGNet is a compact convolutional neural network (CNN) architecture that can be trained with minimal data to extract neurophysiologically interpretable features. A visualization and complete description of the EEGNet model are shown in **Figure 1** and **Table 1**. It primarily included four blocks: convolution, depthwise convolution, separable convolution, and classification.

In the convolution block, we fitted eight 2D convolutional filters of size (1, 100), outputting eight feature maps containing the EEG signal at different band-pass frequencies. Then we added a layer for batch normalization to make the training process more stable and reduce overfitting (25).

As the convolutions in the depthwise convolution block were not fully connected to all previous feature maps, we used a depthwise convolution of size (128, 1) and depth = 2 to learn a spatial filter, which reduced the number of trainable parameters that required fitting. When this operation was used for EEG depression recognition, it provided a direct way to learn spatial filters for each temporal filter and enabled efficient extraction of frequency-specific spatial features. We applied batch normalization along the feature map dimension before applying exponential linear unit (ELU) nonlinearity. Then, we used a dropout layer of probability = 0.5 to help regularize and an average pooling layer of size (1, 4) to reduce the sampling rate.

In the separable convolution block, we used a separable convolution with a depthwise convolution of size (1, 16) followed by a pointwise convolution. The main benefit of separable convolutions is a reduction in the number of parameters that require fitting and explicitly decoupling the relationships within and between feature maps by first learning a kernel that summarizes each feature map, which optimally combines the outputs. When it was used for EEG-specific applications, this operation guided the summarizing of individual feature maps in time (depth convolution) and their optimal combination (pointwise convolution). This operation was also perfectly suited to EEG signals, since different feature maps can represent informative data over different time scales. In addition, average pooling layers of size (1, 8) were used for dimensionality reduction.

TABLE 2 | Confusion Matrix and Evaluation Index.

Confusion Matrix		Predicted Label	
		Normal	**Depression**
True Label	**Normal**	**True Positive (TP)**	**False Negative (FN)**
	Depression	**False Positive (FP)**	**True Negative (TN)**

Evaluation Index

(1) $\text{Accuracy} = \dfrac{TP + TN}{TP + TN + FP + FN}$.

(2) $\text{Precision} = \dfrac{TP}{TP + FP}$.

(3) $\text{Recall} = \dfrac{TP}{TP + FN}$.

(4) $\text{F1-Score} = \dfrac{2 \times Precision \times Recall}{Precision + Recall}$.

(5) $\text{Kappa} = \dfrac{P_a - P_e}{1 - P_e}$, $P_a = \dfrac{TP + TN}{TP + TN + FP + FN}$,

$P_e = \dfrac{(TP + FP)(TP + FN) + (FN + TN)(FP + TN)}{(TP + TN + FP + FN)^2}$.

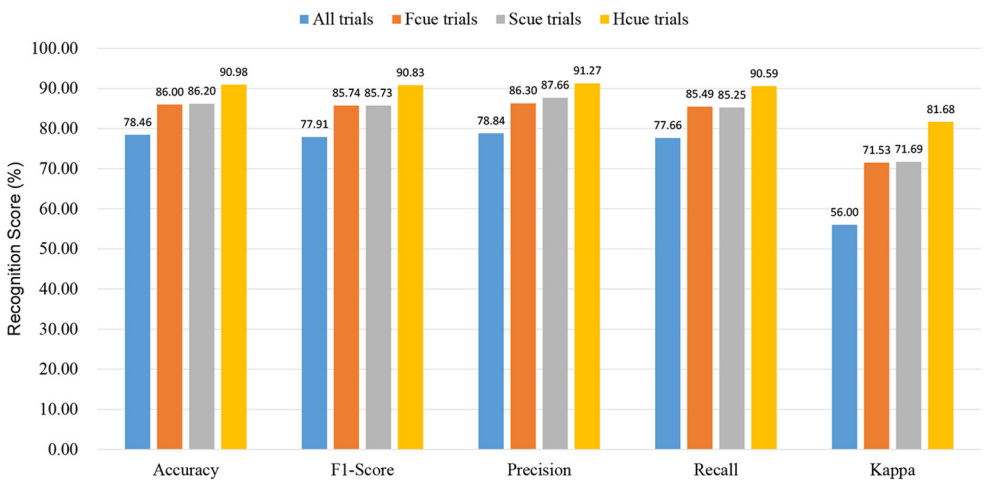

FIGURE 4 | Recognition scores of end-to-end depression recognition.

In the classification block, multi-dimensional features were downsampled to one dimension and directly passed to a softmax classification with 2 units to identify two categories, normal and depression.

2.4. Evaluation Index and Experimental Settings

We adopted the leave-one-subject-out cross-validation (LOSOCV) method to separate the training set from the validation set. Specifically, the training set was used to train the model, and the validation set was used to evaluate its generalization ability, as shown in **Figure 3**. The subject data was divided into 53 folds, with each representing the complete dataset of a subject. This protocol was suitable for small databases, could be trained by almost all the data, and was tested using one dataset. The experiment had no random factors, and the entire process was repeatable.

After modeling, several indicators were needed to measure the generalization ability of the model and further adjust the parameters to gradually optimize the model. As shown in **Table 2**,

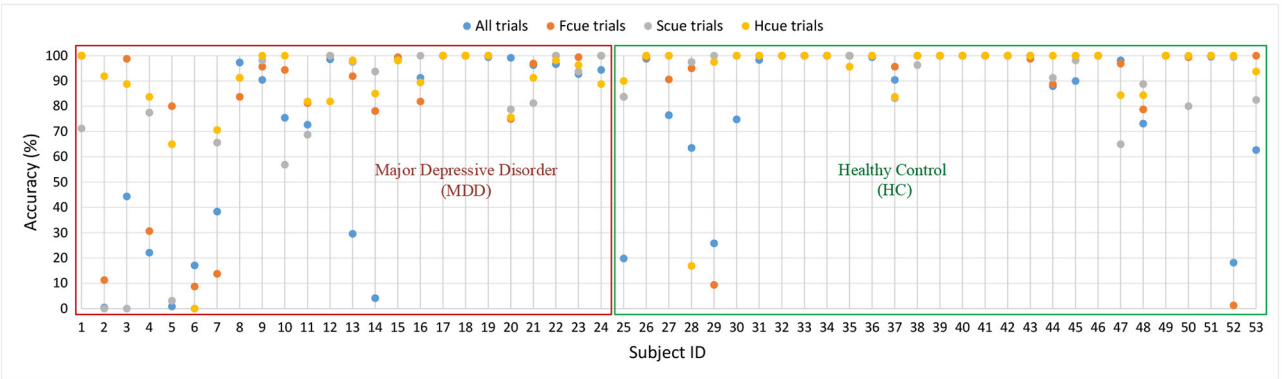

FIGURE 5 | Scatter plot of four experimental results (Accuracy) for each subject.

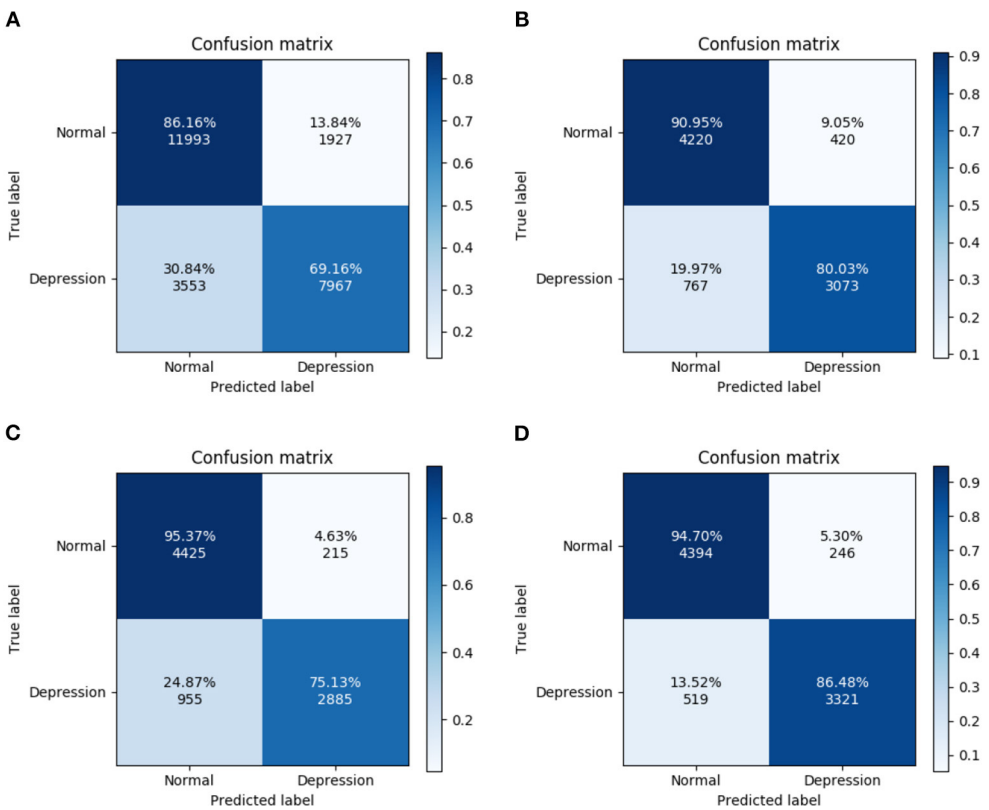

FIGURE 6 | Confusion matrix for four experiments. **(A)** All trials, **(B)** Fcue trials, **(C)** Scue trials, and **(D)** Hcue trials.

the first indicator was the confusion matrix. When the model diagnosed a normal person as normal, it was a true positive (TP); otherwise it was a false negative (FN). The model assigned a true negative (TN) when it diagnosed a depressive patient with depression; otherwise it was a false negative (FN). Five additional indicators were used to evaluate model classification, including (1) Accuracy: the proportion of correct to total samples, with each category treated equally; (2) Precision: the correct proportion of the positive samples predicted by the classifier; (3) Recall: the proportion of correctly predicted positive samples to all positive samples; (4) F1-Score: precision and recall affected each other, so in order to balance the two indicators and take into account the category imbalance, the weighted harmonic mean of precision and recall was used; (5) Kappa coefficient: an index used to test for consistency, usually to measure the effect of classification. Consistency was a measure of whether the model's predicted result was consistent with the actual classification result. The value range of all these indicators was [0, 1]. The larger the value, the better the predictive ability of the model.

We fitted the Adam optimizer model, minimizing the categorical cross-entropy loss function. We ran 50 training iterations (epochs), performed validation stopping and saved the model weights, which produced the lowest validation set loss. During model training, the data was divided into training and validation sets using the train_test_split() function in the Python sklearn library, with the validation set assigned a proportion of 0.3.

3. RESULTS AND DISCUSSION

Four types of experiment in which EEG signals were collected were classified by the type of face-pair stimulus used.

Experiment 1 (All): Subjects were stimulated by all three types of face pairs (480 trials for each subject);
Experiment 2 (Fcue): Subjects were only stimulated by fear-neutral face pairs (160 trials for each subject);
Experiment 3 (Scue): Subjects were only stimulated by sad-neutral face pairs (160 trials for each subject);
Experiment 4 (Hcue): Subjects were only stimulated by happy-neutral face pairs (160 trials for each subject).

3.1. Recognition Scores for End-to-End Recognition of Depression

Figure 4 lists the average values of the five metrics (accuracy, F1 score, recall, precision, and kappa) for the four sets of experiments. With the preprocessed signal used as input, the highest average classification accuracy (90.98%) obtained by LOSOCV was for Experiment 4. Similarly, the values of the other four indicators (F1 score: 90.83%; recall: 91.27%; precision: 90.59%; kappa: 81.68%) were all highest in Experiment 4 (i.e., Hcue trials). The scores from the experiments using the fear-neutral and sad-neutral face pairs were similar, with both being significantly lower than for the Hcue trials. Therefore, happy-neutral face pairs can be used as emotion-evoking materials to effectively discriminate between MDD patients and HCs. However, all the recognition scores in Experiment 1 were low, indicating that brainwaves may depend on the type of stimulus, misleading the network model and thus failing to distinguish depression from normal.

3.2. Accuracy of Experimental Results for Each Subject

In order to analyze the performance of the model, the accuracy of the four types of experiment is shown for each subject

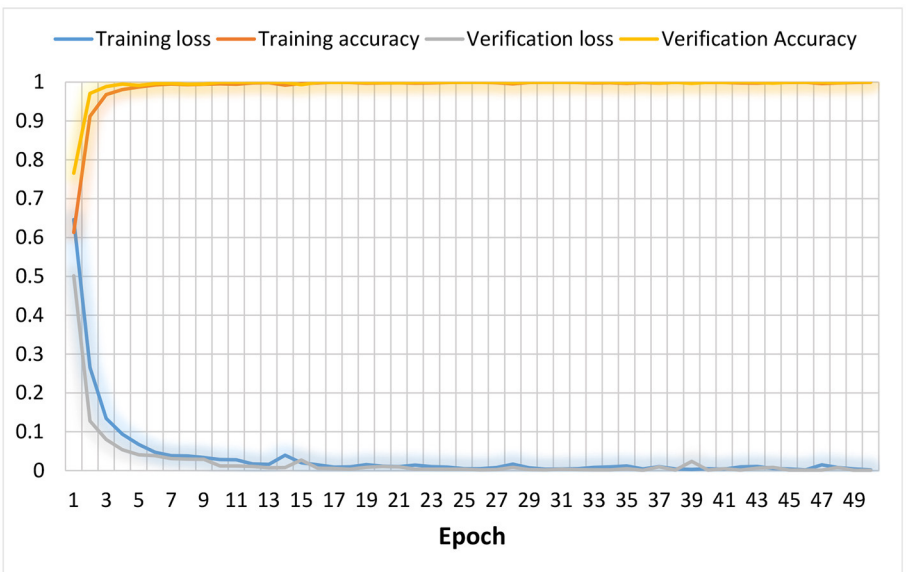

FIGURE 7 | Model optimization curve.

in **Figure 5**. The first 24 subjects in the figure experienced MDD, and subjects 25–53 were HCs. The scatter plot shows the distribution of the four experimental results. Among the MDD subjects, the correct rate for the first seven subjects was relatively low and, except for one experiment, those for subjects 8–24 were above 70%. The results show that recognition was better for HCs than for MDD subjects, and that Experiment 4 (Hcue) elicited results that were better than for the other experiments.

3.3. Confusion Matrix

Figure 6 shows that the highest recognition rate for the confusion matrix (95.37%) was that for HCs from Experiment 3. The highest recognition rate for MDD patients was 86.48% from Experiment 4. Differences in the number of MDD and HC subjects in the database (depressed: 24; normal: 29) and the small number of categories in this model may account for poor learning in some experiments and slightly different recognition rates.

3.4. Model Optimization

The model used the Adam optimizer, cross-entropy loss function, and 30% of the training set as the validation set. The results of 50 iterations of training are shown in **Figure 7**. It can be seen from the figure that the training loss dropped rapidly within 5 rounds, and nearly reached a minimum after 18 rounds. The validation loss had the same downward trend as the training loss, and it also quickly approached a minimum, indicating that the model was optimizing quickly. The training and verification accuracy rates rose to 100% in the tenth round, which shows that the model had a strong learning ability. The model had a high recognition rate when the epoch was very small, indicating that it can learn the discriminative characteristics of depression very well. This performance may have been related to the small size of the database.

3.5. Comparison With Existing Methods

Due to differences in methodology, datasets, and data usage strategies, it is difficult to fully assess the advantages and disadvantages of various methods based entirely on classification accuracy. However, by comparing indicators such as accuracy, the advantages and disadvantages of various methods can at least be partially evaluated. **Table 3** compares the existing state-of-the-art methods with our method in terms of the number of subjects, type and number of channels, research method, number of features, and classification accuracy. Compared to other methods, our method has great advantages. Compared to the other methods, ours has several advantages. First of all, it should be recognized that feature-level fusion (26), multi-variate pattern analysis (27), Case-Based Reasoning Model (29), KNN (31) and our method all have class imbalances (i.e., the difference in the number of subjects between MDD and HC is greater than 1), but nevertheless our method has the highest accuracy. Class imbalances cause models to learn well for a large number of categories but poorly for a small number of categories. Secondly, since depression is classified according to the subject, LOSOCV is more suitable than 10-fold cross-validation, and can ensure that data from the same subject are clustered together. Ten-fold cross-validation may cause data from the same subject to be part of both the training and test sets, which will mislead the classifier to identify the subject itself rather than depression. Therefore, based on this analysis of data balance and test protocol, Brain function networks (33) has the best recognition performance, but our method is only 1.75% less accurate than multi-modal fusion (28). Furthermore, our method need not extract handcrafted features or ensure that the samples are balanced.

4. CONCLUSION

This article proposes an MDD deep learning diagnostic framework for depression recognition. Based on the framework, the EEG signals evoked by happy-neutral face pairs were

TABLE 3 | Comprehensive comparison of existing state-of-the-art methods with proposed method.

Method	Subject (MDD,HC)	Channel	Feature	Protocol	Accuracy (%)
Feature-level fusion (26)	(86, 92)	EEG (3)	60 linear and 36 nonlinear features	Ten-fold CV	86.98
Multivariate pattern analysis (27)	(27, 28)	EEG (128)	249 EEG features	LOSOCV	92.73
Multimodal fusion (28)	(81,89)	EEG (3) and voice(1)	6 EEG features and 15 voice features	Nested CV	86.64
Case-Based Reasoning Model (29)	(86, 92)	EEG (3)	113 EEG features	Ten-fold CV	91.25
SVM (30)	(20, 19)	EEG (64)	3 potential biomarker	Ten-fold CV	89.7
KNN (31)	(92, 121)	EEG (3)	270 features	Ten-fold CV	79.27
Independent component analysis (32)	(13, 13)	EEG (64)	-	-	-
Brain Function Networks (33)	(24, 24)	EEG (64)	LC-CC in theta band	Ten-fold CV	93.31
Correlated Feature Selection (23)	(17, 17)	EEG (128)	10 EEG features	LOSOCV	88.94
Ours	(24, 29)	EEG (128)	-	LOSOCV	90.98

CV, Cross-Validation; LOSOC, Leave-One-Subject-Out Cross-Validation;MDD, Major Depression Disorder; HC, Healthy Control.

the most discriminative for accurate classification. The method performs well in automatically diagnosing MDD based on EEG signals. The proposed framework makes it possible to directly feed EEG signals into EEGNet for training to improve recognition of MDD in patients. In addition, the method may be of value to the medical device industry for developing diagnostic systems for MDD. Future research will focus on EEG classification of different degrees of depression, and development of a plug-and-play deep learning network to automatic classify the severity of depression.

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 author/s.

ETHICS STATEMENT

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

BL and HC: conceptualization. HC: methodology and resources and data curation. XW: formal analysis and investigation. BL: writing—original draft preparation. KP and XW: writing—review and editing and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Depression Assessment Method: An EEG Emotion Recognition Framework Based on Spatiotemporal Neural Network

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The main characteristic of depression is emotional dysfunction, manifested by increased levels of negative emotions and decreased levels of positive emotions. Therefore, accurate emotion recognition is an effective way to assess depression. Among the various signals used for emotion recognition, electroencephalogram (EEG) signal has attracted widespread attention due to its multiple advantages, such as rich spatiotemporal information in multi-channel EEG signals. First, we use filtering and Euclidean alignment for data preprocessing. In the feature extraction, we use short-time Fourier transform and Hilbert–Huang transform to extract time-frequency features, and convolutional neural networks to extract spatial features. Finally, bi-directional long short-term memory explored the timing relationship. Before performing the convolution operation, according to the unique topology of the EEG channel, the EEG features are converted into 3D tensors. This study has achieved good results on two emotion databases: SEED and Emotional BCI of 2020 WORLD ROBOT COMPETITION. We applied this method to the recognition of depression based on EEG and achieved a recognition rate of more than 70% under the five-fold cross-validation. In addition, the subject-independent protocol on SEED data has achieved a state-of-the-art recognition rate, which exceeds the existing research methods. We propose a novel EEG emotion recognition framework for depression detection, which provides a robust algorithm for real-time clinical depression detection based on EEG.

Keywords: depression, emotion recognition, electroencephalogram (EEG), convolutional neural network (CNN), long-short term memory network (LSTM)

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1. INTRODUCTION

The recognition of emotion is a major research direction of affective computing, which had been widely used to detect depression (1, 2). Emotion is crucial to the quality and scope of human daily experience (3). With the development of the brain–computer interface (BCI) and the advancement of artificial intelligence, the recognition of emotions based on EEG signals has become an active research topic of emotion recognition. EEG signals contain a large amount of information related to emotions and have the characteristics of high time resolution, and are not effortless to disguise (4–6), which

shows tremendous advantages in the field of real-time emotion recognition. Accurate and real-time judgment of human emotional state through some technical means has great application value in many areas, for example, driving fatigue detection (7), depression monitoring (8), and real-time monitoring of critically ill patients (9).

