AN EAST MEETS WEST THEORY OF DEPRESSION: FROM ZANG FU TO NEUROSCIENCE

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PhD

The Hong Kong Polytechnic University

2023

The Hong Kong Polytechnic University
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An East Meets West Theory of Depression: From Zang Fu to Neuroscience

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A thesis submitted in partial fulfillment of the requirements for
the degree of Doctor of Philosophy
March 2023

CERTIFICATE OF ORIGINALITY

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgment has been made in the text.

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ABSTRACT

Background: Depression has a high reported prevalence worldwide. The pathologies of depression in Western medicine may involve neurotransmitter, neuroendocrine, gene, and environmental factors. However, traditional Chinese medicine (TCM) has its own views to interpret the concept of depression. Therefore, this study aimed to explore the mechanisms of depression based on an integrated Eastern and Western approach.

Methods: An extensive theoretical review was first performed, summarizing the existing literature to create plausible pathways linking TCM-based organ function and depression. In the second stage of the project, a total of 100 depressed adults were assessed on their clinical performance, neurophysiological biomarkers, and TCM-based organ function. The third stage was a pilot randomized controlled trial to investigate the safety and efficacy of Baduanjin exercise in patients with major depressive disorder (MDD). The Baduanjin group took part in a 10-week Baduanjin program, while the control group continued with their usual routine. Assessments were conducted at baseline and 5 and 10 weeks after the intervention.

Results: The theoretical review found that TCM-based liver, spleen, and heart function might be interpreted by Western medicine as the neuroendocrine system, tryptophan and serotonin deficiencies, and hypoactivation of the frontal cortex. The path analysis targeting the TCM-based liver function of depression found a significant association between TCM-based liver function and cortisol, adrenocorticotrophic hormone (ACTH), and norepinephrine (NE). A marginally significant link was observed between NE and heart rate variability (HRV). Moreover, significant changes were found in the Hamilton Rating Scale for Depression-17 ($HRSD_{17}$), cortisol,

ACTH, and TCM-based liver function after the 10-week Baduanjin intervention compared with baseline scores. The improvement trends in $HRSD_{17}$, TCM-based liver function, cortisol, and ACTH were only observed in the Baduanjin group.

Discussion and implications: Although tremendous differences exist between Eastern and Western medicine theories, this study provides evidence to support the hypothetical model of the relationship between the hypothalamic–pituitary–adrenal (HPA) axis and TCM-based liver function in individuals with depression. This implies that TCM is not only based on clinical experience but also supported by scientific approaches. Additionally, a non-significant association was found between NE, HRV, and TCM-based liver function in depressed adults. This suggests that TCM-based liver function may not be explained by the locus coeruleus and norepinephrine system. Furthermore, significant improvements were found in $HRSD_{17}$, TCM-based liver function, cortisol, and ACTH after a 10-week Baduanjin intervention in patients with MDD. This suggests that Baduanjin exercise had beneficial effects on MDD. Although no between-group difference was found after the Baduanjin intervention, the trends of improvement towards $HRSD_{17}$, TCM-based liver function, cortisol, and ACTH were noticed in the Baduanjin group 5 and 10 weeks after the intervention. Baduanjin is a safe and effective therapy for MDD. These findings serve as a blueprint for further experimental studies, especially integrating Eastern and Western approaches to depression.

PUBLICATIONS AND CONFERENCE PRESENTATIONS ARISING FROM THE THESIS

Journal papers

Ye, J., Yu, Y., Lian, X., Wang, W., Chung, C. K. P., & Tsang, H. W. H. The effects of Baduanjin exercise on neurophysiological outcomes in patients with major depressive disorder: A pilot randomized controlled trial. *Complementary Therapies in Medicine.* (under review).

Ye, J., Yu, Y., Chung, C. K. P., Lian, X., Wang, W., Cheung, W. M., & Tsang, H. W. H. (2023). The relationship between liver function and neurophysiological factors in depressed individuals: A cross-sectional study using an integrated "East meets West" medicine approach. *Frontiers in Psychiatry. 14.*

Ye, J., Cheung, W. M., & Tsang, H. W. H. (2019). The neuroscience of nonpharmacological traditional Chinese therapy (NTCT) for major depressive disorder: A systematic review and meta-analysis. *Evidence-Based Complementary Alternative Medicine Review: A Journal of Clinical Therapeutic.*

Ye, J., Cai S., & Tsang, H.W. H. (2019). An East meets West approach to the understanding of emotion dysregulation in depression: From perspective to scientific evidence. *Frontiers in Psychology. 10*(574).

Conference presentations

Ye, J., & Tsang, H. W. H. (April 2023). An East meets West approach to the understanding of pathology in depression. Presented at the International Conference on Behavioral Health, Psychiatry, Addiction Medicine, Neurology & Brain Disorders (BNB), Tokyo, Japan.

Ye, J. (August 2022). Discussion on Eastern and Western approaches towards depression. Presented at the 2nd Africanising the Art of Acupuncture,

University of Johannesburg, South Africa.