The relationship between EEG and emotion has been reported in past studies. Brain regions implicated in emotional experience include the orbitofrontal cortex, insular cortex, and anterior and posterior cingulate cortices. The amygdala is involved in linking perception with automatic emotional responses and memory (3). The activation of the amygdala seemed to be more related to negative emotions, and the relative activation of the right frontal lobe correlated with negative emotions (such as fear or disgust) (10). Precisely, fear corresponds to the amygdala (11), anger is related to the orbitofrontal cortex and anterior cingulate cortex (12), sadness occurs in the amygdala and right temporal pole (13), and disgust is produced in the anterior insula and anterior cingulate cortex (14). In addition, the power of the alpha band and the asymmetry between the cerebral hemispheres relates to emotions (15–17), the changes in the gamma band connects with happiness and sadness, and the reduction of alpha waves on different sides of the temporal lobe correlates with joy and sorrow (left side is sad, happy on the right) (18, 19).

Extracting emotion-related features to make larger the distance between classes and smaller the distance within classes is helpful to solving cross-database problems. Emotion-related EEG signal feature extraction methods include time domain [such as Hjorth extraction activity, mobility and complexity of EEG signals (20), higher-order crossover features used to describe the oscillation mode of a time series (21) and magnitude squared coherence estimate (22)], frequency domain [such as power spectral density features (23, 24)], time-frequency domain [such as time-frequency spectrum [TFS] features (25)], auto-regressive (26), asymmetric spatial pattern (27), entropy [such as differential entropy (7), sample entropy (28) and approximate entropy (29)], maximum relevance minimum redundancy method (30), common spatial patterns (31), filter bank common spatial pattern (32), higuchi fractal dimension (33), and so on. Regarding EEG feature types, all frequency bands or some frequency bands of delta, theta, alpha, beta, and gamma are mainly utilized (34). These features characterize the signal from different aspects, so a variety of effective features extracted from the signal can be better classified.

To train an excellent model, the user usually needs to collect enough marker data for calibration. This calibration process is typically time-consuming and laborious, which is a significant problem of practical use in emotional brain computer interface. Therefore, reducing or even eliminating the calibration process and realizing Plug-and-Play is a critical challenge for the brain–computer interface from the laboratory to real life. Transfer learning is a crucial technology that can solve this problem by using annotation data from other auxiliary users to help new users build models (35). However, due to individual differences, i.e., different users have different neural responses to the same event, such that need first to perform data distribution adaptation to alleviate the individual differences of EEG features. (36). To this end, in this paper we propose an unsupervised distributed adaptation method to align data between different users, that is, Euclidean alignment (EA) (37).

To improve EEG emotion recognition performance, performing deep neural networks to learn higher-level features would be useful to achieve good results, such as deep belief networks (7), recurrent neural networks (38), graph convolutional neural networks (39), transfer learning (40), and adversarial neural networks (41). Nevertheless, the recognition performance is limited to subject-dependent and cross-subject experiments under the same database, which is still far from realizing a practical emotional brain–computer interface. For this reason, we investigate an interesting and challenging problem in EEG emotion recognition, where training samples and test samples come from different emotional EEG databases. The preliminary research on EEG emotion recognition across data sets have demonstrated the significant drop of the recognition performance because of the inconsistency of feature distribution between the original training samples and test samples (42). Consequently, in this paper we will take advantages of the powerful high-level feature learning ability of deep learning technique to deal with the cross-database EEG emotion recognition problem.

The major contributions of this paper are summarized as follows:

(1) This paper proposes a novel recognition framework on the emotional EEG database, from raw data to recognition results, including preprocessing, feature engineering, classification recognition, and cross-database evaluation protocol.
(2) In feature engineering, we designed a time-frequency-spatial feature extraction method, combining forms of TFS, CNN, and bidirectional long and short memory network (BiLSTM) to extract multi-dimensional effectual features.
(3) Employing an unsupervised data alignment method to project data from different databases into the same space. While considering the inherent topological structure of the EEG electrodes, the preliminary TFS features are converted into three-dimensional tensors, which takes into account the information relationship between the electrodes.

This paper is organized as follows. Section 2 introduces emotion database, data processing methods, and experimental settings. Section 3 specifies the test results on the emotion database and the test results applied to the recognition of depression. Section 4 discusses the methods and results of this research. We conclude the paper in Section 5.

2. MATERIALS AND METHODS

As shown in **Figure 1**, this section mainly introduces emotion database and the algorithms of preprocessing engineering and feature engineering, including filtering, downsampling, EA, short-time Fourier transform, Hilbert–Huang transform (HHT), conversion of 1D sequence to 3D tensor, and the spatiotemporal

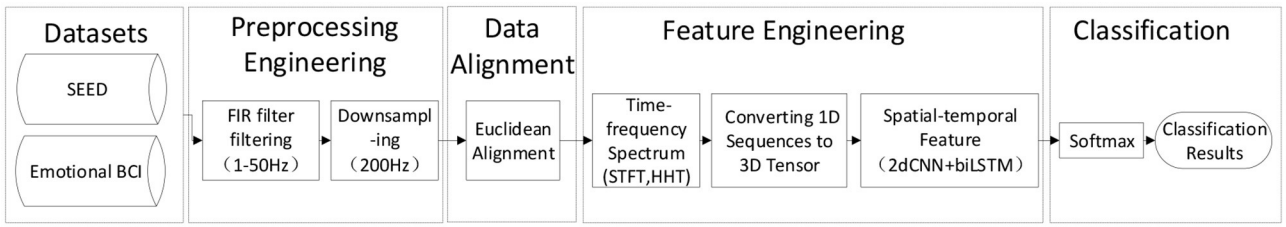


FIGURE 1 | Cross-database emotion recognition framework based on electroencephalogram (EEG) signals. Emotional BCI Competition Database is the training set of the Emotional BCI in 2020WORLDROBOT COMPETITION-BCI CONTROL BRAIN ROBOT CONTEST Emotional BCI in 2020 WORLD ROBOT COMPETITION-BCI CONTROL BRAIN ROBOT CONTEST.

TABLE 1 | Details of the two experimental databases.

	SEED	Emotional BCI Competition Database
Category	Positive, neutral, negative	happy, sad, neutral
Channel	62	62
Subject	15	23
Session	3	2
Positive	49,680	49,110
Neutral	52,650	50,722
Negative	50,400	56,694
Sum	152,730	156,526

feature extraction model combined with convolutional neural network (CNN) and BiLSTM.

2.1. Emotion Database

One of the databases used in this study is SEED (43). This database includes 15 subjects, three sessions for each subject and three emotion categories under video stimulation (i.e., positive, neutral and negative). The data were downsampled to 200 Hz. A bandpass frequency filter from 0 to 75 Hz was applied. The data are cut into one sample per second, with a total of 152,730. The other database comes from the training set of the Emotional BCI in 2020 WORLD ROBOT COMPETITION—BCI CONTROL BRAIN ROBOT CONTEST Emotional BCI in 2020 WORLD ROBOT COMPETITION—BCI CONTROL BRAIN ROBOT CONTEST (Emotional BCI Competition Database), which includes 23 subjects, two sessions (from A and B, respectively), and three emotion categories under video stimulation (i.e., happy, sad, and neutral). The data samples rate of the Emotional BCI Competition Database is 100 Hz. The EEG signals are segmented in seconds and hence results in a total of 156,520 samples. Details of the two databases are shown in **Table 1**. It can be seen from the table that the two databases have differences in categories, subjects, sessions, and the number of samples. In the subsequent processing, the three categories of happy, sad, and neutral in the emotional BCI database correspond to the positive, negative, and neutral emotion, respectively.

2.2. Preprocessing Engineering

EEG recordings measured by the scalp often contain noise and artifacts, such as blinking or movement, and cannot accurately represent signals from the brain. Therefore, it is necessary to preprocess the recorded EEG data. The preprocessing steps include converting or organizing the recorded EEG data, removing insufficient data, and segmenting the continuous original signal without changing the clean data. Appropriate band-pass filtering can effectively reduce the superimposed artifacts of various sources embedded in the EEG recording. Generally, the finite impulse response (FIR) filters are a good choice because they do not distort wave phases (44). EA maps each user's EEG signal to a new space so that the difference in the second-order statistics of the average covariance matrix of the mapped users is minimized, thereby implicitly reducing the difference in the original distribution. EA implements the above mapping for each user (auxiliary user and new user). Since different users have the same average covariance matrix after mapping, they tend to be more consistent in data distribution, meaning models trained on auxiliary users can be better applied to new users.

2.3. Data Alignment

EA is easy to perform and completely unsupervised, in which the basic idea of aligning EEG from different subjects (domains) is as follows (35): for all subjects, EA first calculates the arithmetic mean of all spatial covariance matrices.

$$\overline{R} = \frac{1}{N}\sum_{n=1}^{N} X_n (X_n)^T \tag{1}$$

then performs the alignment by

$$\widetilde{X}_n = \overline{R}^{-\frac{1}{2}} X_n \tag{2}$$

where $X_n \in \mathbb{R}^{c\times t}$ is the nth EEG trial, in which c is the number of EEG channels and t is the number of samples. The aligned EEG trials are whitened, and the average spatial covariance matrix of each subject is the identity matrix (45), so the EEG test distribution of different subjects is more consistent, which is meaningful for subsequent cross-database recognition.

2.4. Time-Fequency Spectrum

The EEG signal is non-linear and non-stationary, so its statistical properties (for example, spectral density) will change greatly over time. Spectrum estimation cannot identify its time-varying spectral components and cannot perform time-frequency positioning simultaneously. Time-frequency analysis technology is capable of revealing the time-varying frequency spectrum of non-stationary EEG signals and can provide a joint time-frequency distribution (TFD) of signal power (46). This paper adopts two methods of short-time Fourier transform (STFT) (47–49) and HHT (50, 51) for time-frequency spectrum (TFS) analysis.The method of calculating TFS using STFT and HHT comes from Song et al. (25).

STFT spectrum is calculated by

$$TFS_{STFT}(t,f) = \left| \int_{-\infty}^{+\infty} w(\tau - t)x(\tau)e^{-j2\pi f\tau}\,\mathrm{d}\tau \right|^2 \quad (3)$$

where $x(t)$ is the time series and $w(\tau - t)$ is the short-time analysis window.

The Hilbert–Huang spectrum is calculated based on HHT. HHT processing non-stationary signals include three basic processes. First, the empirical mode decomposition (EMD) method is used to decompose a given signal into a number of intrinsic mode functions (IMF),

$$x(t) = \sum_{i=1}^{K} IMF_i(t) + r_K(t) \quad (4)$$

where $r_K(t)$ represents the residual of a constant or monotonic signal. These IMFs are components that meet certain conditions. Then, perform Hilbert transform on each IMF to obtain the corresponding Hilbert spectrum, that is, represent each IMF in the joint time-frequency domain. An analytic signal reconstructed by a conjugate pair (IMF and IMF_k^*) can be formulated as

$$Z_k = IMF_k(t) + jIMF_k^* = A_k(t)e^{j\theta_k(t)} \quad (5)$$

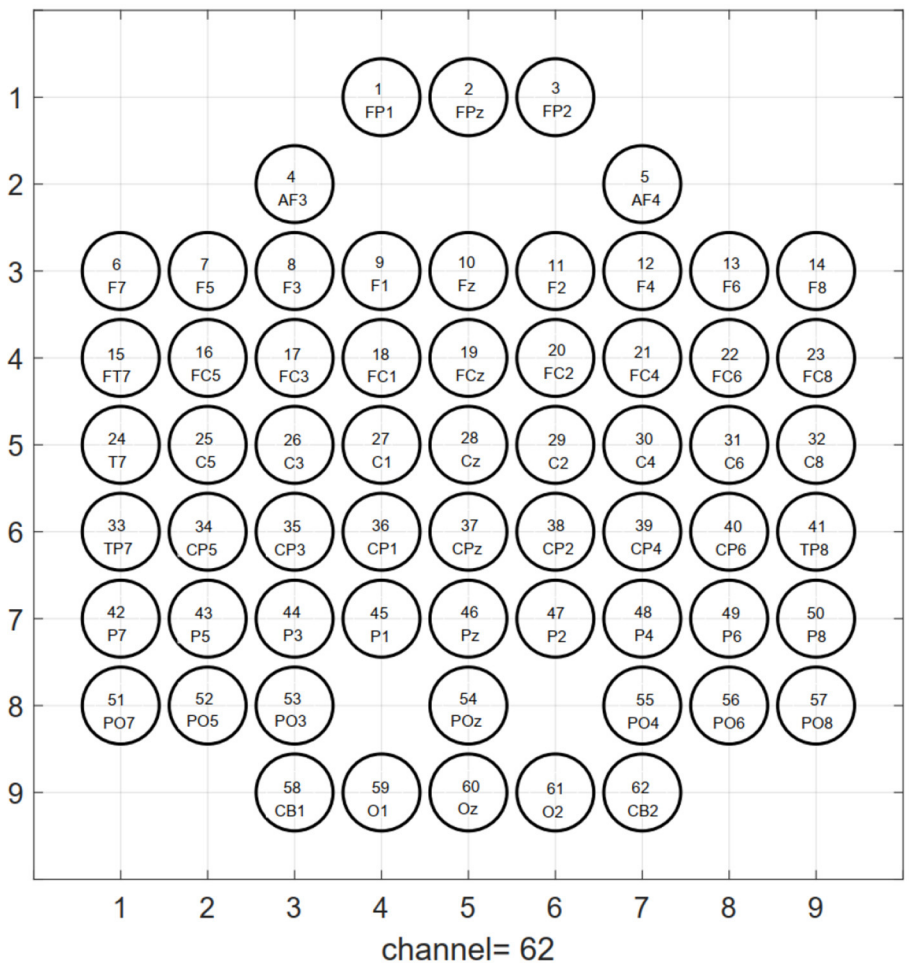


FIGURE 2 | Topological structure map of 64-electrode channels mapped to a two-dimensional picture. The circle represents the electrode, and the label inside is the serial number and name of the electrode. The left and right mastoid electrodes (M1, M2) of the 64-lead electrodes are reference electrodes when collecting signals, so they are not used as signal input for emotion recognition.

where $A_k(t)$ represents the instantaneous amplitude of $Z_k(t)$ and $\theta_k(t)$ denotes the instantaneous phase of IMFk(t). Finally, summarizing all Hilbert spectra of IMF will get the Hilbert spectra of the original signal. The original time series x(t) can be obtained by

$$x(t) = \sum_{i=1}^{K} A_k(t) e^{j2\pi \int f_k(t)\,\mathrm{d}t} \tag{6}$$

and the instantaneous frequency can be evaluated by

$$f_i(t) = \frac{1}{2\pi}\frac{d\theta_i}{dt} \tag{7}$$

where the squared amplitude $A_k^2(t)$ and instantaneous frequency $f_k(t)$ form the time-frequency spectrum.

2.5. Convert 1D Feature Sequence to 3D Tensor

Due to a large amount of noise in the EEG signal and the difficulty in capturing the unobvious relationship between the EEG signal and certain brain activities, the practical interpretation of the EEG signal is still challenging. Most of the existing studies only treat EEG as a chain sequence, ignoring the complex dependence between adjacent signals or the need to convert EEG, such as converting EEG waves into images (52).

According to the inherent topological structure of the EEG channel, as illustrated in **Figure 2**, the one-dimensional sequence data $S_t = [s_f^1, ..., s_f^c, ..., s_f^C]$ (where s_f^c is the TFS feature of the cth electrode channel at frequency f) after extracting the TFS feature is mapped into a three-dimensional tensor $T_n \in R^{H\times W\times F}$, where the first dimension H is height, the second dimension W is width, and the third dimension F is channel (i.e., the number of features extracted per channel) of the nth EEG trial. The conversion function of 1D feature sequence to 3D tensor $T_n(H, W, f)$ is,

$$T_n(H,W,f) = \begin{bmatrix} 0 & 0 & 0 & s_f^1 & s_f^2 & s_f^3 & 0 & 0 & 0 \\ 0 & 0 & s_f^4 & 0 & 0 & 0 & s_f^5 & 0 & 0 \\ s_f^6 & s_f^7 & s_f^8 & s_f^9 & s_f^{10} & s_f^{11} & s_f^{12} & s_f^{13} & s_f^{14} \\ s_f^{15} & s_f^{16} & s_f^{17} & s_f^{18} & s_f^{19} & s_f^{20} & s_f^{21} & s_f^{22} & s_f^{23} \\ s_f^{24} & s_f^{25} & s_f^{26} & s_f^{27} & s_f^{28} & s_f^{29} & s_f^{30} & s_f^{31} & s_f^{32} \\ s_f^{33} & s_f^{34} & s_f^{35} & s_f^{36} & s_f^{37} & s_f^{38} & s_f^{39} & s_f^{40} & s_f^{41} \\ s_f^{42} & s_f^{43} & s_f^{44} & s_f^{45} & s_f^{46} & s_f^{47} & s_f^{48} & s_f^{49} & s_f^{50} \\ s_f^{51} & s_f^{52} & s_f^{53} & 0 & s_f^{54} & 0 & s_f^{55} & s_f^{56} & s_f^{57} \\ 0 & 0 & s_f^{58} & s_f^{59} & s_f^{60} & s_f^{61} & s_f^{62} & 0 & 0 \end{bmatrix} \tag{8}$$

which is the **f**th channel features. Among them, the positions without electrodes were filled with zeros. Each generated data grid contains spatial information of brain activity.

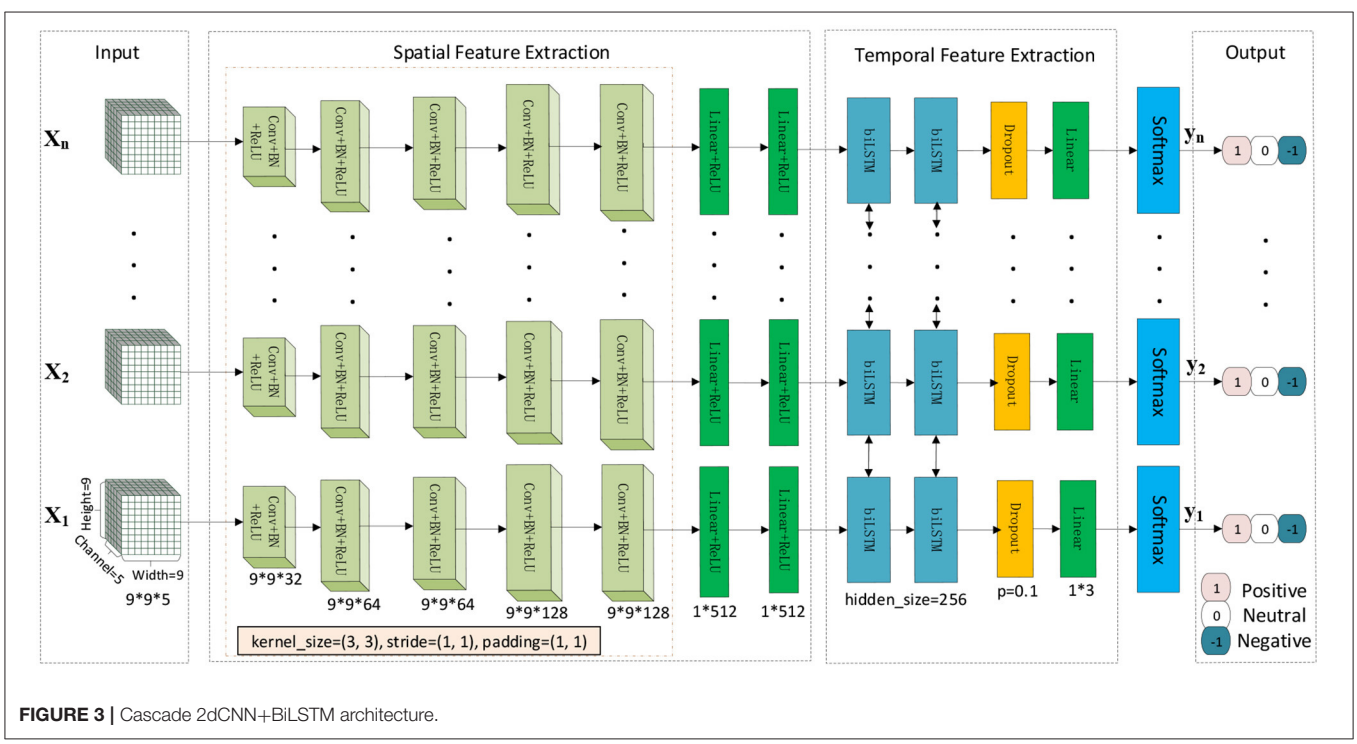


FIGURE 3 | Cascade 2dCNN+BiLSTM architecture.

2.6. 2dCNN+BiLSTM

We designed a cascaded deep convolutional recurrent neural network framework, as shown in **Figure 3**, to capture the spatiotemporal features of EEG. The model's input is the converted 3D tensor T_n that a 3D data structure containing space and time information. First, 2D CNN extracts the spatial features of each data, BiLSTM extracts temporal features, a fully connected layer receives the output of the last step of BiLSTM, and then uses the softmax layer for final emotion prediction.