Ye, J., & Tsang, H. W. H. (September, 2019). East meets West: Comparison between TCM and MOHO. Poster presentation at the Sixth International Institute on the Model of Human Occupation, Illinois, USA.

Ye, J., Cheung, W. M., & Tsang, H. W. H. (November, 2018). The neuroscience of non-pharmacological Chinese medicine interventions for depression: A systematic review and meta-analysis. Presented at the 11th Pan-Pacific Conference on Rehabilitation, The Hong Kong Polytechnic University, Hong Kong.

ACKNOWLEDGEMENTS

My heartfelt appreciation goes to:

- My supervisor, Professor Hector Tsang, for his priceless advice and wonderful support of my academic growth. This PhD project would not have been possible without his direction and instruction. I am deeply grateful for his guidance and trust.
- The staff of the Rehabilitation Sciences, PolyU, especially Dr. Raymond Chung (statistics), Dr. Kino Lam (clinical association), Mr. Dennis Mok, Ms. Alexandra Lo, Ms. Sally Chan, Ms. Renee Wong, and Ms. Mandy Tang (administration), who helped me in times of need.
- Dr. Daniel Ahorsu, Ms. Yvonne Weng, Dr. Wendy So, Dr. Polly Ma, Dr. Erin Liu, Mr. Cody Chinn, and all team members of Prof. Tsang for their comments and assistance during my study period.
- My colleagues at the Rehabilitation Hospital in Fujian, China, especially Dr. Yunying Yu and Prof. Wei Lin, who helped with numerous ways, especially during the data collection period.
- The participants of this study for their support to complete this PhD program.
- My family members for their unconditional love, support, and encouragement during the PhD period.

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5-HT	5-hydroxytryptamine
ACTH	Adrenocorticotropic hormone
ANS	Autonomic nervous system
BD	Baduanjin group
CBT	Cognitive behavioral therapy
CCT	Clinical control trial
CFI	Comparative fit index
CG	Control group
ChiCTR	Chinese Clinical Trial Registry
CNKI	China National Knowledge Infrastructure
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
Cr	Creatine
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CRS	Carroll Rating Scale for Depression
DA	Dopamine
df	Degree(s) of freedom
DMBI	Chan-based Dejian mind–body intervention
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition
E	Adrenaline
ECG	Electroencephalography

EDTA-Na2	Ethylenediaminetetraacetic acid disodium salt
ELISA	Enzyme-linked immunosorbent assay
FFT	Fast Fourier transform
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
GABA	λ-amino butyric acid
GE	Gene–environment
Glu	Glutamine
HF	High frequency
HPA	Hypothalamic–pituitary–adrenal
$HRSD_{17}$	17-Item Hamilton Rating Scale for Depression
HRV	Heart rate variability
IDO	Indoleamine 2,3-dioxygenase
IFN-λ	Interferon-λ
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-Iß	Interleukin-Iß
LC/NE	Locus coeruleus–norepinephrine
LF	Low frequency
LOCF	Last observation carried forward
MADRS	Montgomery–Asberg Depression Rating Scale
MDD	Major depressive disorder
MHPG	3-methoxy-4-hydroxyphenylglycol
MoCA	Montreal Cognitive Assessment

MRI	Magnetic resonance imaging
NAA	N-acetyl-aspartate
NFI	Normed fit index
NTCT	Nonpharmacological traditional Chinese therapy
OFC	Orbitofrontal cortex
Para	Parahippocampus
PEDro	Physiotherapy Evidence Database
PET	Positron emission tomography
PFC	Prefrontal cortex
pgACC	Pregenual anterior cingulate cortex
Pu	Putamen
RCT	Randomized controlled trial
RM ANOVA	Repeated measures analysis of variance
RMSEA	Root mean square error of approximation
SD	Standard deviation
SDS	Self-Rated Depression Scale
SDNN	Standard deviation of normal-to-normal NN (R-R) intervals
SPECT	Single photon emission computed tomography
sgACC	Subgenual anterior cingulate cortex
SSRIs	Selective serotonin reuptake inhibitors
TCM	Traditional Chinese medicine
TNF- α	Tumor necrosis factor-α
VTA	Ventral tegmental area
SCID	Structured Clinical Interview for DSM-5 Disorders

CHAPTER 1

Introduction

This chapter provides an overall view of depression based on traditional Chinese medicine (TCM) theory. It sets out the background of the study and states the problem, the overarching aim and research objectives, and the significance of the study.