This study constructed a 2dCNN+BiLSTM model to learn a good spatiotemporal representation for multi-channel EEG. The diagram for this deep spatiotemporal network is illustrated in **Figure 3**. Since each EEG segment with the duration of 1 s is treated as one sample, we conduct time-frequency spectrum feature (STFT and HHT) extraction for each sample, which was fed into the deep network for deep feature extraction. Each 1-s sample is denoted by $X_i(i = 1, 2, \ldots, n)$ and treated as a spatial image with five channels. Five convolutional layers were followed by ReLU to learn non-linear local spatial features, in which a 3 x 3 convolutional kernel was used. Following the convolutional layers, the fully connected layers were utilized to learn global spatial features. Existing studies showed that spatial features for a temporal signal are insufficient for discriminant information representation. We also employed the BiLSTM to learn temporal representation.

TABLE 2 | Recognition results on emotional database.

No.	Protocol	STFT		HHS	
	Training set → Test set	Acc(%)	F1	Acc(%)	F1
1	Emotional BCI Competition Database → SEED	83.56	0.84	83.60	0.84
2	SEED → Emotional BCI Competition Database	74.33	0.72	70.26	0.70
3	Leave-One-Subject-Out	81.58	0.80	79.29	0.77

2.7. Experimental Settings

First, we utilize the FIR filter to perform 50-order 1–50 Hz band-pass filtering on the EEG original signal, downsampling on the Emotional BCI data to 200 Hz to be consistent with the SEED data, and then perform EA. Then extract the relative energy of the five frequency bands for each electrode channel [i.e. delta (1–4 Hz), theta (4–8 Hz), alpha (8–14 Hz), beta (14–30 Hz), and gamma (30–50 Hz)] using STFT and HHS, respectively. The number of features extracted from each sample is $5 * 62 = 310$, then converted into a 3D tensor of $9 * 9 * 5$. Then feed the 3D tensor to spatiotemporal network for training, the batch size is 32, the frame length is 12 (i.e., 12 s), the epoch set to 100, the cross-entropy used as loss function, the optimizer selects SGD, the learning rate initialized to 0.005. The update calculation is $lr = init\_lr * (0.95^{epoch//10})$, where $init\_lr$ is the initial learning rate.

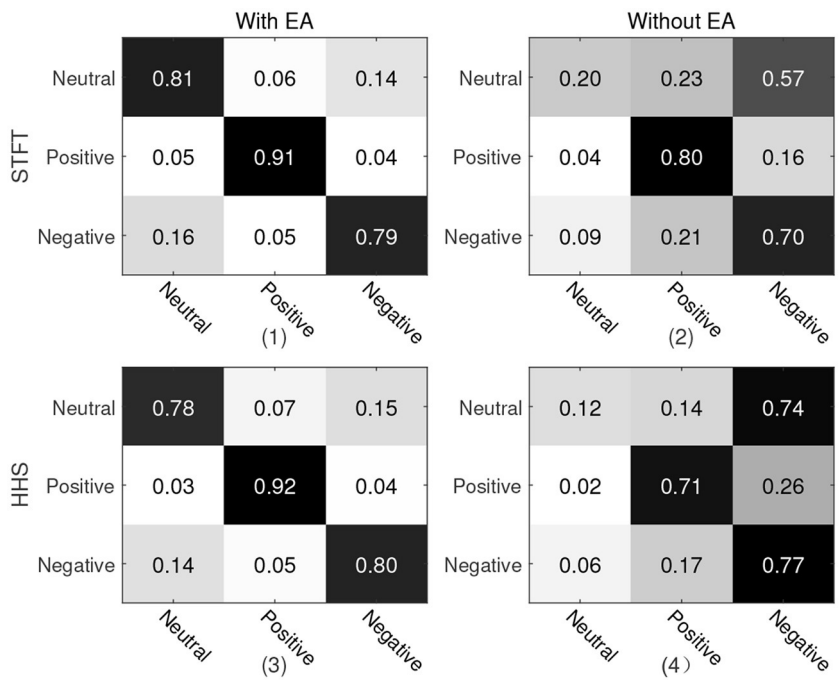


FIGURE 4 | Confusion matrix of protocol 1. The vertical axis is the true label and the horizontal axis is the predicted label. (1) and (2) are the recognition results of STFT features; (3) and (4) are the recognition results of HHS features; (1) and (3) are with Euclidean alignment (EA) module, while (2) and (4) are the recognition result without the EA module.

3. RESULTS

3.1. Emotion Recognition Results

In order to test the performance of the emotion recognition framework system built in various aspects, three protocols are proposed. In the three protocols proposed in this study, the training set and test set data are completely non-overlapping, and the test set data and labels are not used in the training process. The training set and test set of the first two protocols are from different databases. The third protocol is the leave-one-subject-out method. Considering the imbalance of the category, in addition to calculating the accuracy, the F1 score is also calculated. We applied this model to depression recognition and performed five-fold cross-validation.

For the first protocol, all data of Emotional BCI competition database are used as the training set, and all data of SEED are used as the test set. For two different manual features, the recognition accuracy and weighted average F1-score are shown in **Table 2**. It can be seen from the table that the manual feature recognition effect extracted by the STFT method is better. In order to show the true prediction of each category, the confusion matrix of the classification accuracy is analyzed. we present a confusion matrix exploiting the features of STFT and HHS shown in **Figure 4**, from which we can see that neutral emotion has the highest recognition rate among the three types of emotions, whether it is STFT or HHS features. The recognition rate of the three types of emotions under the STFT feature is higher than that of the HHS feature.

For the second protocol, all data of SEED are used as the training set, and all data of Emotional BCI Competition Database are used as the test set. For two different manual features, the recognition accuracy and weighted average F1-score are shown in **Table 2**. The recognition rate under the STFT feature is 4.07% higher than that of the HHS feature, but it is about 9% lower than the protocol 1. Similarly, we present a confusion matrix using the features of STFT and HHS shown in **Figure 5**. The recognition rate

TABLE 3 | EA ablation experiment results.

Training set → Test set	TFS	EA	Acc(%)	F1
Emotional BCI Competition Database → SEED	STFT	With EA	**83.56**	**0.84**
		Without EA	57.29	0.54
	HHS	With EA	**83.60**	**0.84**
		Without EA	53.84	0.49
SEED → Emotional BCI Competition Database	STFT	With EA	**74.33**	**0.72**
		Without EA	52.40	0.48
	HHS	With EA	**70.26**	**0.70**
		Without EA	53.46	0.53

Bold value indicate the same experimental conditions, the maximum index with or without EA comparison.

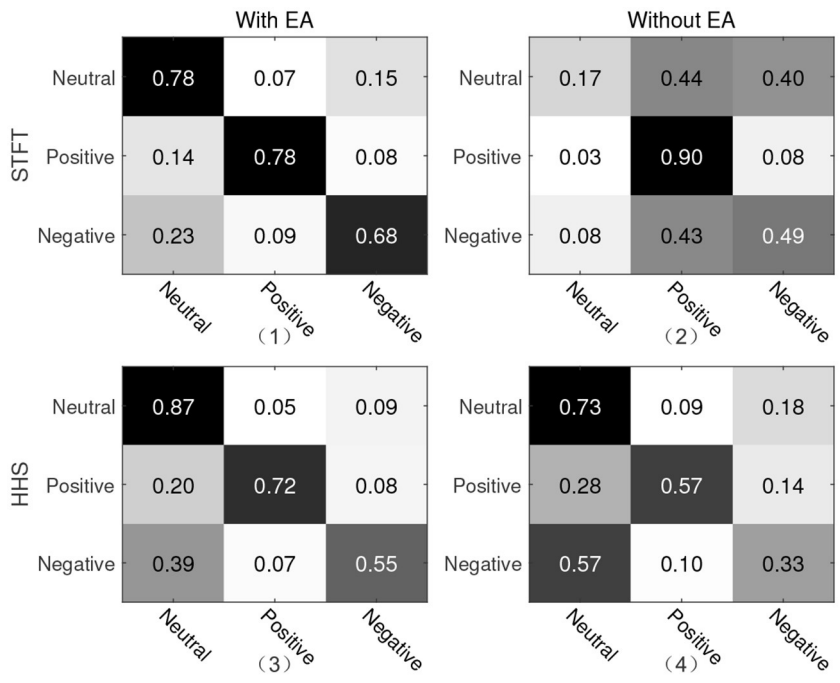


FIGURE 5 | Confusion matrix of protocol two. The vertical axis is the true label and the horizontal axis is the predicted label. (1) and (2) are the recognition results of STFT features; (3) and (4) are the recognition results of HHS features; (1) and (3) are with Euclidean alignment (EA) module, while (2) and (4) are the recognition result without the EA module.

of the three categories under the STFT feature is relatively balanced, while the recognition rate of positive emotion under the HHS feature is significantly higher than the other two categories.

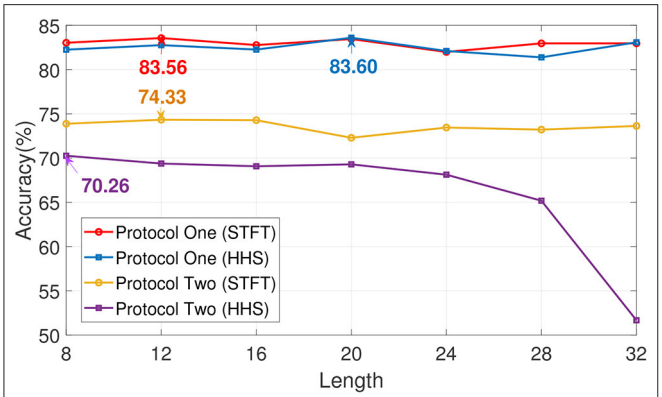


FIGURE 6 | The impact of time length selection on recognition rate. The length of time is in seconds.

For the third protocol, the recognition results of two databases are shown in **Table 2** including the accuracy and weighted average F1-score where the recognition results are sorted according to the database (i.e., the recognition results of the subjects in each database are averaged) and the average recognition rate of all subjects is calculated. It can be seen from the table that the recognition result under the STFT feature is slightly higher than HHS.

In order to explore the influence of EA on experiment, an ablation experiment was performed on this module. As shown in **Figures 4**, **5** and **Table 3**, the difference between the recognition results of the EA module and the absence of the EA module is very obvious, whether it is protocol 1 or 2. At the same time, in order to explore the timing relationship between EEG emotional frames, the frame length is selected from 8 to 32, and the step size is 4 during training. Experiments were carried out on protocols one and two, and the experimental results are shown in **Figure 6**.

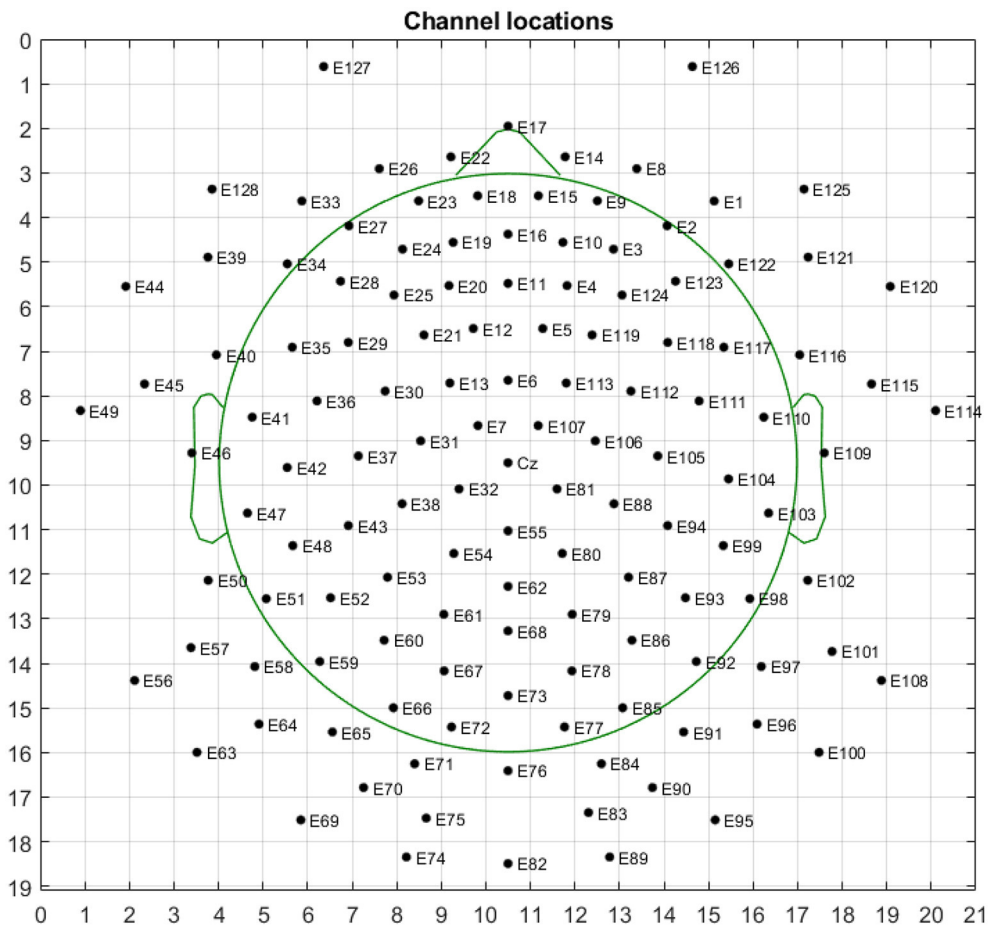
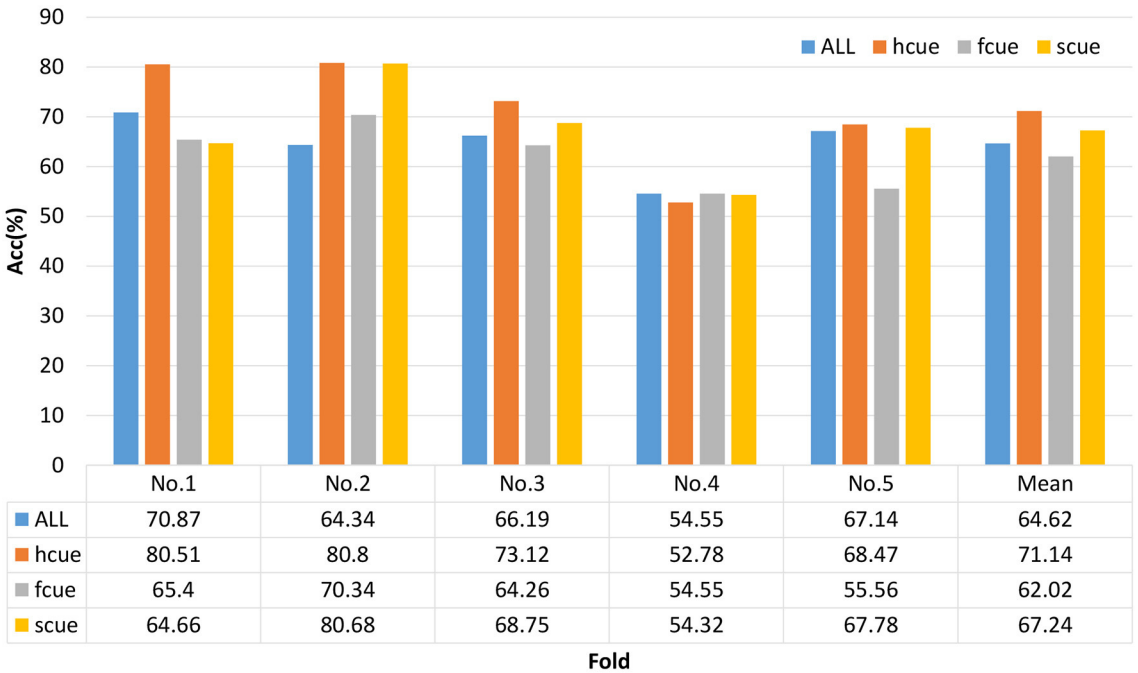


FIGURE 7 | Topological structure map of 128-electrode channels mapped to a two-dimensional picture. The circle represents the electrode, and the label inside is the serial number and name of the electrode.

3.2. Depression Recognition Results

We chose a multi-modal open dataset for depression recognition, i.e., the MODMA dataset. The dataset includes 128-channel event-related potential recordings, of which 24 major depressive disorder subjects and 29 healthy controls, the age range is 16–52 years old (53–55). Since the number of electrodes in the database is 128 and the topology is shown in **Figure 7**, the size of the three-dimensional matrix mapped to it is 21*19*5. Note that 53 subjects, including 24 outpatients and 29 healthy controls, were divided into fivefold. Due to uneven data, the first three folds made up of 5 depressed and 6 normal subjects of each one, and the last fold included 4 depressed and 5 normal subjects. The recognition result of each fold is shown in **Figure 8**. The ERP experiment is a dot-probe task, and its cue stimuli include three kinds of emotional-neutral face pairs, namely Happy-Neutral ("hcue"), Fear-Neutral ("fcue"), and Sad-Neutral ("scue"). Therefore, we not only tested all the experiments but also identified depressed patients and normal subjects on



	No.1	No.2	No.3	No.4	No.5	Mean
ALL	70.87	64.34	66.19	54.55	67.14	64.62
hcue	80.51	80.8	73.12	52.78	68.47	71.14
fcue	65.4	70.34	64.26	54.55	55.56	62.02
scue	64.66	80.68	68.75	54.32	67.78	67.24

FIGURE 8 | Recognition results of spatiotemporal neural network on depression database.

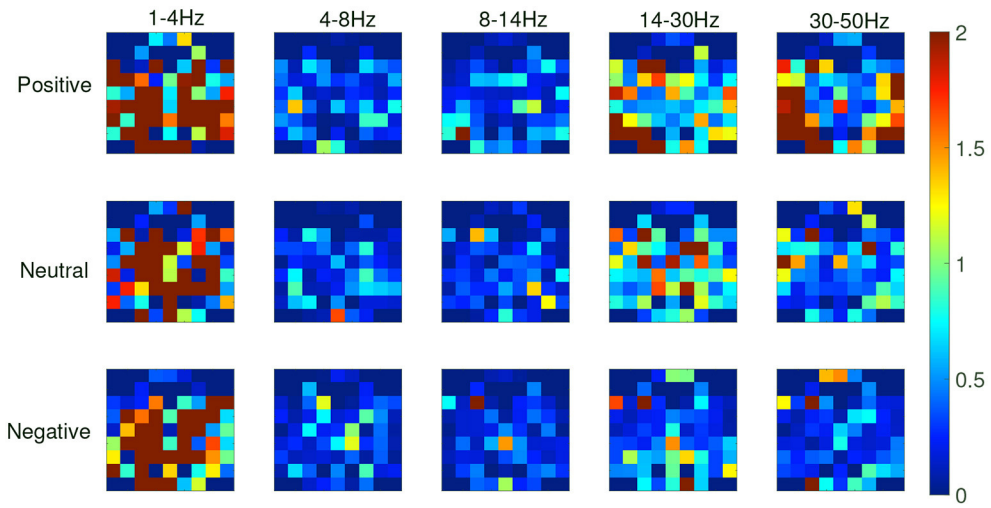


FIGURE 9 | The time-frequency spectrum (TFS) characteristic relative energy map (based on the short-time Fourier transform [STFT] algorithm) corresponds to the electrode arrangement in **Figure 2**.

different stimuli. Among them, the overall recognition rate on "hcue" is the highest, reaching 71.14%.

4. DISCUSSION

This paper proposes a complete pipeline from preprocessing to EEG-based emotion recognition, with a recognition rate of over 80%. The preprocessing part follows with the unsupervised EA method to map the data of different databases to the same space, where STFT, CNN, and BiLSTM are combined to extract multi-domain features in the time-frequency space. Before the CNN operation, according to the spatial arrangement of the EEG electrodes, the one-dimensional time series feature is converted into a three-dimensional tensor, such that the correlation between EEG electrodes can be fully considered. Moreover, we use 2D CNN to extract spatial features, and BiLSTM to capture the timing relationship of features.

It can be seen from the confusion matrix of protocol 1 that the recognition rates of the three categories under the two methods of STFT and HHS are relatively balanced, and the positive emotion recognition rate is the highest. The neutral emotion recognition rate under the HHS method of protocol 2 is the highest, and the negative emotion recognition rate is the lowest. There is a 9% difference between the accuracy of protocols 1 and 2. Since the three categories of data in the Emotional BCI database are more diversified (the first 15 people and the bottom eight people in the three categories of the Emotional BCI database in **Table 1** are different).

From the recognition results of all protocols, the accuracy and F1 score of the TFS features extracted by STFT are higher than those of the HHS method. **Figure 9** shows the STFT method and **Figure 10** shows the HHS method. The three categories are displayed in five frequency bands, and each spectrum is shown per the electrode arrangement in **Figure 2**. The features extracted by the two methods are pretty different in the high-frequency range. The relative energy of the two frequency bands, beta (14–30 Hz) and gamma (30–50 Hz), under the STFT method, is relatively high, and the three categories have apparent differences. In contrast, the HHS method has relatively high positive and neutral relative energies in these two frequency bands. Negative emotions have always been low energy in the entire frequency band. Hence, the recognition rate of the HHS method is lower than that of STFT, and it performs well in positive and negative emotions.

To further validate the proposed method, we compared our model with the start-of-the-art methods. **Table 4** presents a summary of the current subject-independent recognition algorithms on the SEED database, including linear support vector machine (SVM) (56), kernel principal component analysis (KPCA) (57), transfer component analysis (TCA) (58), transductive parameter transfer (TPT) (59), domain adversarial neural network (DANN) (60), dynamical graph convolutional neural network (DGCNN) (39), bi-hemispheres domain adversarial neural network (BiDANN) (61), BiDANN-S (41), hierarchical spatial-temporal neural network (R2G-STNN) (62), and instance-adaptive graph (IAG) (63). It can be seen

TABLE 4 | The mean accuracies (Acc) and standard deviations (Std) on SEED dataset for subject-independent EEG emotion recognition experiment.

Method	Acc/Std(%)
SVM (56)	56.73/16.29
KPCA (57)	61.28/14.62
TCA (58)	63.64/14.88
TPT (59)	76.31/15.89
DANN (60)	75.08/11.18
DGCNN (39)	79.95/09.02
BiDANN (61)	83.28/09.60
BiDANN-S (41)	84.14/06.87
R2G-STNN (62)	84.16/07.63
IAG (63)	86.30/06.91
ours	**86.42/05.26**

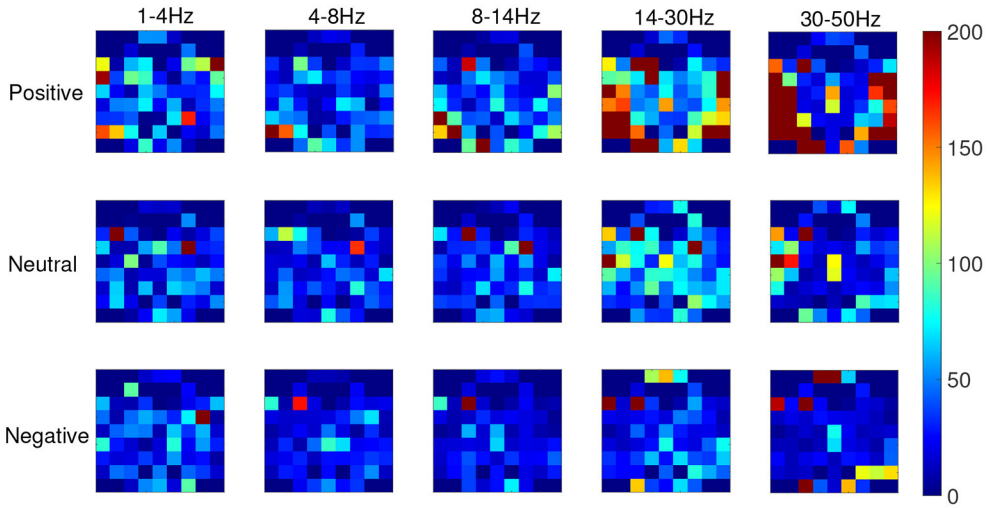


FIGURE 10 | The time-frequency spectrum (TFS) characteristic relative energy map (based on the HHS algorithm) corresponds to the electrode arrangement in **Figure 2**.

from the table that our method has achieved the highest accuracy and the smallest standard deviation. Unlike these methods, our training set adds the Emotional BCI database. The training set's increase makes the training model's generalization better, proving that the proposed method can effectively extract spatiotemporal multi-view features and classify emotions well across databases or subjects.

5. CONCLUSIONS

This study designed a complete pipeline from preprocessing to the classification of emotion recognition based on EEG, which achieved a correct rate of more than 80%. It is significant that we apply this model to the recognition of depression based on EEG signals. The preprocessing combined with the unsupervised EA method maps the data of different databases to the same space. The three methods of STFT, CNN, and BiLSTM are combined to extract the time-frequency-space multi-domain features. Before the CNN operation, the one-dimensional time series feature was converted into a three-dimensional tensor according to the spatial arrangement of the EEG electrodes. In the future, we will study end-to-end real-time emotional brain–computer interfaces for depression recognition.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://bcmi.sjtu.edu.cn/∼seed/index.html; http://modma.lzu.edu.cn/data/application/#data_1; https://oneuro.cn/n/index.html?code=d349d58c825b4041a0e53ea55b5157ae/state=#/chinabci, Emotional BCI.

AUTHOR CONTRIBUTIONS

HC and YZ: conceptualization. HC: methodology and writing and original draft preparation. WZ: formal analysis and funding acquisition. CT: investigation. JZ: resources. XL: data curation. CT and JZ: review and editing. All authors have read and agreed to the published version of the manuscript.

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Does Childhood Adversity Lead to Drug Addiction in Adulthood? A Study of Serial Mediators Based on Resilience and Depression

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Drug addiction is a common problem worldwide. Research has shown adverse childhood experiences (ACEs) to be an important factor related to drug addiction. However, there are few studies on how ACEs lead to drug addiction and the role of resilience and depression in this process. Thus, the main purposes of the study were to determine the proportion of those with adverse childhood experiences who take drugs in adulthood and how resilience and depression affect this relationship. The results showed that (1) greater severity of ACEs made individuals more likely to take drugs; (2) ACEs were positively correlated with depression, and resilience was negatively correlated with ACEs and depression; and (3) ACEs not only affected drug addiction through resilience or depression alone but also through the combined action of resilience and depression, indicating that depression led to drug addiction while resilience weakened the effect of ACEs on depression and drug addiction. Furthermore, in the serial mediation model, abuse, neglect, and family dysfunction were significant predictors of drug addiction. Our results are encouraging in that they provide guidance in understanding the complex relationships among ACEs, resilience, depression, and drug addiction.

Keywords: adverse childhood experiences, drug addiction, resilience, depression, mediating effect

INTRODUCTION

Adverse childhood experiences (ACEs) are typically defined as stressful and/or traumatic experiences that occur during childhood (1, 2). A study have shown that more than 60% of adults report having at least one adverse childhood experience, and 17% report four or more adverse childhood experiences (3). There is increasing evidence that adults with ACEs are at greater risk for diseases (e.g., alcoholism, myocardial infarction, stroke, depression, diabetes, and coronary heart disease) and disability due to health status (4–8). Moreover, ACEs are a major risk factor for drug abuse. For instance, childhood abuse is closely related to marijuana use (9, 10). Individuals with ACE scores $\geq$5 are seven to 10 times more likely to report illicit drug addiction compared to those without ACEs (11), and are four to 12 times more likely to become drug abusers (6). In short, ACEs not only affect physical and mental health but also increase the risk of drug abuse in adulthood.

Depression is one of the most common and main negative emotions induced by ACEs. Compared with other negative emotions, the impact of depression on drug addiction has more

important clinical significance. Many studies have identified a relationship between ACEs and depression, as adults with ACEs are more likely to suffer from depression compared to adults without such experiences (12–15). Emotional, sexual, and physical child abuse are the most important risks factors for depression (12). A retrospective cohort study showed that the risk of depressive disorders increased for decades after ACEs (16). Compared with adults without ACEs or those who have not experienced trauma in adulthood, individuals with ACEs (including sexual and physical abuse) are more likely to suffer from long-term PTSD and depression; simultaneously, they are more likely to take drugs, use more types of drugs, and have more serious drug dependence (17, 18). Thus, there is a noticeable relationship between ACEs and depression. Further, multiple studies have uncovered the comorbidity of depression and drug addiction; that is, depression can lead to drug addiction, and drug addiction can lead to or exacerbate depression (19–21). Drug-addicted individuals tend to express themselves negatively, and negative stimulation can aggravate their negative emotions and exacerbate drug abuse (22, 23). Avoidance of negative affect is the predominant motive for drug abuse (24).

Resilience is a dynamic process in which individuals can adaptively overcome stress and/or traumatic events (25). It is the ability to overcome life challenges with perseverance, self-awareness, and one's own internal coherence by activating a personal growth project (26). ACEs may produce negative outcomes, such as depression; however, some individuals with ACEs will bounce back rather than suffer long-term negative consequences, and they are considered to have better resilience (27). It is beneficial to help individuals establish and improve resilience and to promote mental health education interventions, which facilitate recovery from trauma and stress and mitigate the influence of ACEs on depression (28, 29).

In summary, there is a strong relationship between ACEs and drug addiction. ACEs can produce and exacerbate depression, and depression may be an important cause of drug abuse. Additionally, resilience seems to impact the relationship between ACEs, depression and drug addiction. However, how ACEs affect drug addiction directly is much less studied, and the roles of resilience and depression in drug addiction are still unclear. Therefore, this study first examined the relationship between ACEs and drug addiction and then examined resilience and depression as potential contributors of this relationship. In order to show the complicated relationship between ACEs, drug addition, depression and resilience more clearly, a graphic illustration is created in **Figure 1**.

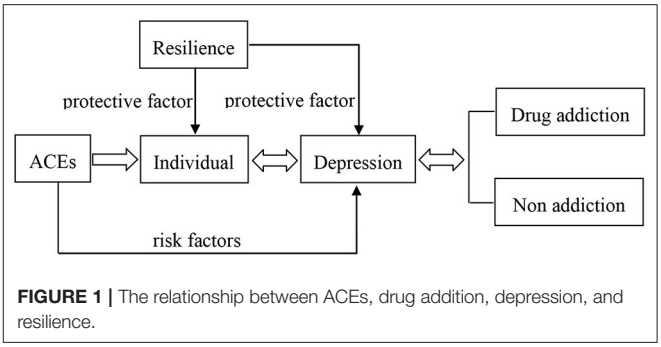

FIGURE 1 | The relationship between ACEs, drug addition, depression, and resilience.

METHODS

Participants

We used random sampling to recruit 937 participants including 459 individuals with drug addictions (252 males, 207 females) and 478 individuals without them (138 males, 340 females). Those with drug addictions were recruited from two drug rehabilitation centers in Sichuan Province, China. Approximately 70% of this group were methamphetamine addicts and the rest were heroin, Magu, and K powder addicts. Those without drug addiction were also recruited from southwest China[1].

All participants whom we recruited met the following criteria: (1) age 18–50 years, (2) no serious mental illness, and (3) educational background of elementary school or above. Moreover, participants with drug addictions met the DSM-V diagnostic criteria for psychoactive substance abuse or dependence, completing physiological detoxification and providing negative urine tests. All participants provided informed consent before beginning the study.

MEASURES

Adverse Childhood Experiences

We used the ACEs questionnaire to collect information on participants' exposure to ACEs (prior to age 18). The questionnaire consists of 28 items divided into three categories and 10 subscales, which include childhood abuse (emotional, physical, and sexual), childhood neglect (emotional and physical), and growing family dysfunction (substance abuse, mental illness, domestic violence, criminal household members, and parental marital discord). One ACE was recorded for each subscale that met the conditions of exposure to ACEs. We used the ACE scores (10 ACEs subscales; 0-10 possible ACEs) to evaluate the cumulative effect of multiple ACEs, with higher ACE scores indicating more serious exposure to ACEs (31). ACE scores can be divided into four levels according to the degree of ACE exposure: no exposure = 0 ACEs; mild = 1-2 ACEs; moderate = 3–4 ACEs; and severe ≥5 ACEs. In this study, the Cronbach's alpha value for the ACEs questionnaire was 0.629.

Connor-Davidson Resilience

We measured the resilience of participants over the past month using the Connor-Davidson Resilience Scale (CD-RISC), which consists of 25 items scored on 5-point Likert scales ranging from 1 (not at all) to 5 (almost exactly). Connor and Davidson proposed the five-factor scoring method to differentiate the five dimensions of resilience (32): F1 (personal ability, high standards, and tenacity), F2 (belief in instincts, tolerance of

[1]The sample size of this study was determined according to the research on childhood adversity increases the risk of substance (30). According to G*power, we need at least 853 sample sizes to maintain power values above 0.9. Therefore, we investigated a total of 937 samples, which was enough to infer the relationship between ACEs and drug addiction, and the power values of *post hoc* test was 0.92.

TABLE 1 | Characteristics of sample and ACE group comparisons for all variables.

	Total $N = 937$	ACE group (n)				χ^2, F (p)
		No exposure (203)	Mild exposure (396)	Moderate exposure (215)	Severe exposure (123)	
Age (M ± SD)	28.51 ± 11.10	29.43 ± 11.69	28.07 ± 11.14	28.83 ± 11.35	27.82 ± 9.34	$F = 0.89$ ($p = 0.45$)
Sex-Female (%)	547 (58.4)	142 (70.0)	235 (59.3)	113 (52.6)	57 (46.3)	$\chi^2 = 21.67$ ($p < 0.001$)
Addiction (%)	459 (48.99)	71 (40.6)	172 (47.9)	131 (64.2)	84 (70.2)	$\chi^2 = 51.66$ ($p < 0.001$)
CD-RISC (M ± SD)	83.75 ± 14.86	86.12 ± 14.84	85.31 ± 14.56	82.74 ± 14.98	79.65 ± 13.95	$F = 6.59$ ($p < 0.001$)
BDI (M ± SD)	12.62 ± 11.07	8.35 ± 8.91	10.95 ± 10.21	15.38 ± 10.81	20.20 ± 12.48	$F = 41.49$ ($p < 0.001$)

negative events, and resistance to stress), F3 (active acceptance of change and secure relationships), F4 (control), and F5 (religious influence). Higher scores indicate better resilience, and total scores range from 1 to 105. The scale's Cronbach's alpha was 0.913.

Depressive Symptoms

The Beck Depression Inventory (BDI) is a self-report questionnaire with 21 items, which we used to assess participants' degree of depression. Each item is rated from 0 to 3, yielding lowest and highest possible total scores of 0 and 63, respectively (33). Higher total scores indicate higher degrees of depression. The scale has demonstrated satisfactory test-retest reliability and internal consistency. To improve the structural equation model's fit and control the multi-item measurement error of latent variables, we used the factor balance method to package the 21 single-dimensional items into three indicators (D1, D2, D3), with each indicator containing seven items (34, 35). The BDI's Cronbach's alpha value was 0.916.

Procedures

Before starting the survey, we informed all participants that all data collected from them would remain confidential and be used for scientific research purposes only. All who met the inclusion criteria signed informed consent before voluntarily participating in the survey. Participants completed the ACEs questionnaire, CD-RISC, and BDI separately, which took them a total of 25–30 min. We collected and checked the completed questionnaires on site and distributed small gifts as compensation.

Data Analysis

We performed data preprocessing, χ2-tests, analysis of variance (ANOVA), and correlation analysis in SPSS 23.0 (χ2-tests for categorical variables and ANOVA for continuous variables). Additionally, we conducted structural equation modeling (SEM) analyses in Mplus 8.3. We used the robust weighted least squares estimation (WLSMV) extraction procedure to test the model fit to the data. The WLSMV does not assume normally distributed variables and provides the best option for modeling categorical or ordinal data (36, 37). Further, we used bias-corrected bootstrap analysis with 1,000 bootstrap samples to test the mediating effect.

We utilized an item parceling strategy to control the multi-item inflation error of the latent variables (35). Specifically, we divided the unidimensional BDI into three indicators using the factor balance method. Drug addiction was treated as a dummy variable in the mediation model. As recommended by Hu and Bentler (38), a model is considered to fit the data well if the standardized root mean square residual (SRMR) and the root mean square error of approximation (RMSEA) values are below 0.08 and the comparative fit index (CFI) and Tucker-Lewis index (TLI) values are above 0.90.

RESULTS

Sample Description

Table 1 shows the demographic characteristics of participants. ACE exposure levels of participants were as follows: no exposure (ACE score = 0; $n = 203$), mild exposure (ACE score = 1–2; $n = 396$), moderate exposure (ACE score = 3–4; $n = 215$), and severe exposure (ACE score $\geq$ 5; n = 123). There were no significant differences in the average age of participants across ACE exposure levels ($F = 0.89$, $p = 0.45$). The number of participants with drug addictions who were exposed to severe ACEs was higher than those without exposure (84 vs. 71; $p < 0.001$). Additionally, CD-RISC scores decreased with increased ACE exposure levels (86.12 vs. 85.31 vs. 82.74 vs. 79.65; $p < 0.01$); In contrast, higher ACE exposure levels were associated with higher BDI scores (8.35 vs. 10.95 vs. 15.38 vs. 20.20; $p < 0.001$).

CORRELATIONAL RESULTS

Relationship Between ACE Exposure and Drug Addiction

A bar chart (**Figure 2**) was used to show the proportion of drug users reporting different ACE exposure levels. We designated the degree of ACE exposure as the abscissa and the rates of drug addiction and non-addiction as the ordinate, as shown in **Figure 2**. With increased ACE exposure levels, the rate of drug addiction also increased, which indicated that the more serious

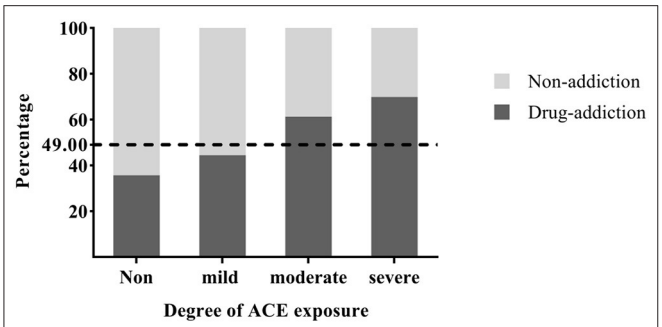

FIGURE 2 | Proportions of drug users with different ACE exposure levels. The dotted line represented the proportion of participants with drug addiction in all.

TABLE 2 | Correlations among ACEs, resilience, and depression.

	1	2	3	4	5	6
1. ACEs	-					
2. Childhood Abuse	0.74**	-				
3. Childhood Neglect	0.59**	0.27*	-			
4. Family Dysfunction	0.83**	0.35**	0.25**	-		
5. Resilience	−0.15**	−0.07*	−0.21**	−0.09**	-	
6. BDI	0.35**	0.28**	0.22**	0.27**	−0.26*	-

*$p < 0.05$, **$p < 0.01$.

ACEs participants suffered, the more likely they were to take drugs. Similarly, higher ACE exposure levels were associated with lower rates of non-addiction.

Correlational Analysis

There were significant correlations among all variables (**Table 2**). ACEs (childhood abuse, childhood neglect, and family dysfunction) and resilience were negatively correlated. ACEs (childhood abuse, childhood neglect and family dysfunction) and BDI scores were positively correlated. Additionally, resilience was negatively correlated with BDI scores.

Confirmatory Factor Analysis

We used confirmatory factor analysis to test whether the measurement model adequately fit the sample data. Two latent variables were included in the full model (resilience and depression) along with eight observed variables. Results showed that the measurement model fit the data well ($\chi 2$ (19) = 64.181, CFI = 0.989, TLI = 0.984, RMSEA = 0.050, SRMR = 0.024). All factor loadings were significant ($p < 0.001$), indicating that the structural equation model could be used in the next step of the analysis.

Common Method Bias Test

The questionnaires used in our survey were self-report, so we also conducted principal components analysis with all questionnaire items (i.e., a common method bias test). Based on the Harman single-factor method, we contend that common method bias was negligible because the variance of the maximum factor interpretation was 16.185, which is less than 40% (39).

Structural Equation Model

First, we found that the direct effect of the predictor (ACEs) on the dependent variable (drug addiction) in the model without mediators was significant (β = 0.288, $p < 0.001$, 95% CI = 0.207 to 0.366). Next, we built Model 1 and Model 2 with resilience (M1) and depression (M2) as the respective mediators. The bias-corrected bootstrap analyses (1,000 samples) showed that both mediating effects were significant (**Figure 3**).

Based on the single-factor mediation model results, we established a serial mediation model with resilience and depression as the serial mediators (**Figure 3C**). This structural equation model fit the data well, $\chi^2(31) = 166.199$, CFI = 0.938, TLI = 0.909, RMSEA = 0.068, SRMR = 0.039. In the serial mediation model, ACEs were negatively associated with resilience (β = −0.167, $p < 0.001$, 95% CI = −0.234 to −0.098) and positively associated with BDI scores (β = 0.325, $p < 0.001$, 95% CI = 0.252 to 0.388) and drug addiction (β = 0.108, $p < 0.001$, 95% CI = 0.018 to 0.193); resilience was negatively associated with BDI scores (β = −0.248, $p < 0.001$, 95% CI = 0.367 to 0.527) and drug addiction (β = −0.102, $p = 0.016$); and BDI was positively associated with drug addiction (β = 0.442, $p < 0.001$). As presented in **Table 3**, the indirect effect of resilience and depression as serial mediators in the relationship between ACEs and drug addiction was significant (β = −0.010, $p < 0.001$, 95% CI = 0.005 to 0.016). Moreover, the mediating effects of resilience (β = 0.009, $p < 0.001$, 95% CI = 0.002 to 0.019) and depression (β = 0.078, $p < 0.001$, 95% CI = 0.057 to 0.100) were also significant.

As ACEs included three subcategories (childhood abuse, childhood neglect, and household dysfunction), we built additional serial mediation models accordingly (Models 4–6). Results showed acceptable fit for these three models (CFI = 0.916 to 0.922, TLI = 0.887 to 0.900, RMSEA = 0.056 to 0.068, SRMR = 0.039 to 0.055). Further, the indirect effect of resilience and depression as serial mediators in the relationship between the subcategories of ACEs (childhood abuse, childhood neglect, and family dysfunction) and drug addiction were all significant (β = 0.011 to 0.046, $p < 0.001$). Specifically, the mediating effect of resilience was significant only when childhood neglect was the predictor ($p = 0.019$). **Figure 4** provides further information.