1.1 Depression: A global health concern

Depression is defined as a mental disorder that causes a persistent feeling of sadness and loss of interest in activities (Blazer Ii, 1993). A depressive episode can be classified into three categories according to the severity of symptoms: mild (26.4–49% of cases), moderate (9.5–19%), and severe (13–16%; Mossie, Kindu, & Negash, 2016; Shim, Baltrus, Ye, & Rust, 2011; World Health Organization [WHO], 1992, 2018). An individual experiencing a mild depressive episode may have difficulties participating in social activities. Those experiencing a major depressive episode are likely to have serious problems developing normal relationships with others and participating in routine social or work activities. Moderate episodes represent an intermediate severity (Mossie et al., 2016; WHO, 2008). Different types of depression may have various clinical symptoms. According to the Fifth Edition of the *Diagnostic and Statistical Manual of Mental Health Disorders* (DSM-5), depression is categorized into seven types: major depressive disorder (MDD), dysthymia, premenstrual dysphoric disorder, substance- or medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder (American Psychiatric & American Psychiatric Association, 2013). Given the diversity of depression, its clinical symptoms also vary greatly. They may include a change in body weight, loss of appetite and interests, irritability, reduced self-esteem, sleep problems, poor concentration, feelings of guilt and uselessness, and suicidal thoughts. These symptoms may lead to reduced life satisfaction or hospitalization (Mossie et al., 2016). Depression is a leading cause of disability. The WHO (2021) proposed that depression may have the greatest worldwide burden of disease by 2030. Depression may be increasing due to unemployment and the loss of productivity (Wang et al.,

2017).

Depression is common (McCarron et al., 2021), affecting 280 million people around the world (WHO, 2021). The global prevalence of depression is approximately 3.8%, and higher rates have been observed in adults (5.0%) and older adults aged 60 and above (5.7%; Evaluation, 2021; WHO, 2021). Depression is more common in women than in men, with a twofold greater risk (Merikangas & Low, 2004; Weissman et al., 1996). The lifetime prevalence of depression ranges from 7% to 12% in men and 20% to 25% in women (Mutangadura, 2004). Kessler (2003) found that the lifetime prevalence of depression was 16.2%, and the 12-month prevalence was 6.6%, among American adults. A systematic review showed that the prevalence of depression varied greatly in middle-income countries (Akena et al., 2012). The highest rate was found in South Africa, with a prevalence of around 53% (Spies et al., 2009), followed by the Middle East, with 48.5% (Puertas et al., 2004), and West Africa, with 43.3% (Baggaley et al., 2007). The lowest burden was in East Africa, with a prevalence of about 11.1% (Kaaya et al., 2002). A survey conducted by Hay et al. (2017) found that mental health disorders, especially depression, were the second most common disorder, after musculoskeletal disorders, in a middle-aged population.

1.2 Understanding depression based on the traditional Chinese medicine approach

TCM is a holistic approach that has been used for the prevention, diagnosis, treatment, and cure of diseases and promotion of good health. This Eastern medicine theory has been developed based on knowledge and practice accumulated over centuries in the Chinese population (Xu et al., 2013). Major TCM practices for depression may include acupuncture, Chinese herbs, Qigong, Tai Chi, and massage (Tang et al., 2008). More than 200 million patients around the world have adopted

TCM treatments (Ye et al., 2019). The value of industrial output from TCM was around US $70 billion, according to the Chinese National Bureau of Statistics (Friesen, 2013). The global TCM market is annually increasing by 10-20% (Friesen, 2013; Liu et al., 2015).

The Yellow Emperor's Classic of Internal Medicine, also known as *Huangdi Neijing*, is the origin of the TCM pathologies of different disorders and diseases (Li et al., 1990). According to this classic book, depression is closely related to the dysregulation of Yin and Yang, Qi, and Blood, concerning the liver, spleen, and heart (Tang et al., 2008). Yin and Yang can be recognized as a dualistic mode of viewing substances and their activities; they function in pairs, but in opposite ways (Chen & Chen, 1998). Qi means vital energy according to TCM theory, and the imbalance of Qi may lead to clinical signs and symptoms. According to the TCM-based theory, dysregulation of the liver may be caused by extreme emotional changes such as increases in anger, depressive mood, and anxiety because these may influence the circulation of Qi and Blood in the liver. If the liver function cannot be quickly restored, it may affect the function of the spleen and then eventually affect the function of the heart. Because the function of the heart is to control the Blood and maintain normal mental activities, with its dysregulation, the circulation of heart Qi and Blood will be disrupted, which may lead to clinical symptoms such as irritability, insomnia, and depression (Tang et al., 2008; Ye et al., 2019). This TCM depression theory is commonly accepted and widely practiced by Chinese medicine practitioners. However, scientific communities, particularly in the Western world, still have many concerns about its empirical support and underpinnings by well-accepted sciences such as physiology, pathology, and neuroscience.

1.3 Baduanjin exercise

Baduanjin, also called Eight-Session Brocade, is a form of traditional Chinese Qigong exercise characterized by the coordination of body movements, meditation, deep breathing, and mental focus (Tsang et al., 2013; Ye et al., 2014; Yeung et al., 2018; Zou et al., 2017). Recently, this exercise has received increasing attention around the world given its therapeutic effects and low cognitive demand (Tsang et al., 2013; Xiao et al., 2018).

1.3.1 The history of Baduanjin

The development of Baduanjin exercise has a history of more than 1,000 years, dating back to the Song Dynasty (960–1279; Zeng et al., 2020). The earliest documentation of Baduanjin is in the story collection *Yijian Zhi* (夷坚志; Xu, 1999), but it does not mention the details of the training movements.

The exercise was substantially developed in the Ming and Qing Dynasties (1368–1912). Its name derives from "Ba" (eight), "Duan" (sections or pieces), and "Jin" (brocade; Baduanjin, 1977). Ancient Chinese practitioners suggested that Baduanjin should be practiced at midnight, including both sitting and standing forms, based on the theory of "midnight–midday ebb and flow" (子午流注; Xu, 1999). Many versions of the movements have evolved since the Song Dynasty.

The current most widely practiced version of Baduanjin was developed by the Department of Taiji and Qigong of the Chinese National Sports Committee based on scientific studies. The movements in this version were designed for effective treatment and health promotion (Abbott & Lavretsky, 2013; Health-Qigong & China, 2005; Lavretsky et al., 2011).

1.3.2 Effects of Baduanjin exercise on mental illness

Baduanjin exercise, as a holistic mindfulness-based therapy, has been applied to

relieve the clinical symptoms caused by emotional disturbances (Ng & Tsang, 2009; Tsang et al., 2013; Ye et al., 2019). Previous systematic reviews have suggested that Baduanjin exercise may have beneficial effects on depression and its comorbidities such as sleep problems and anxiety (Liu et al., 2015; Wang et al., 2016; Wang et al., 2017; Zhu et al., 2018; Zhu et al., 2017; Zhuo, 2017). A randomized controlled trial (RCT) by Tsang et al. (2003) reported that 12 weeks of Baduanjin exercise may improve the biopsychosocial health of elderly people with chronic physical illness. Another RCT by Tsang et al. (2013) also supported the finding that 12 weeks of Baduanjin training, with a frequency of three sessions per week, could significantly improve depressive symptoms and self-efficacy in depressed patients. A more recent RCT from Taiwan suggested that 12 weeks of Baduanjin exercise significantly reduced depressive symptoms in individuals with depression (Lee et al., 2019). Given these findings, Baduanjin exercise can be an alternative therapy for improving the mental health of patients with depression.

Although the clinical effectiveness of Baduanjin exercise in mental illness has been well-documented by researchers, the underlying mechanism of this technique remains elusive. Tsang et al. (2002) proposed that the hypothalamic–pituitary–adrenal (HPA) axis might an underlying mechanism of Baduanjin exercise to alleviate depressive symptoms, but this theory still needs more empirical support.

1.4 Problem statement

Despite many years of accumulated knowledge and practice regarding TCM, it still lacks compelling scientific evidence in support of its theory and clinical practice. The theory of depression in TCM has evolved over thousands of years, but the pathology of depression is still unknown.

1.5 Objectives of the study

The objectives of the study were:

(1) To propose an integrated Eastern and Western medicine model of depression

(2) To support the hypothesized pathological pathways linking liver dysfunction and depression

(3) To explore the safety and efficacy of Baduanjin exercise in patients with major depressive disorder (MDD)

1.6 Significance of the study

This is a pioneering scientific study to test the possible pathological pathways (HPA axis and locus coeruleus–norepinephrine [LC/NE] system) based on the TCM theory of depression concerning liver function and neurophysiological approaches. It contributes to our understanding of depression based on the integration of the Eastern tradition and Western medical sciences. Furthermore, it provides scientific evidence to support the application of the Zang Fu (臟腑) theory of depression, which may be useful in future studies. Lastly, it offers insight into the delivery of evidence-based practice of Baduanjin exercise for clinical professionals.

CHAPTER 2

An East meets West approach to understanding emotion dysregulation in depression: From perspective to scientific evidence

This chapter presents a theoretical review based on the Eastern and Western approaches to understanding depression. It also builds some plausible neurophysiological models for a better understanding of the pathologies of depression using modern knowledge and technologies.

2.1 Introduction

Depression, an emotion regulation disorder, is one of the most prevalent psychiatric disorders worldwide. People with depression will spend approximately 8.2% of their lifespan managing the associated disabilities (General Office of the State Administration of Traditional Chinese Medicine and School of Management of Beijing University of Chinese Medicine, 2006).

Emotion regulation refers to the interaction between the occurrence, intensity, duration, and expression of emotion (Gratz & Roemer, 2008). Emotion regulation strategies are closely associated with mental health (Aldao et al., 2010). Depression is characterized by the emotion of sadness and the inability to extract pleasure from positive situations. Previous studies have suggested that patients with depression lack the emotion of anger because of their inability to handle stressful situations (Gu et al., 2016). People with depression can regulate their emotions in many ways, including coping strategies and motivation (Campbell-Sills et al., 2006; Kring & Werner, 2004). Several experimental studies on emotion regulation support the view that a deficit in emotion regulation can be a crucial clue to understanding the etiology of depression (Soygüt & Savaşır, 2001). Therefore, emotion dysregulation is closely related to depression, and understanding emotion regulation is vital to unravel the pathogenesis of this disorder.