DISCUSSION

Many previous studies have demonstrated the close relationship between ACEs and drug addiction (6, 9–11) and the significant comorbidity of depression and drug addiction (19–21). Our research results also support this. However, how ACEs affect drug addiction and the relationships among ACEs, depression, and drug addiction remain unclear. Therefore, we established a serial mediation model including ACEs, depression, and drug addiction to clarify their relationships (**Figure 3**). Our research showed that ACEs may not lead directly to drug use but may lead to depression, which in turn leads to drug addiction. Additionally, we showed that resilience played a

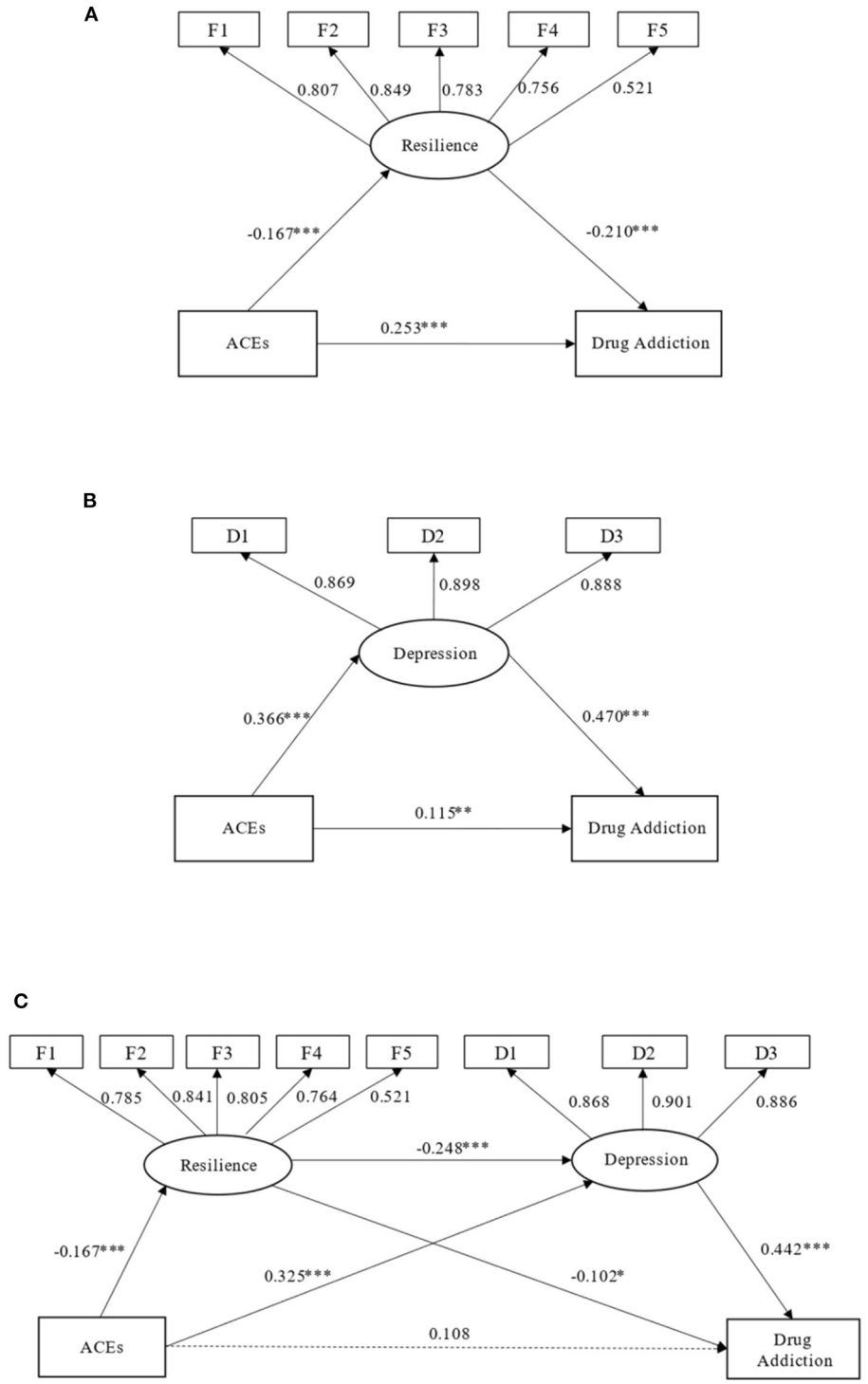

FIGURE 3 | Single-factor mediation models (Models 1 and 2) were established with resilience **(A)** or depression **(B)** as the mediator, respectively. Model 3 was established with resilience and depression as serial mediators **(C)**. Path coefficients are standardized. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

mediating role between ACEs, depression, and drug addiction (**Figure 3C**). It showed that improving the resilience levels of people can not only directly mitigate drug use, but also weaken the effect of depression on drug addiction, which provided a guidance for the clinical treatment of drug addicts patients to some extent.

TABLE 3 | Indirect effects with bootstrap 95% CIs.

Model	Pathway	Estimate	Bootstrap 95% CI	*p*
Model 1	ACEs → Resilience → Drug Addiction	0.019 (0.006)	0.009, 0.032	<0.001
Model 2	ACEs → BDI → Drug Addiction	0.093 (0.012)	0.072, 0.115	<0.001
Model 3	ACEs → Resilience → Drug Addiction	0.009 (0.004)	0.002, 0.019	0.036
	ACEs → BDI → Drug Addiction	0.078 (0.011)	0.057, 0.100	<0.001
	ACEs → Resilience → BDI → Drug Addiction	0.010 (0.003)	0.005, 0.016	0.003
Model 4	Abuse → Resilience → Drug Addiction	0.011 (0.007)	0.002, 0.029	0.101
	Abuse → BDI → Drug Addiction	0.156 (0.024)	0.112, 0.203	<0.001
	Abuse → Resilience → BDI → Drug Addiction	0.014 (0.006)	0.003, 0.027	0.022
Model 5	Neglect → Resilience → Drug Addiction	0.040 (0.017)	0.010, 0.076	0.019
	Neglect → BDI → Drug Addiction	0.137 (0.030)	0.083, 0.197	<0.001
	Neglect → Resilience → BDI → Drug Addiction	0.046 (0.011)	0.028, 0.071	<0.001
Model 6	Family dysfunction → Resilience → Drug Addiction	0.010 (0.005)	0.002, 0.023	0.061
	Family dysfunction→ BDI → Drug Addiction	0.098 (0.016)	0.068, 0.131	<0.001
	Family dysfunction → Resilience → BDI → Drug Addiction	0.011 (0.004)	0.003, 0.019	<0.001

Drug Addiction Often Associated With More Severe ACE Exposure

As shown in **Figure 2**, more serious exposure to ACEs yielded higher rates of drug addiction. This is consistent with previous research results (11). In other words, as exposure to ACEs increased, rates for non-addiction decreased significantly, which may explain why some people use drugs to alleviate the negative effects of childhood trauma to some extent. Namely, those who have suffered from severe ACEs might not have been able to address their negative consequences until adulthood (6), choosing to use drugs to reduce the stress or trauma (24).

The Negative Role of Depression in the Choice on Whether to Use Drugs

The results indicated that the direct effect of ACEs on drug addiction was not significant. However, we found a significant indirect effect in the relationship between ACEs and drug addiction in this study (**Figure 3C**). ACEs significantly affected depression, which increased the likelihood of drug use. This also supports Farrugia's results showing that individuals with ACEs were more likely to suffer from depression and to use drugs (18). Additionally, the results showed that childhood abuse, childhood neglect, and family dysfunction all significantly affected depression, in turn affecting drug use (**Figure 4**). Notably, among the three subcategories of ACEs, family dysfunction not only directly affected drug addiction but also indirectly affected drug addiction through depression (**Figure 4C**), illustrating that the substance abuse, mental illness, domestic violence, criminal household members, and parental marital discord experienced in childhood were more likely to lead to depression in adulthood. For example, parents' drug abuse increases their children's risk for major depression later in life (40). Children are more likely to have ACEs and increased risk for depression if they have alcohol-abusing parents (41). Domestic violence is strongly associated with depression, and it is an indicator of increased exposure to other forms of adversity (14).

Resilience Mitigates Drug Use

Our study found that resilience played a significant mediating role with respect to ACEs, depression, and drug addiction (**Figure 3C**). Resilience weakened the effect of ACEs on drug addiction. On the other hand, more serious exposure to ACEs led to lower resilience. Meanwhile, resilience was negatively correlated with depression. Resilience weakened the impact of ACEs on depression and then weakened the effect of depression on drug addiction. The protective role of resilience against depression has been reported previously. For instance, whether in childhood or adulthood, emotional regulation can effectively reduce the negative effects of ACEs and promote physical and mental health (42, 43). Resilience interventions can reduce the impact of ACEs (28). Further, early recognition of ACEs, teaching resilience, and health education can reduce the trauma, stress, and other behavioral and emotional consequences of ACEs (44).

Limitations and Future Directions

The results of the current study must be interpreted in light of several limitations. First, there are many factors affecting whether an individual takes drugs, and experiencing ACEs may be only one of them. Second, the potential for recall bias is inevitable when participants recall childhood experiences, which may have affected the accuracy of the results. Additionally, self-reports of ACEs are likely to lead to inconsistencies due to underreporting (45). Third, depression may be only one of many negative emotions caused by ACEs, which could make us ignore the impact of other negative outcomes of ACEs on drug addiction. Therefore, future research should explore the impact of multiple factors on drug addiction, the psychosocial mechanism of resilience and how to improve it to combat negative emotions optimally.

CONCLUSIONS

Exposure to ACEs was significantly associated with drug addiction in our study. The more serious ACE exposure

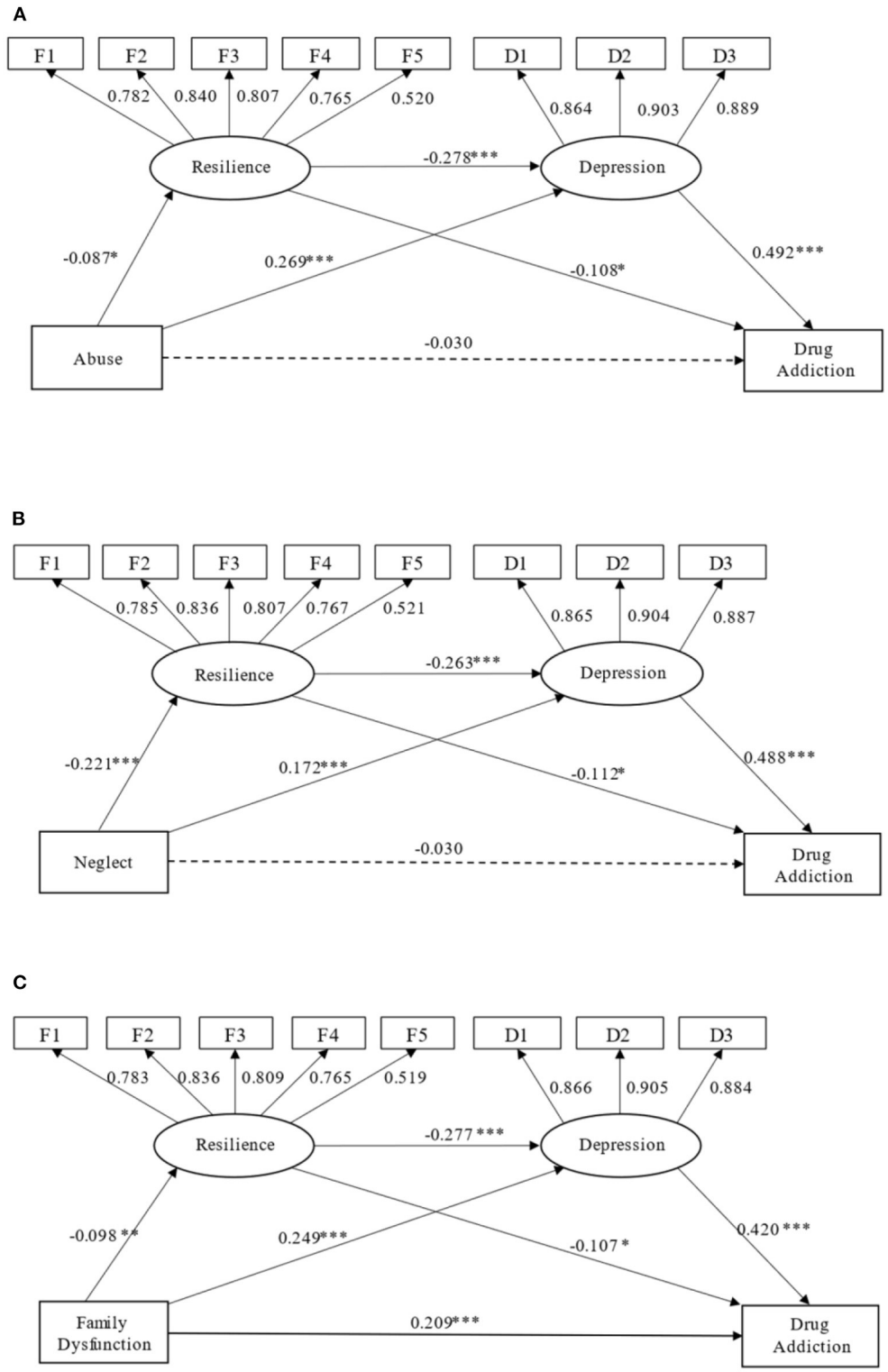

FIGURE 4 | (A–C) Serial mediation models (Models 4–6) were established with different subcategories of ACEs (childhood abuse, childhood neglect, family dysfunction) as their respective predictors. Path coefficients are standardized. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

was, the more likely it was to lead to drug addiction. ACEs affected drug addiction through depression, and there was a significant correlation between depression and drug addiction. As a protective factor, resilience reduced the effect of ACEs on drug addiction and the effect of depression on drug addiction by reducing the effect of ACEs on

depression. Therefore, we should pay more attention to the possible negative effects of ACEs, especially depression. Simultaneously, we should aim to prevent ACEs from the outset. Moreover, we should support ACE sufferers' mental health. Practitioners should provide resilience skills training for those with ACEs to improve their resilience levels and mitigate drug abuse and other negative consequences as much as possible.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

All survey processes involving human participants were reviewed and approved by the review committee of Sichuan Drug Rehabilitation Administration. All participants provided informed consent before participation.

AUTHOR CONTRIBUTIONS

RW designed research, collected data, and conceptualized the study. JH conceptualized the study, performed literature review, wrote the article, and revised the article. XY analyzed data and revised the article. JZ and JL provided resources and opinions. CZ and YZ organized investigation and data curation. All authors contributed to this manuscript and approved the submitted version.

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REVIEW
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The Relationship Between 5-Hydroxytryptamine and Its Metabolite Changes With Post-stroke Depression

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Post-stroke depression (PSD) is the most common and serious sequelae of stroke. Approximately 33% of stroke survivors were affected by PSD. However, many issues (e.g., incidence, diagnostic marker, and risk factor) related to PSD remained unclear. The "monoamine hypothesis" is a significant hypothesis for depression, which suggests that three monoamines play a key role in depression. Therefore, most current antidepressants are developed to modulate the monoamines on PSD treatment, and these antidepressants have good effects on patients with PSD. However, the potential mechanisms of three monoamines in PSD are still unclear. Previously, we proposed "three primary emotions," which suggested a new model of basic emotions based on the three monoamines. It may provide a new way for PSD treatment. In addition, recent studies have found that monoamine-related emotional intervention also showed potential effects in the treatment and prevention of PSD. This study discusses these issues and attempts to provide a prospect for future research on PSD.

Keywords: post-stroke depression, 5-Hydroxytryptamine, monoamine hypothesis, three primary emotions, emotional intervention

INTRODUCTION

Post-stroke depression (PSD) is a common and serious complication after stroke, which is often regarded as the inevitable reaction toward stroke-related disability (1). A recent meta-analysis reported that the incidence of PSD within the first 5 years after stroke ranged from 25 to 33% (2). PSD adversely affects recovery and the life quality in patients with stroke. Evidence suggests that PSD is related to a large number of adverse health outcomes, such as increased morbidity, disability, and mortality (3–5). However, as the mechanisms of PSD diagnosis are unclear, the specific critical periods for most interventions are still uncertain and most antidepressants used for PSD have been reported to have serious side effects, until present some of the patients remain untreated or not be adequately treated (6).

At present, the main therapeutic approach to PSD is essentially pharmacological (7), and the most commonly used pharmacotherapeutic agents for treating PSD are antidepressants (1). Three

monoamines, namely, dopamine (DA), 5-hydroxytryptamine (5-HT), and norepinephrine (NE), play key roles in the etiology and treatment for major depressive disorders (MDD) (8). The monoamine hypothesis assumes that depression is associated with low levels of monoamines, especially DA, 5-HT, and/or NE (8, 9). So the major antidepressants for MDD are designed to increase monoamine transmission either by inhibiting neuronal reuptake or by inhibiting degradation (8, 10).

In addition, these three monoamines might be the primary substrate for emotions (11). Previously, we have proposed the "three primary color model" of basic emotions based on the three monoamines Wang et al. (2020). In the hypothesis, we suggested that all emotions are composed of some basic emotions, such as happiness, sadness, and anger and fear, which are subsided, respectively, by the three neurotransmitters: DA (happiness), 5-HT (disgust), and NE (fear and anger) (12). Depression and other affective disorders (such as PSD and anxiety) are related to the dysfunctions of the monoamine system (13, 14).

It might be easy to suggest that the etiology of PSD may be the ischemic lesions caused by stroke interrupting the projections ascending from the midbrain and brainstem, leading to a decreased bioavailability of the biogenic amines, including DA, 5-HT, and NE (4, 7). Even though traditional antidepressants are the first-line treatment used for PSD, the mechanisms of PSD are still unclear (4). Therefore, this study aims to review the relationship of PSD with three monoamines and emotions. First, we briefly introduced the incidence, risk factors, and diagnosis of PSD. Then, we reviewed the application of three monoamines in the treatment of PSD drugs and the "three primary color model" of basic emotions. Finally, we summarized the advantages of psychological therapy in recent years and posted some suggestions for the pharmacology and psychotherapy of PSD.

POST-STROKE DEPRESSION

Stroke and depression are two leading causes of disability worldwide (6, 15). They not only negatively affect patients' life quality but also lead to socioeconomic burden (15, 16). PSD is the most frequent and important neuropsychiatric consequence of stroke (17). According to a report by World Health Organization (WHO), approximately one-third of the 15 million patients with stroke (2) suffer from PSD every year globally (18). Despite the similarities between PSD and MMD, there are some significant differences between them (4, 15). First, PSD is a complication of stroke, which is closely linked to vascular injury (19), while MMD is majorly due to monoaminergic systems. Second, PSD and MMD are different in symptoms in that PSD tends to have more severe cognitive impairment than MMD but less anhedonia and disturbances in sleep and cyclic functions than MMD (20, 21). Third, patients with PSD have a higher prevalence of physical disability, which may be related to stroke (22). Therefore, the clinical characteristics of PSD are not identical to those of MMD, and PSD needs to be specifically discussed.

INCIDENCE OF PSD

As a common stroke complication, PSD has been investigated by many scientists in many countries around the world (23). In addition, many meta-analysis studies have investigated the incidence and etiology of PSD (2, 24, 25). In his pioneering studies of PSD, Hackett et al. (26) conducted a systemic review and meta-analysis, which included 17,934 patients from 20 studies and revealed a pooled frequency estimation of PSD of 33%. Hackett et al. (2) updated the systematic review with a meta-analysis about the frequency of PSD in the next 10 years. They revealed that the pooled frequency was estimated to be 31%, which was consistent with the results found in a 10-year earlier review. Recently, a new study reported the incidence of PSD within the first 5 years following stroke to be 39–52%, which is far higher than the incidence of MDD (about 4.4% of the world's population) (27).

Similar to Hackett et al., Ayerbe and his colleagues revealed a similar pooled frequency of PSD of 29% and a cumulative incidence of 39–52% within 5 years of the stroke (24). The interesting finding of this research is that the frequency of PSD remained quite consistent for the first year but then started to decline. However, another study has provided an opposite result as to the time course of PSD. Werheid et al. (28) reported a two-phase pathogenetic model of PSD based on 10 prospective longitudinal studies, which revealed a rise in the incidence of PSD within the first 6 months, a slight drop at about 1 year, and a new increase within the second year following a stroke.

In a recent study, Eman et al. (29) used DSM-IV TR as diagnosis criteria of depressive disorders, they found that the frequency of PSD was 36.9%, and 21.4% of which had MDDs, meanwhile 15.5% had minor depressive disorders. Even though these studies have provided the frequency and severity of PSD, still there exist one limitation in these studies because there were no standard diagnostic criteria for specific mood disorders in most studies (16). In other words, these meta-analyses did not distinguish major depression from other forms of depressive disorders occurring after stroke (23). In addition, an obvious finding was that there were differences in the results of different PSD incidence studies due to the differences in sample size, geographical location, the selection of patients, etc. (30).