TCM originated in ancient China and has evolved over thousands of years. Today, a growing number of people around the world are using TCM to prevent or cure diseases. In 2006, over 200 million outpatients and 7 million inpatients received TCM therapies. Most of the principles of TCM are derived from the philosophical basis of Taoism and Confucianism (General Office of the State Administration of Traditional Chinese Medicine and School of Management of Beijing University of

Chinese Medicine, 2006). The main TCM therapies include herbal medicine, acupuncture, acupressure, moxibustion, massage, cupping, and physical exercise such as Qigong. TCM theory is based on clinical experience instead of scientific evidence. On the other hand, Western medicine is based on scientific investigation and tested by animal experiments and clinical trials. The two systems differ in their diagnoses, treatments, and theories (Stein, 2017). Despite a long history of clinical experience, the fundamentals of TCM remain largely unchanged. Similarly and unfortunately, the scientific elements underlying its theories remain largely unknown (Keji & Hao, 2003). The lack of scientific evidence has led to skepticism, criticism, and even rejection of TCM (Ted, 2000a).

Given the high prevalence of depression and the increasing attention given to TCM, this theoretical review attempts to explore the etiological mechanism of depression via the Eastern and Western or integrative approach. In the long run, this paper will broaden and deepen our understanding of the etiology, signs, and symptoms of depression. Hopefully, this will give us insight into the development of innovative intervention strategies.

2.2 Traditional Chinese medicine's views of emotion and depression

The TCM theory of emotion has a history of more than 2,000 years and embraces well-established diagnosis and treatment systems. TCM is a holistic health care philosophy deeming that the relationship between humans and nature is interactive and inseparable. It considers the relationships between humans and society, as well as between the internal organs as a whole. This has critical impacts on the natural and social environment concerning health and illness. Many ancient Chinese texts have content pertaining to the symptoms, etiologies, and treatment of depression caused by extreme emotional changes, using the concept of Yu or Yu-

zheng, which literally means “not flowing, entangled, blocked, or clogged” (Ou, 1988). *The Yellow Emperor’s Classic of Internal Medicine* is usually considered the earliest Chinese classic medical text in the world (General Office of the State Administration of Traditional Chinese Medicine and School of Management of Beijing University of Chinese Medicine, 2006). It expounds on the relationship between emotional changes and the five viscera: the heart, spleen, kidney, liver, and lung. According to TCM theory, emotional change is closely related to the etiology of diseases. The five viscera parallel the five elements (metal, wood, water, fire, and earth), which are transformed to create joy, anger, sadness, missing, and fear (Veith, 2016). This is derived from the five elements theory, which can be used to understand the physiology and pathology of the human body and the etiology and pathogenesis of diseases (Maciocia, 1989). The transformation of emotion is based on the productive cycle of the five elements theory. The interaction of elements and organs is as follows: sadness is related to the lung, and joy can oppose it; fear is related to the kidney, and missing can oppose it; anger is related to the liver, and sadness can oppose it; joy is related to the heart, and fear can oppose it; missing is related to the spleen, and anger can oppose it (Gu et al., 2018; Maciocia, 1989). If extremely emotional changes (e.g., anger, fear, and sadness) can be managed in the short term, this will not bring about negative influences on the human body (Zhuet al., 2018). If extremely emotional changes are strong and prolonged, this will cause the dysregulation of the autonomic nervous system (ANS) because it exceeds the adjustable range of physiology, and depression will occur.

Many ancient Chinese practitioners proposed definitions of Yu. Tao Hongjing (Tao & Shang, 1963), the author of *Shennong Bencao Jing Jizhu*, a variorum of Shennong’s classic materia medica, and a physician of the North and South Kingdoms

Period, reported the treatment of Yu using antelope horn. In another text, Chen Wuzhe (Chen & Lu, 1995), a famous TCM practitioner in the Song Dynasty (960–1279), proposed the concept of the "seven emotions," which indicated that emotional changes may lead to disharmony of the internal organs and then to Yu. Zhang Congzhen (Zhang et al., 2011), the most famous TCM practitioner in the Jin Dynasty (265–420), put forward the pathogen concept. Zhang proposed the methods of sweating, emesis, and diarrhea to treat Yu-zheng caused by a pathogen. Although several concepts regarding Yu were proposed in ancient times, the most useful concept for understanding its progression is Zhu Danxi's theory of the six depressions, which is regarded as the mainstay of TCM theory for understanding depression. The theory of the six depressions involves the stagnation of either Qi, Blood, Dampness, Phlegm, Food, or Fire. It is built on earlier Chinese medical texts such as the *Treatise on Cold Damage and Miscellaneous Disorders* and *The Yellow Emperor's Classic of Internal Medicine* (Chen et al., 2015; Scheid, 2013). Zhu Danxi's approach focused on the understanding of disease dynamics. He wrote that Qi was responsible for the movement and transformation of Blood, Dampness, Phlegm, Food, and Fire. If the Qi is stagnant, either Blood, Dampness, Phlegm, or Food cannot move or transform properly in the body. These obstructions of substances might accumulate and eventually turn into Fire (Park, 2002; Figure 2.1).

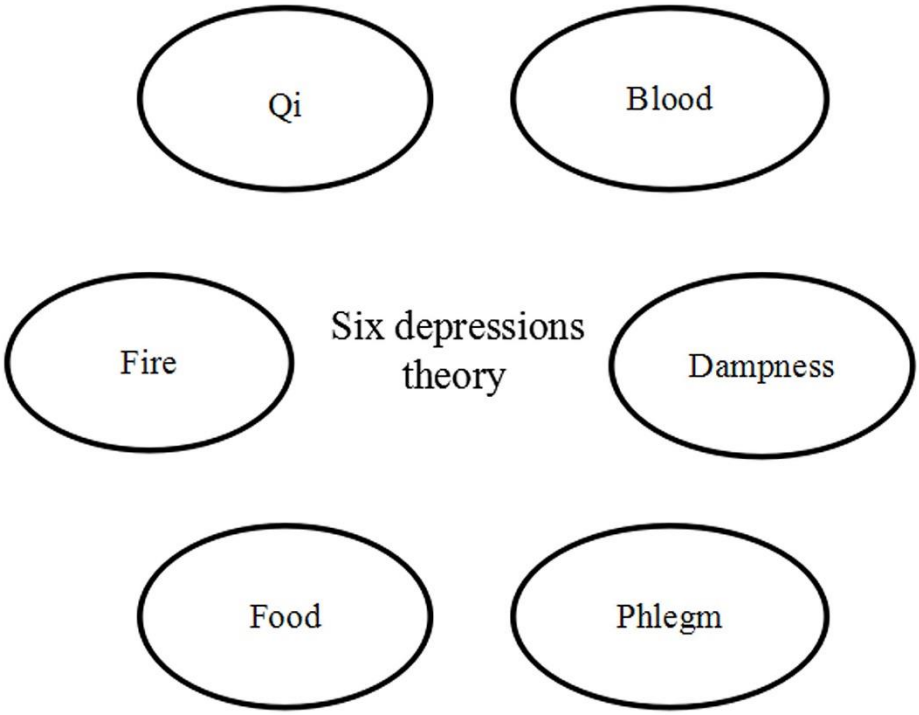

Figure 2.1 The structure of the six depressions theory in traditional Chinese medicine theory.

2.3 Western medicine's views of emotion and depression

Many studies have been devoted to investigating the etiology of depression (Krystal et al., 2002; Liu et al., 2015; Moret & Briley, 2011; Smith & Vale, 2006). However, the underlying pathophysiology of depression is still not fully understood. Several possible theories may explain the potential processes involved in depression, but neurophysiological factors play a vital causal role in the process (General, Services, Abuse, Administration, & Health, 2001).

2.3.1 Regulation of neurotransmitters

2.3.1.1 Norepinephrine therapy

Norepinephrine (NE) is responsible for the regulation of cardiovascular activity, pain sensation, and body temperature. Previous studies have shown a close link between NE and anxiety (Liu et al., 2015; Schildkraut, 1965). The possible relationship between depression and disturbance of NE in the brain was first proposed in 1965 (Schildkraut, 1965). An animal study (Schildkraut, 1965) reported that a lower concentration of NE in the brain caused by reserpine might lead to depression. Evidence showed that people with depression had either low or high levels of urinary 3-methoxy-4-hydroxyphenylglycol (MHPG), the metabolite of NE degradation, which indicated significant differences in the amount of NE in terms of synthesis and release between people with depression and healthy individuals (Samson et al., 1994). Because noradrenergic pathways in the brain arise from the locus coeruleus and project to the frontal cortex, limbic system, and spinal cord, neuroimaging studies suggest that abnormal metabolism in the limbic and paralimbic structures of the prefrontal cortex (PFC) is associated with emotional dysregulation and depression. This might indicate that medicine that increases NE activity in the brain could be one of the most effective therapeutic agents (Drevets et al., 2002).

2.3.1.2 Serotonin therapy

Serotonin (5-HT), biochemically derived from tryptophan, is primarily found in the central nervous system (CNS), gastrointestinal tract, and blood platelets (Young, 2007). Seven serotonin receptor subtypes generally exist and influence various biological and neurological processes, such as aggression, anxiety, appetite, sleep, mood, and thermoregulation (Glennon & Dukat, 1991; Weso owska, 2002). Coppen et al. (1965) developed a hypothesis on 5-HT and the treatment of depression in 1965. They proposed that decreased levels of 5-HT in the synaptic cleft might result in depression. Pandey (1997) found that suicidal patients had lower levels of 5-HT compared to healthy people. Wägner et al. (1990) showed that taking fluoxetine, a selective inhibitor of 5-HT uptake, significantly reduced the content of 5-HT compared to its original level based on a platelet sample and relieved the symptoms caused by depression. Clinical studies showed that 5-HT_2 receptors were likely to be involved in the pathophysiology and treatment of depression among various 5-HT receptor subtypes (Hoyer et al., 1986; Nyberg et al., 1993). In addition to 5-HT_2, 5-HT_{1A} receptors influence the regulation of mood. A review suggested that 5-HT_{1A} receptors were particularly related to antidepressant and anxiolytic responses in humans (Blier & Ward, 2003). The presynaptic 5-HT_{1A} receptors are located in the raphe nuclei, where they act as cell body auto-receptors to inhibit the firing rate of 5-HT neurons. On the other hand, the postsynaptic 5-HT_{1A} receptors are located in the limbic and cortical regions, where they also attenuate firing activity. This indicates that 5-HT_{1A} receptors have a negative feedback influence on firing activity in the brain (Aghajanian & Lakoski, 1984; Blier & De Montigny, 1987; Blier & Ward, 2003).