DIAGNOSIS OF PSD

A longstanding problem was that a vast majority of patients with stroke are not screened for PSD (15) because PSD was confused with many mood disorders in symptoms, such as post-stroke apathy (PSA) (31) and catastrophic reaction (32). PSA is generally defined as a disorder of diminished motivation caused by a stroke (31). The symptoms of PSA are loss of interest, diminished emotional response, and loss of initiative (33), which are quite similar to those of PSD. In addition, based on physiology, both PSD and PSA are related to fronto-striatal circuit dysfunction and small vessel ischemia (34, 35). A catastrophic reaction is also a common emotional reaction

TABLE 1 | Main tools to screen and diagnose the PSD.

Scales	Full name	Authors	Diagnostic criteria	Sensitivity (95% CI)	Specificity (95% CI)
DSM-IV	Diagnostic and statistical manual of mental disorders	American Psychiatric Association	• presence of depressed mood or anhedonia • symptoms are pathophysiologically related to the stroke • symptoms are not better explained by other psychiatric disorders • disturbance does not occur exclusively in the presence of delirium • symptoms cause significant distress or impairment		
PHQ-9	9-item Patient Health Questionnaire	Spitzer RL	Self-rating scale; all items are graded from 0 to 3; score greater than 4 is diagnosed as having depressive symptoms	0.86 (0.70 to 0.94)	0.79 (0.60 to 0.90)
HAMD	Hamilton Depression Rating Scale	Hamilton	Two trained assessors conduct joint inspections on the assesses; score greater than 7 is diagnosed as having depressive symptoms	0.82 (0.69 to 0.90)	0.75 (0.62 to 0.84)
CES-D	Center of Epidemiological Studies-Depression Scale	Sirodff	20 items; self-rating scale; according to the frequency of the corresponding condition or feeling in the past 1 week; it focuses more on the emotional experience of the individual; score greater than 15 is diagnosed as having depressive symptoms	0.64 (0.48 to 0.78)	0.85 (0.52 to 0.97)
BDI	Beck Depression Inventory	Beck AT	13 items; all items are graded from 0 to 3; score greater than 4 is diagnosed as having depressive symptoms	0.90 (0.62 to 0.98)	0.55 (0.19 to 0.86)
HADS	Hospital Anxiety and Depression Scale	Zigmond AS and RP Snaith	Divide into anxiety subscale and depression subscale with 7 items each; score greater than 10 is diagnosed as having depressive symptoms	0.87 (0.46 to 0.98)	0.73 (0.65 to 0.79)
MADRS	Montgomery-Asberg Depression Rating Scale	Montgomery SA, Asberg M	10 items; all items are graded from 0 to 6; score greater than 12 is diagnosed as having depressive symptoms	0.85 (0.78 to 0.90)	0.79 (0.70 to 0.86)
GDS	Geriatric Depression Scale	Brank	30 items; self-rating scale; suitable for the elderly; score >20 is diagnosed as having depressive symptoms	0.81 (0.65 to 0.91)	0.77 (0.62 to 0.82)

after stroke. The definition of catastrophic reaction is an intense emotional reaction to the inability to perform tasks after neurological damage (36), which is characterized by severe frustration, sadness, anger, or aggression (15). Although these symptoms are similar to those of post-stroke diseases, the treatments are quite different. For example, substantial evidence shows that PSA is better treated by psychotherapy interventions instead of antidepressants (37), but antidepressants in fact have shown good therapeutic effects in PSD treatment (7). Therefore, the diagnosis and treatment of PSD are particularly important. The diagnosis and screening of PSD mainly use the traditional depression scales (38), such as Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory (BDI), and Hospital Anxiety and Depression Scale (HADS) (39). We summarized the main PSD diagnosis instruments in **Table 1** according to recent reports; however, Nick et al. (40) conducted a meta-analysis on these diagnostic methods for PSD. They found that all the tools used in the clinics were not so correct for case findings. In all these scales, the Center of Epidemiological Studies-Depression Scale (CESD), HAM-D, and the Patient Health Questionnaire (PHQ-9) showed the best results. PHQ-9 is the shortest of these options, with only nine questions based on the DSM-IV criteria for MDD (41). As a result, the PHQ-9 is one of the fastest and most practical tools that can be administered in the screening and diagnosis of PSD (15) (**Table 1**).

RISK FACTORS OF PSD

Depression is a common symptom following a stroke; however, the risk factors and predictors are yet to be delineated (1). The benefit of understanding PSD risk factors is beneficial to the

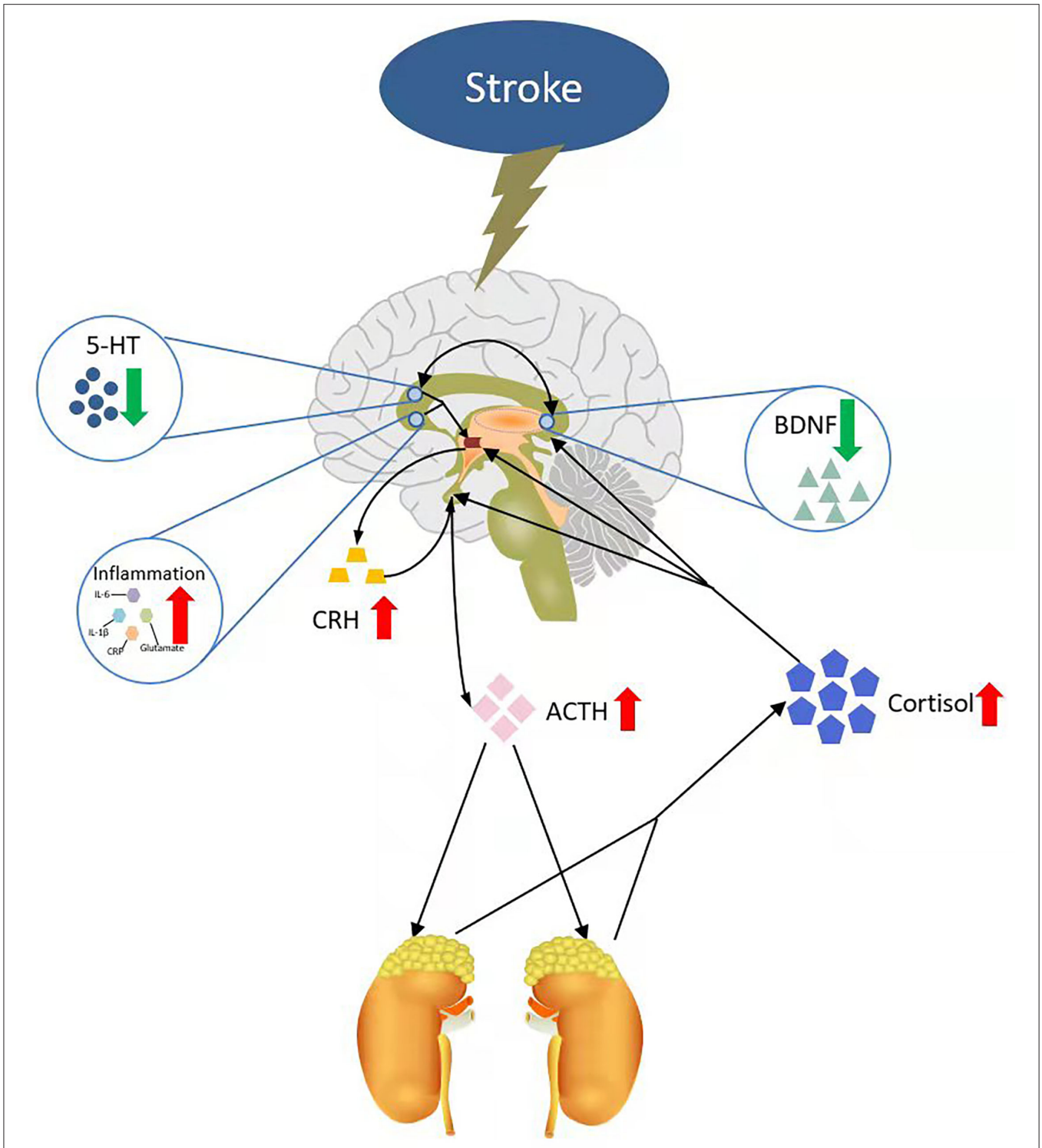

FIGURE 1 | A neural mechanism model of PSD. IL-6, interleukin-6; IL-1β, interleukin-1β; CRP, C-reactive protein; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; 5-HT, 5-hydroxytryptamine; BDNF, brain-derived neurotrophic factor.

prevention and treatment of this disease. Many studies during the past decades have reported many causing factors for PSD. The main factors are summarized in the following sections.

Stroke-Related Factors

A series of studies have found that the type, severity, and lesion location of stroke were related to the PSD (30). Jørgensen et

al. (42) conducted a large sample study by collecting data from 157,243 patients with stroke between January 2001 and December 2011. They reported that patients with ischemic stroke had a higher incidence of PSD than patients with hemorrhagic stroke. In another study, Vataja et al. (43) also found that patients with PSD had more sites and a larger volume of infarcts. However, another study did not find different rates of PSD based on the type of stroke (44).

A lot of studies have provided evidence for the relationship between stroke severity and PSD incidence (24, 45, 46). One meta-analysis study of PSD by Hackett et al. (26) found that there was a positive correlation between stroke severity and PSD. Recently, a multiple regression analysis from Taiwan also found a correlation between the severity of stroke and the incidence of PSD (46). Another study by Jørgensen et al. (42) also found that a higher depression score was significantly associated with PSD, regardless of gender.

In addition, the lesion location of the brain was strongly associated with PSD. In a series of studies (23, 47, 48), Robinson and his colleagues revealed that patients with stroke in the left hemisphere had a higher incidence of PSD and the severity correlated significantly with the proximity of the lesion to the frontal pole. Meanwhile, Starkstein et al. (49) found that the location of subcortical lesions had a greater influence than cortical lesions on PSD. Similarly, in patients with subcortical damage, the closer the lesion to the frontal lobe, the more severe the PSD. Therefore, the frontal pole may play a key role in the severity of PSD. In other ways, Jorge et al. (50) found that focal brain stimulation using repetitive transcranial magnetic stimulation is only effective when it is applied to the left dorsolateral prefrontal cortex in patients with vascular depression. Robinson (23) also considered that PSD is associated with left frontal or left basal ganglia lesions within 2 months of a first clinical stroke. Therefore, left frontal or left basal ganglia lesions may be used as the screen basis of PSD.

Demographic Factors

Similar to MDD, many demographic factors, such as sex, age, and history of psychiatric illness, are related to the PSD. During the past decades, there was no agreement on sex as a risk factor for PSD. Some studies identify female sex as a risk factor for PSD. In a meta-analysis study of the risk factors for PSD, Shi et al. (17) found that sex (female) was significantly associated with PSD [OR = 1.77, 95% CI = 1.26–2.49]. This result was also reported in other studies (46, 51, 52). However, a systematic review by Ryck (44) found that gender was not a significant risk factor for PSD in 13 out of all 21 studies.

Age was another factor that yielded the most controversial results. In a study of 216 patients with ischemic stroke, Li et al. (53) revealed a difference in age between patients with PSD and patients without PSD. Carota et al. (54) also found the association between PSD and age. However, Ryck et al. (44) revealed that age was not associated with PSD in 16 studies. Therefore, the relationship between age and PSD is still unclear.

Finally, the history of psychiatric disorders was also associated with PSD, particularly MDD and anxiety disorders. A meta-analysis study by Ried and his colleagues found the rate of PSD was found to be 5–6 times higher among those with pre-stroke depression (55). A recent study has also revealed depression before stroke notably increased odds of PSD (56). Anxiety disorder is also a risk factor for PSD. De Ryck reported that a personal history of anxiety was a significant risk factor in some studies (44).

Social Support

Apart from the above risk factors, social support is also associated with the PSD. But, the available studies concerning PSD and social support are contradictory (23). A systematic review of the relationship between social support and PSD reported that some factors (such as family life, friends, acquaintances, and social participation) of social support were associated with PSD, and lack of social support may cause more severe PSD symptoms (57). Other studies have reached similar results (18, 58). Even though a lot of evidence indicated that social support was related to PSD, Jessica et al. (59) reported that living conditions and marital status have not been consistently associated with PSD.

MONOAMINE TRANSMITTERS IN THE TREATMENT OF PSD

In their study performed 2,500 years ago, Hippocrates and Galen suggested that individual differences are due to fluid components in the body, and that a balanced mixture of these vital chemicals can induce at least four kinds of temperaments: choleric (aggressive), melancholic (depressive), phlegmatic (fear and social detached), and sanguine (cheerful) (60). The further that research in the neurochemistry of emotionality advances, the more that neurochemical systems are linked to emotional regulation (61). In fact, dysregulation in practically all neurochemical families, especially monoamines, hormones, neuropeptides, opioid receptors, and transcription factors, appears to contribute to PSD (62). There are two main theoretical views about the determinants of PSD. One of them focuses on brain locations such as the amygdala and hippocampus, prefrontal cortex, and hypothalamus. Another one emphasizes neurochemicals such as disruption of biogenic amine neurotransmission and release of proinflammatory cytokines (63). The monoamine hypothesis assumed that PSD was related to abrupt damage of cortical circuits involved in mood regulation and monoamine production (64). Dopamine (DA), 5-HT (5-HT) and norepinephrine (NE) are the three main monoamine transmitters in emotion regulation (11), which play a key role in antidepressant drugs for PSD treatment. In the following section, the roles of 5-HT, DA, and NE in the treatment of PSD are discussed.

Monoamine Hypothesis

The "monoamine hypothesis" of depression originated from early clinical observations (8), which posited that depression was caused by an alteration in one or more of the monoamines (65). Robinson (48) assumed that ischemic lesions may interrupt the biogenic amine-containing axons ascending from the brainstem to the cerebral cortex and lead to a decreased availability of monoamines (5-HT, DA, and NE) in limbic structures of frontal,

temporal lobes, and basal ganglia. Monoaminergic neurons in the midbrain dynamically alter their firing patterns, which were associated with motivation-related behavior in animal studies (66). Motivation-related behavior included salience, reward and punishment learning, incentive processing, decision-making, goal-directed behavior, and anxiety (67). Recent studies have revealed three different monoaminergic dynamics that regulate diverse aspects of motivation-related behavior (68–71). Therefore, it appeared that specific aspects of motivation-related behavior were regulated by distinct synaptic and cellular mechanisms in specific brain regions that underlie the transient and sustained effects of the monoamine signaling (66). The different neural systems of three monoamines may involve different symptoms of depression (mood, cognition, and pain). Serotonergic (5-HT) neurons originate from the median raphe nucleus and innervate the limbic system, prefrontal cortex, and other related structures involved in the regulation of mood (4). In addition, 5-HT projected to the basal ganglia has been confirmed to be associated with motor control (72). Dopaminergic projections originated from the ventral tegmental area (VTA) and substantia nigra (SN), reaching different regions of nucleus accumbens (Nac), had been proven to be related to reward and aversion (73). Norepinephrinergic neurons originated from the locus coeruleus (LC) project to the limbic system to participate in the regulation of emotional arousal (74). Furthermore, the monoaminergic descending pathways projecting through the dorsolateral spinal column played an important role in the regulation of pain.

Since the 1950s, reserpine has been found to inhibit vesicular monoamine transporters and deplete brain monoamines, which provided evidence for the role of monoamines in the treatment of depression. In 1959, the Food and Drug Administration (FDA) approved imipramine for the treatment of MDD, which established the class of drugs called tricyclic antidepressants (TCA) as the first class of drugs to target monoamines. Later, selective 5-HT reuptake inhibitors (SSRIs) and 5-HT and norepinephrine reuptake inhibitors (SNRIs), which are based on the "monoamine hypothesis," were approved for depression in 1987 and 1993, respectively. In recent years, some drugs targeting the glutamate system (such as ketamine) showed good effects (75). In all, the introduction of TCAs and monoamine oxidase inhibitors based on the monoamine hypothesis revolutionized the treatment of depression. Since then, most of antidepressants have been developed by primarily acting through modulation of monoaminergic neurotransmission (76). Even though the monoamine hypothesis alone was no more generally accepted (16), the current main treatment of PSD drugs is still based on the monoamine hypothesis (77).

Serotonin (5-HT)

5-Hydroxytryptamine is a significant neuromodulator with unique neuroplastic capabilities (78). The main gathering area for 5-HT neurons is the dorsal raphe nucleus (DRN). The 5-Htergic neurons of the DRN send projection to the entire brain and throughout the neuraxis and receive major inputs from the hypothalamus, amygdala, midbrain, and anterior neocortex (66). There are 14 types of serotonergic receptors, which can be divided into seven main families according to differently coupled G-proteins (79). Each group of receptors may have different functions. For example, 5-HT_{1A} and 5-HT_{1B} receptors are associated with anxiety (80) and reward behaviors (81); 5-HT_{2A} receptors are correlated to appetite control, thermoregulation, and sustained attention (82); 5-HT_3 receptors are related to aggression behaviors (83); and 5-HT_4 receptors affect memory, depression, and feeding (84).

In addition, abundant evidence has justified the role of 5-HT in depression (85), as well as in patients with PSD (86). Furthermore, 5-HT levels can be affected by three neurobiologically related factors of PSD: increased inflammation and trauma, decreased cerebral brain-derived neurotrophic factor (BDNF), and dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis. Raison et al. (87) reported that the metabolisms of 5-HT are affected by the central nervous system (CNS) inflammatory response (88). A peripherally administered cytokine could activate a CNS inflammatory response in humans that interacted with 5-HT metabolism, which was associated with depression. The association of BDNF and 5-HT also showed a special feature in depression (89). BDNF injected into the midbrain increased the level of 5-HT and also enhanced the expression of genes encoding 5-HT_{1A} and 5-HT_{2A} receptors. These changes can only be observed in depression mice but not in nondepression mice (90). In patients with PSD, 5-HT and other monoamine (DA and NE) release might be affected by abnormal HPA axis activity after stroke. Therefore, Guo et al. (30) posted a model of the PSD mechanism based on four main hypotheses of PSD: the monoamine hypothesis, HPA hypothesis, neurotrophic hypothesis, and inflammation hypothesis. The model considered that stroke could trigger a robust inflammatory response and severe monoamine system damage in the injured brain region (91). Then, this change would increase the activity of HPA, which works through the following processes. First, the inflammatory response and the 5-HT decrease made the paraventricular nucleus of the hypothalamus release more corticotropin-releasing hormone (CRH), which stimulated the pituitary to release more adrenocorticotropic hormone (ACTH). The increase in ACTH release causes an increase in glucocorticoid synthesis and release in the adrenal cortex (92). Glucocorticoid is also called cortisol in the human body, which is the major component of the HPA axis. Many studies have shown that the cortisol levels were higher in depression patients (93, 94). An increase in cortisol, in turn, could lead to a decrease in BDNF, which played a key role in the emotion system. On the one hand, lacking cerebral BDNF contributed to the development of negative mood states (95). On the other hand, BDNF was closely associated with 5-HT, and the functional activity of the 5-HT system was linked with depression and suicide (89). 5-HT decrease in the limbic system and cerebral cortex might be an important factor for depression in patients with stroke. Therefore, 5-HT and its receptors can be used as a biomarker for PSD (**Figure 1**).

Furthermore, the major antidepressant drugs mainly target 5-HT and its receptors. Currently, there are three main types of antidepressant drugs, including tricyclic antidepressants (TCAs),

selective 5-HT reuptake inhibitors (SSRIs), and 5-HT and norepinephrine reuptake inhibitors (SNRIs) (96). The first-line therapeutic treatment for PSD is using antidepressants, as can be seen in a recent meta-analysis, which confirmed that antidepressant drugs had a significant effect in the treatment of PSD vs. placebo (97). TCAs are a group of traditional antidepressant drugs, and some drugs of this kind are still used in PSD treatment, such as amitriptyline and nortriptyline, which are 5-HT_2 receptor antagonists. Xu et al. (97) found a significant advantage of TCAs over placebo in a meta-analysis study. However, both amitriptyline and nortriptyline have been reported to have serious side effects. Some elderly patients with stroke showed orthostatic hypotension, cardiac arrhythmia, glaucoma, or prostate hyperplasia after using the two drugs (98). SSRIs and SNRIs are two groups of new antidepressant drugs, which is introduced after the 1980s (7). Nowadays, there are at least 6 SSRI drugs (fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, and escitalopram) and 3 SNRI drugs (i.e., milnacipran, duloxetine, and duloxetine) available in PSD treatment. Anyway, a series of studies have shown that the SSRI drugs also had great effects on PSD treatment (99–105), such as gastrointestinal symptoms, headache, sexual dysfunction, and insomnia (7).

In addition, using SSRIs may increase mortality in patients with stroke (24). However, these studies did not reach a consensus result, even opposite results (106, 107). Compared with SSRIs, SNRIs may be useful in improving painful physical symptoms due to their noradrenergic action. Some studies have also found that SNRIs show a great effect on PSD prevention and treatment (103, 108, 109). In addition to these three types of drugs, some new antidepressant drugs also target 5-HT receptors and show great effects on patients with PSD. For example, vortioxetine, a new antidepressant with multimodal activity, shows great therapeutic effects on cognition. It can act on multiple 5-HT receptors, including 5-HT_{1A}, 5-HT_{1B}, 5-$HT_{1D,}$ 5-HT_3, 5-HT_7, and 5-HT transporter (SERT) (110). In addition, vortioxetine shows fewer side effects than current first-line antidepressants. In all, these studies showed that antidepressant drugs targeting 5-HT can play a role in the treatment of PSD (**Table 2**).

TABLE 2 | Main 5-HT drugs and their receptors for PSD.

Drugs	5-HT receptors	Clinical application	References
Fluoxetine	5-HT2C (-)	depression, premenstrual dysphoric disorder, hypochondriasis, bulimia nervosa	(111)
Paroxetine	5-HT2C (-), 5-HT2A (-)	depression, PTSD, OCD, generalized anxiety disorder, premenstrual dysphoric disorder	(112, 113)
Fluvoxamine	5-HT1A (-)	anxiety disorders, schizophrenia, delusional depression	(114, 115)
Sertraline	5-HT2C (-)	major depression, panic disorder, OCD, PTSD	(116)
Citalopram	5-HT3 (-), 5-HT1A (-), 5-HT2C (-)	major depression, OCD	(117, 118)
Escitalopram	5-HT1A (+)	depression, anxiety disorder	(119)
Amitriptyline	5-HT2 (-)	schizophrenia,	(120)
Nortriptyline	5-HT2 (-)	depression	(121)
Clomipramine	5-HT1A (+), 5-HT1B (-)	OCD, major depression	(122)
Milnacipran	5-HT1A (-)	major depression	(123)
Duloxetine	5-HT (-)	generalized anxiety disorder, major depression	(124)
Mirtazapine	5-HT2A (-)	depression, PTSD	(125, 126)
Venlafaxine	5-HT1B (-)	major depression, OCD	(127)
Doxepin	5-HT2A (-), 5-HT2C (+)	insomnia	(128)

Dopamine and NE

Dopamine and NE are two other monoamines and also play a key role in the emotion system. The dopaminergic system is a unique modulatory system in the brain as it has discrete projections to specific brain regions, including motor behavior, cognition, and emotion (110). Unlike 5-HT or NE, separate groups of DA neurons project to different brain regions. Different groups of DA neurons project to different brain regions to moderate and regulate different behaviors and functions (129). Dopaminergic neurons are mainly located in the VTA and SN (130). Dopaminergic neurons in these two areas project to the reward-related Nac and ventral striatum (VS), which is called the mesolimbic DA system (22). In addition, the dopaminergic neurons in the lateral SN primarily project to the dorsomedial striatum and participate in the formation of motor learning and habit behavior (131). The functions of DA are mainly mediated by DA receptors, which are composed of five different but closely related G protein-coupled receptors, D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors (Beaulieu, Gainetdinov, & Sibley, 2011). D1-like receptors can enhance the activity by activating the Gαs/olf family, but the D2-like receptors activate Gs/ol family and inhibit the activity (79, 132). More and more studies have shown that dopaminergic system dysfunction is linked to the pathology of depression (133–136). Anhedonia and amotivation are two main symptoms seen in depression, which are related to dysfunctions in the dopaminergic system (137). Animal models of depression showed stress-induced impairments of VTA dopaminergic neurons are related to the increasing susceptibility of depression in rats (138), which is due to stress increased activity of dopaminergic neurons in the circuit of the hippocampus—VS-ventral pallidum. However, increased activity in the ilPFC-amygdala-ventral pallidum circuit caused a compensatory, long-duration downregulation of the VTA. The downregulation of the VTA was maintained after stress, which might be the reason for anhedonia and depression (139). Therefore, we could speculate that stroke led to serious monoaminergic system damage, which led to reduced release of VTA dopamine to the reward-related Nac and VTA, and thus anhedonia and depression. In addition, antidepressant drugs targeting DA and its receptors also showed great benefits in

PSD treatment. For example, fluoxetine and paroxetine, two of the most commonly used drugs in PSD treatment, could prevent the degeneration of nigrostriatal dopaminergic neurons (140). A recent study has revealed that SNRIs achieve a fast antidepressant effect by elevating the DA concentrations in the mPFC and the Nac (96). Furthermore, a new antidepressant drug, bupropion, which primarily acts through the NE transporter and DA transporter, shows a significant therapeutic effect (141).

Norepinephrine, a catecholamine neuromodulator, projects to all the brain regions except some dopaminergic neuron regions, such as the striatum, globus pallidus, NAc, and SN (142). NE is mainly released from neurons originating from locus coeruleus (LC), a small nucleus situated in the pons of the brainstem. The LC-NE system has long been considered to be critical in arousal (71). NE exerts its effects through binding to G-protein coupled α-adrenergic receptor (α-AR) and β-adrenergic receptor (β-AR). A-AR receptors can be divided into two families: α1 and α2. Each of them has three subtypes: α_{1A}, α_{1B}, and α_{1D}; α_{2A}, α_{2B}, and $\alpha_{2C;}$ while β-Ars has two groups: β1and β2 (143). NE has the highest affinity for the α2 receptors and the lowest affinity for β adrenergic receptors. In addition, α1 receptor stimulation has been found to enhance excitatory processes in many brain regions (144). Animal models offered the evidence that reduction of the levels of presynaptic NE, such as 5-HT, or DA, plays a key role in the pathophysiology of depression (145). In all, the LC-NE system is also related to the low arousal state of depression (74). A meta-study showed a significant correlation between baseline 3-methoxy-4-hydroxyphenylglycol (sMHPG) levels and Beck Depression Inventory (BDI) score, and sMHPG was the major NE metabolite in the cerebrospinal fluid (146). Leonard et al. (147) proposed a model about the relationship between NE and depression. They proposed that chronic stress activated the release of corticotropin-releasing factor (CRF), leading to the increased release of pro-inflammatory cytokines, prostaglandins of the E series, and nitric oxide, which influenced the central neurotransmitter function. If these changes persisted, they may contribute to the degenerative changes in noradrenergic neurons, which would lead to depression. In patients with stroke, stroke might change NE levels and thus PSD. In terms of depression medications, SNRIs showed faster antidepressant effects than SSRIs, and the underlying mechanisms of faster antidepressant effects of SNRIs may be related to NE (96). In all, SNRIs showed a great effect in improving painful physical symptoms due to their noradrenergic action (7). A meta-study showed in recent clinical studies that NE may play an important role in aberrant regulation of cognition, arousal, and valence systems that are associated with depression (143).

Monoamine and Related Chemicals

Even though the monoaminergic systems are implicated in the regulation of basic emotions, there is a functional overlap of neurochemical systems related to PSD. The neurochemicals involved in PSD can be divided into two groups: neuromodulators and neuropeptides (**Table 3**). The neuromodulators are small molecules, such as monoamines, and have specific functions, such as joy, disgust, and fear, like the three primary colors. While the peptides such as oxytocin, orexin, and neuropeptides are more complex and carry more flexible functions, which might be secondary to the neuromodulators. Anyway, the monoamines and other secondary neurochemicals can interact with each other to produce different kinds of emotions (**Figure 2**). The difference might be that the neuropeptides are involved in more specific functions, such as thirst, hunger, and pain (**Table 3**).

TABLE 3 | Monoamine and chemicals for PSD.

Neuropeptide	Emotional feelings	References
Substance P	Pain and anger	(148, 149)
Angiotensin	Thirst	(150)
Oxytocin	Orgasm, maternal feelings	(151, 152)
ACTH	Stress	(153)
Insulin	Energy	(154)
Vasopressin	Male sexual arousal, dominance	(155, 156)
Bradykinin	Pain	(157)
CCK	Satiety, disgust	(158, 159)
Prolactin	Maternal and love	(160, 161)
TRH	Playfulness	(162)
LH-RH	Female sexual arousal	(163)
Bombesin	Satiety-disgust	(164)
Neurotensin	Seeking	(165)
Enkephalin	Pain	(166, 167)
Endorphin	pleasure	(168, 169)
DSIP	Boring-disgust	(170)
Dynorphin	Hunger	(171)
CRF	Panic, anxiety	(172, 173)
NPY	Hunger	(174)

THE THEORY OF THREE PRIMARY EMOTIONS

Although the "monoamine hypothesis" proposed that the mood symptoms of depression were mainly related to decreased levels of monoamines, the relationship between monoamine transmitters and emotion was never clarified. Nowadays, there are two widely accepted theories in emotional studies: basic emotion theory and dimensional theory (175). The basic emotion theory suggests that all emotions are composed of a limited number of emotions (11). Basic emotions have evolutionarily preserved biological and social functions (175). After many experimental studies, Ekman (176) suggested that people have six basic emotions: joy, sadness, fear, anger, disgust, and surprise. Robert Plutchik proposed eight primary emotions in a color wheel: anger, fear, sadness, disgust, surprise, anticipation, trust, and joy (175). In recent years, Jack et al. (177) proposed four basic emotions: fear, anger, joy, and sadness. The dimensional theory proposes that emotions could be defined by some different dimensions, and all emotions could be defined as a combination of these dimensions (178). The dimensional theory was first proposed by Wundt, who suggested

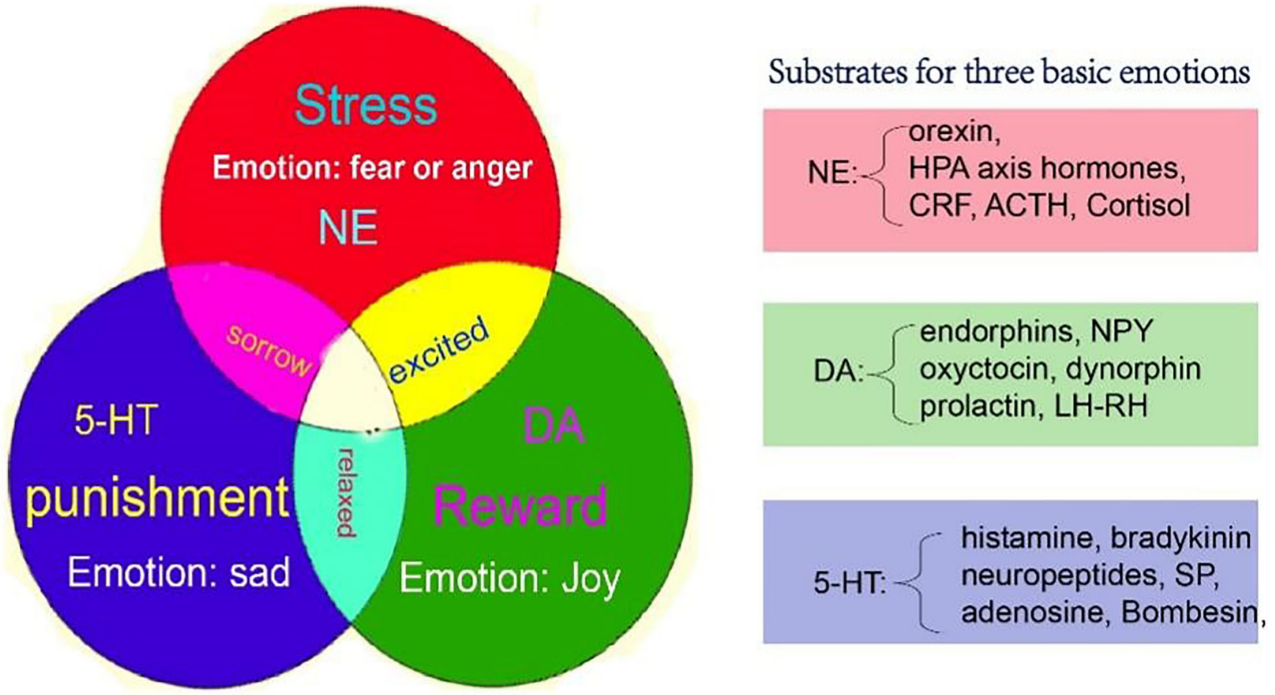

FIGURE 2 | A new model for basic emotions, which might be the neural mechanisms of PSD. The monoamine (NE, DA, and 5-HT) might be the substrate for basic emotions, which include joy, sadness (disgust), and fear (anger). [A figure from our previous paper, (61)]. NE, norepinephrine; DA, dopamine; 5-HT, 5-hydroxytryptamine.

that emotion had three independent dimensions: pleasant-unpleasant, tension-relaxation, and excitation-calm (179). The most famous dimensional theory was proposed by Russell et al., who invented the circumplex, which is composed of two dimensions: hedonic (pleasure-displeasure) and arousal (rest-activated). They proposed that all emotions could be arranged in a circle, and the different locations of each emotion in the circle reflected varying amounts of hedonic and arousal properties (180). Even though both theories were supported by more studies, no previous reports have connected emotion with neurotransmitters. Wang et al. (61, 79, 178, 179) posted a new theory of three primary emotions, which not only compromised both basic emotion theory and dimensional theory but also associated with neurotransmitters, especially monoamines, with emotions.

Basic emotions are instinctive, primitive, and developed throughout evolution (175), and each basic emotion should have a specific neural basis. Therefore, Wang et al. (12, 61, 170) proposed the theory of three primary emotions *via* a large number of basic emotional studies. They proposed three basic emotions: joy, disgust, and fear (anger), which were subsided, respectively, by the three monoamine neurotransmitters: DA, happiness; 5-HT, sadness; and NE, fear (anger). Fear and anger are twin emotions that are like two sides of the same coin (61). Fear and anger are associated with unanticipated ways things happen: fear is associated with uncertainty about the situation; and anger is related to trying to control the situation (181), which can induce the individuals to generate the so-called fight or flight response (182). Similarly, in the emotional dimension, DA and 5-HT represent two poles of the horizontal dimension, which is the valence dimension, while the NE represents the vertical dimension, which means arousal (11). This model might be the first theory to connect monoamine neurotransmitters with basic emotions and emotional dimensions.

EMOTION-BASED INTERVENTIONS IN TREATING PSD

If patients are diagnosed with PSD, they are usually treated with antidepressants (183). However, the effectiveness of antidepressants in clinical practice is only approximately 50% (184). Therefore, it is necessary to provide additional effective and safe treatment for PSD. Emotional control for PSD showed great potential in the treatment and prevention of PSD in recent studies (7). The effects of several major psychotherapies in recent studies are summarized in the following section.

Cognitive reappraisal is an effective and common intervention therapy for the treatment of depression (185). In a recent meta-study, cognitive behavioral therapy (CBT) interventions yielded a larger short-term decrease in depression scores (126). CBT was also widely used in clinical treatment for PSD (186). A

single-blind randomized controlled trial of PSD revealed that CBT was as effective as citalopram for late-onset post-ischemic depression and was more effective than rehabilitation alone (100). A recent meta-study also reported that both CBT alone and CBT with antidepressants all showed significantly improved depressive symptoms in PSD (18). However, most studies have not considered the time of depression onset. Hou et al. (187) found that antidepressants and psychological therapy may not improve the symptoms of depression in patients during the first 3 months. Gao et al. (100) also reported that the most positive results of CBT for treating post-ischemic stroke depression occurred 3 months later. It may be associated with the biological changes in the brain tissue caused by stroke. Therefore, CBT is effective in treating PSD, but this effect usually occurs after the biological changes in brain tissue stabilize. In addition, a recent study has demonstrated the relevance of the MAOA gene for the treatment outcome of CBT, while the MAOA gene plays a key role in the degradation of monoamines, especially 5-HT and NE (188).

In a recent study, mindfulness meditation showed potential benefits for PSD (189). Mindfulness is defined as a process of openly attending, with awareness, to one's present moment experience (190). Mindfulness meditation includes at least three components: improved attention control, enhanced emotion regulation, and altered self-awareness (191). In a recent randomized controlled trial, Wang et al. (189) revealed that mindfulness intervention had positive effects on depression, social wellbeing, and emotional wellbeing of patients with PSD.

In addition, other treatments of implicit emotional control were also recommended for patients with PSD, such as literature therapy and art treatment (192–194). Literature therapy is psychotherapeutic, which helps patients develop insight and awareness of negative thoughts and emotions, provides answers to problems, and supports them to practice these approaches in their daily life (195). Art treatment is defined as the therapeutic use of verbal treatment methods, using rhythms, sensory stimulation, symbolic motions, and colors that could facilitate the addressing of the patients' psychological issues (196). All of these treatments have been proved to work well for depression by changing the unconscious minds, which can be called implicit emotional control (194, 195, 197). Therefore, Eum et al. (195) suggested that literature therapy and art treatment could serve as a useful emotional control to help patients with stroke in their rehabilitation process (195).

Even though many studies have reported that emotional control has a great potential effect on PSD, there are still more questions that remain unanswered, e.g., the best time for emotional intervention in PSD. Most of the studies have not considered time, e.g., Hou et al. (187) found that antidepressants and psychological therapy only play a role after 3 months. In addition, there is no standard process for emotional control for PSD. Most researchers appealed to make a more individualized plan for different patients (193, 198). Therefore, a series of studies (18, 179) showed that the evidence for emotional control in PSD is still inconclusive.

CONCLUSION AND PERSPECTIVES

In this study, we briefly introduced the incidence, risk factors, and diagnosis of PSD. Then, we introduced the "monoamine hypothesis," the role of three monoamines in PSD, and the antidepressant drugs primarily targeting these three monoamines and their receptors. Next, we elaborated on a new model of emotion based on the "monoamine hypothesis." We hope to clarify the relationship between the three monoamines, emotion, and PSD. Patients with PSD have some changes in their microbiome and metabolism, and these potential biomarkers and microorganisms may aid in the diagnosis and treatment of the disease. Finally, since all drugs have side effects and the effectiveness of antidepressants in clinical practice is less than ∼50%, we introduced some emotional controls for PSD. We hope this study could help with the diagnosis and treatment of PSD.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Brain Activation During Processing of Depression Emotion in College Students With Premenstrual Syndrome in China: Preliminary Findings

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Background: This study aimed to investigate the neural substrates of processing depression emotion in premenstrual syndrome (PMS) and healthy subjects of college students using blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI).

Methods: During BOLD-fMRI scanning, 13 PMS patients and 15 healthy controls (HC) performed a picture visual stimulation task during luteal and follicular phases, in which participants and HC were asked to see pictures containing depression and non-depression emotions. Simultaneously, self-rating depression scales (SDS) were employed to evaluate the emotional status of participants.

Results: Compared to HC, right inferior occipital gyrus, right middle occipital gyrus, right lingual gyrus, right fusiform gyrus, right inferior temporal gyrus, cerebelum_crus1_R, cerebelum_6_R, culmen, the cerebellum anterior lobe, tuber, and cerebellar tonsil of PMS patients showed enhanced activation. In contrast, sub-lobar, sub-gyral, extra-nuclear, right orbit part of superior frontal gyrus, right middle temporal gyrus, right orbit part of inferior frontal gyrus, limbic lobe, right insula, bilateral anterior and adjacent cingulate gyrus, bilateral caudate, caudate head, bilateral putamen, and left globus pallidus exhibited decreased activation.

Conclusion: The findings indicate that abnormal functional regulation of brain regions such as occipital lobe and cerebellum leads to abnormal changes in emotional regulation, cognitive ability, and attention distribution in PMS patients, implying significant central pathogenesis.

Keywords: PMS, task state, BOLD-fMRI, depression emotion, college students

BACKGROUND

Premenstrual syndrome (PMS) is a disorder that substantially impairs normal life activities and interpersonal relationships and is associated with a woman's menstruation cycle (1, 2). Premenstrual dysphoric disorder (PMDD) is a severe form of PMS (3). Established research indicated that PMS prevalence was 35.3% among Sharjah university students (4), 62.7% among Puducherry college students (5), 64.9% among female medical students in Saudi Arabia (6), and even higher in some regions. PMS causes various symptoms in women, commonly including affective symptoms, behavioral symptoms, and difficulty concentrating, impairing their quality of normal life (7, 8). Among them, women with PMS had difficulty in regulating their emotions (9), such as prominent depression (10), making them at higher risk of suicidality (11).

Although PMS pathogenesis remains unclear, the application of brain imaging technology has facilitated its intrinsic neural mechanism of neuropsychiatric disorders (12). Among them, blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) has had a tremendous influence on human neuroscience over the last two decades (13). Qing Liu demonstrated decreased connectivity in the middle frontal gyrus (MFG) and parahippocampal gyrus (PHG) in PMS patients, as well as increased connectivity in the left medial/superior temporal gyri (MTG/STG) and precentral gyrus within the default mode network (DMN) using fMRI (14). Hai Liao revealed elevated regional homogeneity (ReHo) mainly in the bilateral precuneus, left inferior temporal cortex (ITC), right inferior frontal cortex (IFC), and left middle frontal cortex (MFC), as well as decreased ReHo in the right anterior cingulate cortex (ACC) of PMS patients during the luteal phase (15). Besides, structural MRI revealed increased gray matter (GM) volumes in precuneus/posterior cingulate cortex (precuneus/PCC) and thalamus, as well as decreased GM volumes in the insula of PMS patients (16). Concurrently, Demao Deng's research indicated that PMS patients have greater bilateral amygdalae volumes, increased FC between amygdala and certain regions of frontal cortex, the right temporal pole, and the insula, as well as decreased FC between bilateral amygdalae and right orbitofrontal cortex and right hippocampus (17). In addition, Peng Liu discovered decreased prefrontal-thalamic connectivity and increased posterior parietal-thalamic connectivity in PMS patients using resting-state fMRI (18).