2.3.1.3 Dopamine therapy

Dopamine (DA), which participates in emotion regulation, is produced by the dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain, the substantia nigra pars compacta, and the arcuate nucleus of the hypothalamus. Its notable functions are associated with the mediation of mood, behavior, and cognition (Martini, 2015). The relationship between DA and depression was first described by Molander & Randrup (1976). Willner (1983) found that the concentration of DA was lower in patients with depression compared to healthy people. A study with post-mortem human subjects showed that the metabolite rate of DA was critically decreased in suicidal patients with depression, specifically in the regions of the caudate, putamen, and nucleus accumbens (Bowden et al., 1997). Evidence from recent studies also supports this finding. An animal study showed depletion of DA in brain samples from animals with behavioral depression after 3 weeks of reserpine injections (Ikram & Haleem, 2017). A clinical study found that the D_2 receptor of DA might be supersensitive in patients with depression compared to controls by means of a novel neuroendocrine challenge test, which indicated that dopaminergic mechanisms might be a target of therapeutic interest (Verbeeck et al., 2001).

2.3.2 Relationship of possible factors

2.3.2.1 Glutamine and λ-amino butyric acid

Glutamine (Glu) and λ-amino butyric acid (GABA) are respectively the main excitatory and inhibitory amino acids in the CNS mediating general mood states (Crabtree et al., 2013). Increasing evidence from clinical studies shows that Glu levels decrease in depressed patients compared with healthy controls (Auer et al., 2000; Liu et al., 2015). GABA concentrations in the occipital cortex and prefrontal regions of patients with depression also decrease compared with control groups (Hasler et al.,

2007; Sanacora et al., 1999). Studies on TCM have reported that levels of Glu and GABA might be increased by taking Chinese herbs (Gao et al., 2014; Liu et al., 2015). Because the levels of Glu and GABA are vital to maintaining normal brain function, the two neurotransmitter systems may be possible therapeutic targets in depression (Zorumski et al., 2013).

2.3.2.2 Gene and environment interaction

Previous research on twins has demonstrated that genetic factors play a vital role in the development of depression. Scientific findings show that the heritability of depression accounts for 31–42% of the variance in adolescents' depressive symptoms (Barclay et al., 2015; Sullivan et al., 2000). Scientists have recently theorized that genetic vulnerability factors can interact with environmental factors to make depressive symptoms more severe. An empirical study suggested that social context has a function in triggering and compensating for a genetic diathesis (Heath et al., 2002). Social context also acts as a control to prevent "genetic predisposition behaviors" (Heath et al., 2002). The diathesis–stress process of the gene–environment (GE) interaction might occur when those who have genetic vulnerability are in a stressful environment (Shanahan & Hofer, 2005).

2.3.2.3 Cognition

Cognition refers to the mental actions or processes of (a) gaining new knowledge and understanding and (b) recalling memories that involve perceiving, recognizing, conceiving, and reasoning. Apart from the factors of neurotransmitters and GE interaction, Beck's cognitive theory of depression must also be considered. The cognitive theory of negative automatic thoughts and underlying dysfunctional assumptions schemas were proposed by Beck in the mid-1960s (Beck, 1979). Beck found that negative thinking came from previously unpleasurable experiences that

could guide people's perceptions or interpretations, leading to a negative worldview and causing depression (Soygüt & Savaşır, 2001). The cognitive theory of depression indicates that early relevant experiences might result in the formation of dysfunctional beliefs, which might lead to negative self-beliefs. When those who have negative self-views encounter a specific circumstance, they are more likely to feel hopeless and useless and ultimately be depressed (Soygüt & Savaşır, 2001). A study by Allen (1990) based on students showed that negative attitudes toward the future were related to depressive mood. Depression-prone students were found to negatively process personal information, leading to the development of symptoms of depression. Evidence from Abela and D'Alessandro (2002) was in line with previous findings and suggested that dysfunctional attitudes and an increase in depressive mood were significantly associated with students' negative beliefs about the future (Figure 2.2).