Until now, few studies have been reported on the processing mechanism of depression emotion in PMS (3). Accordingly, this study aims to investigate the neural substrates of depression emotion processing in PMS using BOLD-fMRI.

Abbreviations: PMS, premenstrual syndrome; HC, healthy control; BOLD-fMRI, blood oxygenation level-dependent functional magnetic resonance imaging; ACOG, American Society of Obstetrics and Gynecology; SDS, self-rating depression scales; MFG, middle frontal gyrus; PHG, parahippocampal gyrus; MTG/STG, left medial/superior temporal gyri; DMN, default mode network; ReHo, regional homogeneity; ITC, inferior temporal cortex; IFC, inferior frontal cortex; MFC, middle frontal cortex; ACC, anterior cingulate cortex; GM, gray matter; PCC, posterior cingulate cortex; IAPS, International Affective Picture System; EPI, echo-planar image; MNI, Montreal Neurological Institute; NEG, negative emotion picture; NEU, neutral emotion pictures.

MATERIALS AND METHODS

Ethics Statement

The Medicine Ethics Committee of the First Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Shandong, China, approved this study. All research procedures were conducted following the Declaration of Helsinki. All participants were apprised of the entire experimental procedure and signed an informed consent form.

Participants

Thirteen right-handed PMS females were recruited to participate in this study and matched with a control group of 15 comparison subjects. In each group, subjects were matched according to their age and educational level. In addition, all subjects completed the Self-rating depression scale (SDS), which aims to determine depression severity. All subjects provided written informed consent.

Inclusion and Exclusion Criteria

Inclusion Criteria for PMS

It firstly meets the international diagnostic standards for PMS of the American Society of Obstetrics and gynecology (ACOG). The subjects were college students, 20–25 years old, right-handed, and voluntarily participated in the study. Inclusion criteria also included good mental state, sleep quality, and appetite. Those who have clear consciousness, and independent judgment ability, can understand the purpose of this study and cooperate voluntarily. There are no major diseases such as heart, liver, and kidney, no brain tumor or other brain diseases, and no history of taking psychotropic drugs. Both eyes have a normal naked vision or corrected vision.

Inclusion Criteria for HC

The participants were healthy and had no history of nervous system diseases such as headache, dizziness, and seizures. And they were college students, 20–25 years old, right-handed, and voluntarily participated in the study. At present, the participants are in a good mental state, have good sleep quality and appetite, clear consciousness, independent judgment ability, able to understand the purpose of this study, and voluntarily cooperate with the experiment. The naked or corrected visual acuity of both eyes is normal.

Exclusion Criteria

Participants will be excluded if they are mentally ill, have serious physical diseases, have a history of drug abuse (including drugs used to treat PMS within 3 months), have blood system diseases, or have aphasia, disturbance of consciousness, dementia, and other conditions that cannot cooperate with the examination, have a chronic history of five visceral diseases such as heart and liver and have clinical symptoms, or undergo unilateral oophorectomy or abortion within 6 months, take contraceptives, or the head translation monitored during motion correction exceeds 3 mm; or rotate more than 1 degree in any direction in

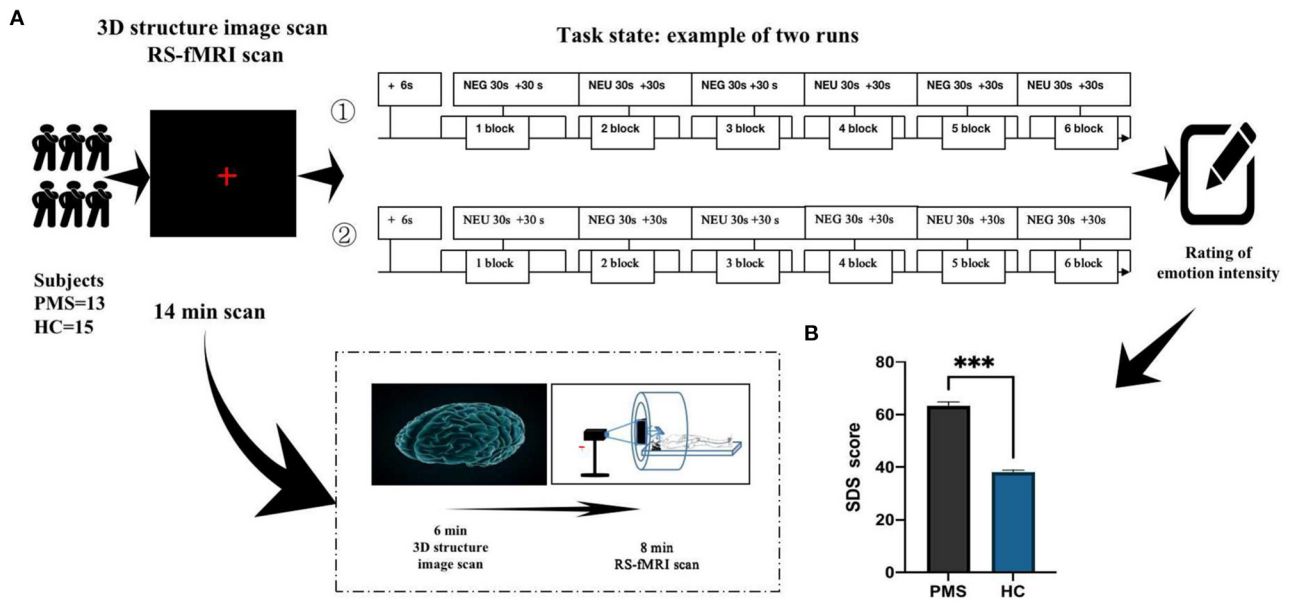

FIGURE 1 | Timeline of experiments (fMRI). **(A)** Demonstrates the overall operating flow of emotional stimuli experiments during fMRI. **(B)** Illustrates depression degree in PMS patients after depression picture stimulation during the luteal phase of the menstrual cycle. $^{***}P < 0.00$.

the three-dimensional direction. Those who put metal objects in their bodies (including pacemakers, metal dental materials, wearing braces, etc.) were excluded.

Stimuli Paradigm

The picture visual stimulation task consisted of depression and neutral emotional pictures filtered by the international emotional picture library. Stimuli were presented using the experimental visual stimulus program (Electronic Technology in Medicine Co., Ltd., Shenzhen, China). Each stimulus onset (masked face or crosshair) was triggered directly by a pulse from the scanner. The images were projected onto a computer screen behind the subject's head within the imaging chamber. The screen was viewed by a mirror positioned ∼8 cm above the subject's face.

During fMRI, all subjects were shown depression and neutral emotional pictures in a block design [See **Figure 1A** Examples of depression pictures from the International Affective Picture System (IAPS) chosen referring to previous study (19)]. The task state contains two runs and six blocks. Each block had neutral emotional pictures interspersed with emotional pictures in a pseudo-random order. This ensured that emotional pictures occurred unpredictably. Depression emotional picture stimulus consisted of a 30-s presentation (each picture was presented for 5 s, six pictures in a block), followed by a 30-s presentation of neutral pictures (each picture was presented for 5 s, six pictures in a block). The subject saw 30 negative emotional pictures within the emotional stimuli blocks in a predetermined random order. The subject also saw 30 neutral emotional pictures within the neutral picture blocks in a predetermined random order. Picture stimuli were presented at a rate of one per echo-planar image (EPI) sequence. Following each face block, a control period of 30 cross-hair stimuli fixation points (+) was presented at the same rate as the emotional pictures (see **Figure 1**).

The presentation order of emotional pictures was identical for all subjects across runs. The first run consisted of + Negative emotion pictures (NEG) + Neutral emotion pictures (NEU). The second run was + NEU + NEG. Each run lasted 6 min. Each subject viewed two runs. Following the scan, subjective reports of pictures evoking emotional effects were evaluated using SDS. Higher scores indicated that subjects experienced higher emotional strength. Subjects must carefully choose while assessing emotional intensity, which may induce different emotions.

Image Acquisition and Data Analysis

Functional magnetic resonance imaging images were obtained on a 3.0-T MR scanner equipped with a prototype fast gradient system for echo-planar imaging (EPI) at the Institute of Medical Imaging of Shandong. Functional images were obtained using an echo-planar imaging sequence with the following parameters: TE = 35 ms; TR = 2,000 ms; slice thickness = 4 mm; gap = 1 mm; flip angle = 90°; FOV = 24 cm; and in-plane resolution = 64 × 64.

Functional MRI data were preprocessed using Statistical Parametric Mapping (SPM8). We discarded data of subjects whose head motions of more than 3.0 mm maximum displacement in *X*, *Y*, or *Z* directions or 2.5 degrees in any angular direction. The first three volumes of functional images were discarded due to signal equilibrium and participants' adaptation to the scanning noise. For each participant, functional images were realigned using least-squares minimization without higher-order corrections for spin history and were normalized to Montreal Neurological Institute (MNI) template from structural

images. Images were re-sampled to $3 \times 3 \times 3$ mm^3 and smoothed with a 6-mm full-width at half maximum.

Statistical Analysis

Individual data were analyzed by creating a generalized linear model (GLM) in SPM. First level analysis was performed using a General Linear Model [GLM, (53)] applied to the time series, and convolved with the canonical hemodynamic response function.

TABLE 1 | Demographics of PMS and HC groups.

Variables	PMS ($n = 13$)	HC ($n = 15$)	*P*-value
Age (years)	24.421 ± 0.838	24.762 ± 1.338	0.346
Menophania (years)	13.737 ± 1.240	13.476 ± 0.981	0.463
Length of menstrual cycles (days)	6.211 ± 1.228	5.714 ± 1.189	0.202
Menstruation (days)	31.053 ± 2.483	30.286 ± 2.077	0.294

All values are mean ± standard deviation (SD).

A high pass filter of 128 seconds was applied in order to remove slow signal drifts and improve signal to noise ratio. For each emotional condition, two conditions were defined: depression emotional pictures and neutral emotional picture. In GLM analysis, when setting the model matrix, NEG vs. NEU, the block in NEG is set to 1, and the block in NEU is set to −1. When looking at the main effect of NEG alone, the trail in NEG is set to 1, and the rest are set to 0. Whole-brain voxel-based activation analysis was used to calculate the activation strength in each voxel in each subject and convert it into con-maps (con-maps is a contrast file, which represents the comparison operation of beta values under different conditions).Group-level statistical analyses were performed using a random-effects model in SPM8. Two-sample *t*-test was conducted on the individual con-maps of the two groups with small volume correction for the one sample results masks. The volume threshold for each cluster was >389 consecutive voxels; the single voxel threshold for brain regions was $P < 0.05$ (corrected). Multiple comparison correction for the results was performed using simulation (see program AlphaSim by B.D. Ward, http://afni.nimh.nih.gov/pub/

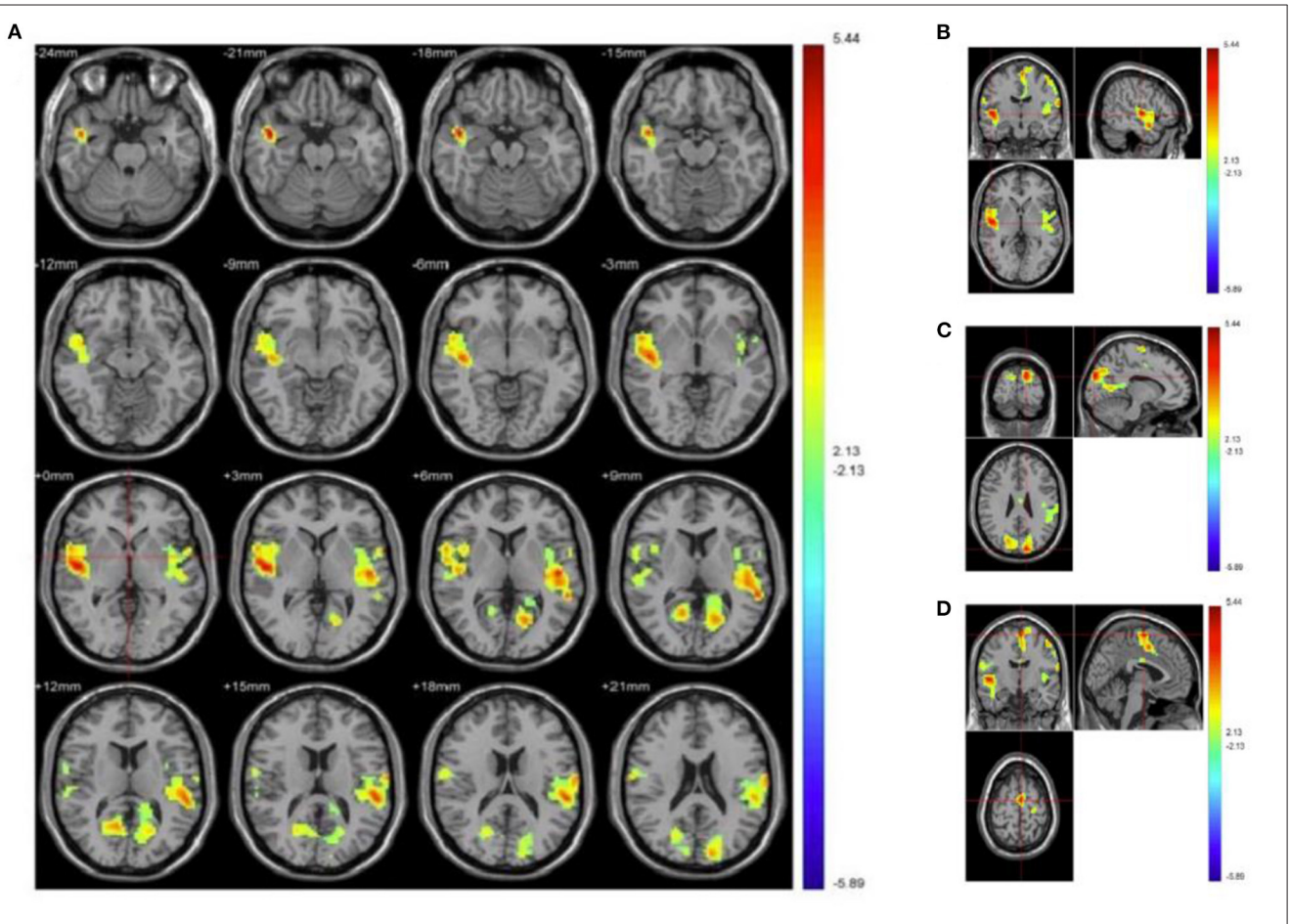

FIGURE 2 | Increased and decreased activation of PMS patients' brain regions than healthy controls when processing depression vs. neutral pictures. **(A)** Depicts overall activation of the brain area by negative emotional picture task in PMS patients. **(B)** Manifests bilateral temporal lobe. **(C)** Illustrates bilateral precuneus, posterior cingulate, and cuneiform. **(D)** Demonstrates the brain areas activated in motor areas. Red indicates enhanced activation of brain regions in PMS patients, while blue indicates that activation is decreased.

TABLE 2 | Difference area of two sample *t*-test under the condition of subtracting neutral picture from negative emotion picture between PMS group and HC group in BOLD-fMRI.

Brain region		Peak MNI coordinate			BA	*T*-Value	Sub-brain region	
Clusters peak voxel	Cluster voxels	X	Y	Z			Sub-cluster	Sub-cluster voxels
Putamen_L	1,418	−12	6	−9	BA 25	−4.3294	Orbit part of superior frontal gyrus	105
							Middle temporal gyrus	67
							Orbit part of inferior frontal gyrus	57
							Rectal gyrus	73
							Sub-lobar	289
							Sub-Gyral	124
							Extra-nuclear	113
							Right insula	22
							Amygdala hippocampus	142
							Anterior and adjacent cingulate gyrus	47
							Caudate	107
							Caudate head	78
							Putamen	126
							Caudate	45
							Globus pallidus	23
Cerebelum_Crus1_R	642	39	−75	−18	BA 19	3.7694	Cerebelum_Crus1_R	123
							Cerebelum_6_R	60
							Culmen	54
							Cerebellum anterior lobe	54
							Tuber	35
							Cerebellar tonsil	29
							Right inferior occipital gyrus	111
							Lingual gyrus	12
							Right fusiform gyrus	104
							Fusiform gyrus	32
							Inferior temporal gyrus	28

BA, Brodmann's areas.

dist/doc/manual/AlphaSim.pdf), with a statistically significant difference. A double-sample *t*-test was used to analyze the case and control groups.

RESULTS

Demographics

This study included 13 women with PMS and 15 matched HC. The sample size was determined prospectively and was bigger than existing published studies evaluating brain activity in PMDD women (20–22). The groups did not differ significantly in age (years), menophania (years), length of menstrual cycles (days), menstruation (days), all *p*s > 0.1 (see **Table 1**).

Degree of Depression

After the subjects completed the experiment, they were asked to identify depression severity using SDS. Depression degree in PMS patients was significantly higher than that in the HC group ($P < 0.001$; **Figure 1B**).

Group Differences in BOLD-FMRI

Compared with HC group, PMS patients exhibit increased activation in the following brain regions: right inferior occipital gyrus, right middle occipital gyrus, right lingual gyrus, right fusiform gyrus, right inferior temporal gyrus, cerebelum_crus1_R, cerebelum_6_R, culmen, cerebellum anterior lobe, tuber, and cerebellar tonsil. Simultaneously, PMS patients have decreased activation of the following brain areas: sub-lobar, sub-gyral, extra-nuclear, right orbit part of superior frontal gyrus, right middle temporal gyrus, right orbit part of inferior frontal gyrus, limbic lobe, right insula, bilateral anterior and adjacent cingulate gyrus, bilateral caudate, caudate head, bilateral putamen and left globus pallidus, (**Figure 2** and **Table 1**).

DISCUSSION

According to established research, women with PMS appear to experience emotional dysregulation throughout the menstrual cycle (23). Additionally, students experienced more emotional regulation deficits (24). Among premenstrual symptoms, depression was the most prominent feature of PMS diagnosis and should be properly evaluated and treated (10). Our findings indicated that the depression degree in PMS patients was significantly higher than in the HC group (**Figure 1B**), which

is consistent with our findings in PMDD (19). Women with PMS/PMDD show significant depression, which is a response to abnormal changes in the brain. When PMS patients are exposed to emotional stimuli, the function of the spindle gyrus in occipital and temporal lobes, as well as activation of the right infratemporal gyrus and cerebellum, are enhanced, while sub lobar, sub gyral, extra nucleus, frontal, marginal, and basal nuclei are weakened (**Table 2** and **Figure 2**). It demonstrates that the above-mentioned brain area function regulation is abnormal before menstruation, followed by emotional, cognitive, and attention distribution changes, all of which are associated with PMS pathogenesis.

Our findings corroborate other research conducted both domestically and internationally. The frontal lobe is involved in spiritual activities associated with an individual's emotions (25). The prefrontal cortex (PFC) plays a critical role in emotion generation and regulation (26). Furthermore, the prefrontal cortex edge, especially the orbitofrontal cortex, influenced decision-making and emotional regulation (27). When untreated depression patients viewed negative emotional stimuli, the right orbitofrontal cortex (28) (middle frontal gyrus) oxygen-dependent reaction weakened, which may be linked to depression emotion.

Besides, insular is involved in emotional processing and influences individual decisions (29). In the task state, insula and insular cortex activity of PMDD patients significantly increased during the luteal phase (29). Our findings revealed that right insula activation decreased in task state, which is a new discovery in PMS research that is not identical to PMDD (19). Additionally, there were changes in the hippocampus cortex of PMDD patients (30). Amygdala, hippocampus, and anterior cingulate belong to the limbic lobe, which is intimately connected to emotional, functional activities (31). Cerebellum was linked to cognitive function (32). PMDD subjects had greater cerebral gray-matter volume than controls in the posterior cerebellum (33). The cerebellar activity of PMDD patients increased from follicular phase to late luteal phase (34), especially cerebellar vermis, which was correlated with emotional deterioration, as confirmed by our study. Additionally, our findings indicated that culmen, cerebellum anterior lobe, tuber, and cerebellar tonsil were intimately associated with PMS.

Limitations

For now, our findings in college students with PMS in China have suggested their basic neural mechanism, and we need to aim at the deeper mechanism of PMS/PMDD and explore correlation between BOLD fMRI and SDS in the future study. Besides, the physiological components induced by heart rate and respiration were not considered in our study. We will pay more attention to the analysis of influencing factors such as heart rate.

CONCLUSIONS

In summary, PMS's abnormal brain regions were localized using BOLD-fMRI in college students, indicating pathological brain changes. However, these new findings must be confirmed and replicated in the future using larger sample size and animal models.

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 Medicine Ethics Committee of the First Affiliated Hospital of Shandong University of Traditional Chinese 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

DG and MG designed the study, wrote the draft, and revised it. MG and YH performed the experiment. MG, QX, and LR collected data. MG performed the statistical analyses and finally edited manuscript. YY, LA, and JW provided key assistance. All authors contributed to and have approved the final manuscript.

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