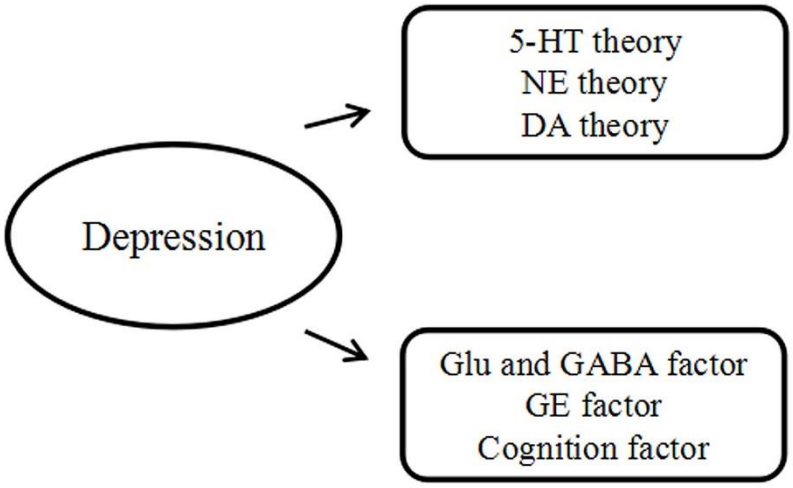

Figure 2.2 Etiologies of depression in Western medicine theory.

2.4 An integrated East meets West approach to closing the gap

In TCM, Zang Fu can be translated as “internal organs.” It may be regarded as a core concept of TCM that views the physical body as an integrated whole. It also describes an integrated relationship between mental activities, sense organs, tissues, the five solid and six hollow organs, and environment influences (Maciocia, 2005).

The theory of internal organs is entirely different from the anatomical structure in Western medicine. However, this does not mean that TCM entirely disregards anatomy. The concept of organs in Western medicine is based on anatomy, whereas the concept of organs in TCM is based on a system concept that embraces anatomy, physiology, and psychology. In TCM, the function of internal organs is basically related to various substances, emotions, tissues, and senses. For example, the basic substances of TCM are Qi (Energy), Xue (Blood), Jing (Essence), Shen (Spirit), and Jin Ye (Body Fluids). Each substance is related to one or more organs (e.g., the spleen governs Food and Qi and influences Body Fluids, and the heart governs Blood).

In Western medicine, the liver, the largest internal organ, has various functions in the body, including the synthesis of proteins, blood clotting factors, triglycerides, cholesterol, and glycogen and the production of bile. However, TCM theorists believe that the liver is responsible for controlling dispersion in all organs and all directions to ensure the smooth flow of Qi throughout the body. This is the most salient of all the liver’s functions, especially as far as depression is concerned. Concerning depression, the liver is postulated by Western medicine to be related to the functioning of the neuroendocrine system (Li & Wang, 1985; Yue & Tian, 1995).

To our knowledge, every organ’s energy has a normal direction of flow: the Qi of some organs flows downward (such as that of the stomach), and the Qi of other organs flows upward (such as that of the spleen). The normal direction of the

movement of the liver Qi is upward and outward in all directions to make sure that the flow of energy is smooth and unimpeded. The liver has three functional activities in terms of this movement: regulating emotions, regulating the secretion of bile, and assisting the digestive function of the spleen and stomach (Maciocia, 1989; Ross, 1985).

The emotional state of an individual depends on the smooth flow of energy and blood. When the liver Qi flows smoothly, the emotional status of the individual is calm and peaceful. In contrast, if the liver is not functioning well, the energy of the liver stagnates, which leads to an abnormal increase in liver Qi and emotional disturbances, such as depression, accompanied by physical symptoms, such as a sensation of oppression in the chest and hypochondriac pain (Maciocia, 1989). Scientific studies of animals and humans have provided preliminary support for the postulation that the liver function in TCM is associated with the neuroendocrine system that includes the regulation of the NE system located in the LC/NE system and the HPA axis (Wang & Lu, 2002; Yan & Xu, 2005; Guang et al., 2005; Yue & Tian, 1995).

2.4.1 LC/NE system

Studies have explored the symptoms of the abnormal increase of liver Qi that are correlated with a lack of regulation of the ANS (Yue & Tian, 1995), a deficiency of serotonin, and an excessive level of NE (Spiegelhalder et al., 2011; Wei et al., 2012). However, another study that NE level is not related to the severity of depression because of the different stages of depression (Yuan et al., 2004). The LC/NE system may be involved in the regulation of the neuroendocrine system based on the symptoms of liver Qi stagnation. The locus coeruleus is the central site of the LC/NE system in the brain, which is the center of the synthesizing adrenergic nerve. The

ascending fibers of the adrenergic nerve are mainly projected into the amygdala, hippocampus, and limbic cortex, which are responsible for emotional changes, memory, and behavioral changes. The descending fibers of the adrenergic nerve are mainly projected into the lateral dorsal horn of the spinal cord, which is involved in regulating the activity of the sympathetic nerve and the secretion of catecholamines. The activated amygdala may stimulate the release of corticotrophin-releasing hormone (CRH), which increases the activity of the sympathetic nerve via the mediating lateral dorsal horn of the spinal cord. Once the sympathetic nerve is activated, the adrenaline medulla releases NE and epinephrine (E) due to the activated adrenal gland (Copstead & Banasik, 2010, Figure 2.3).

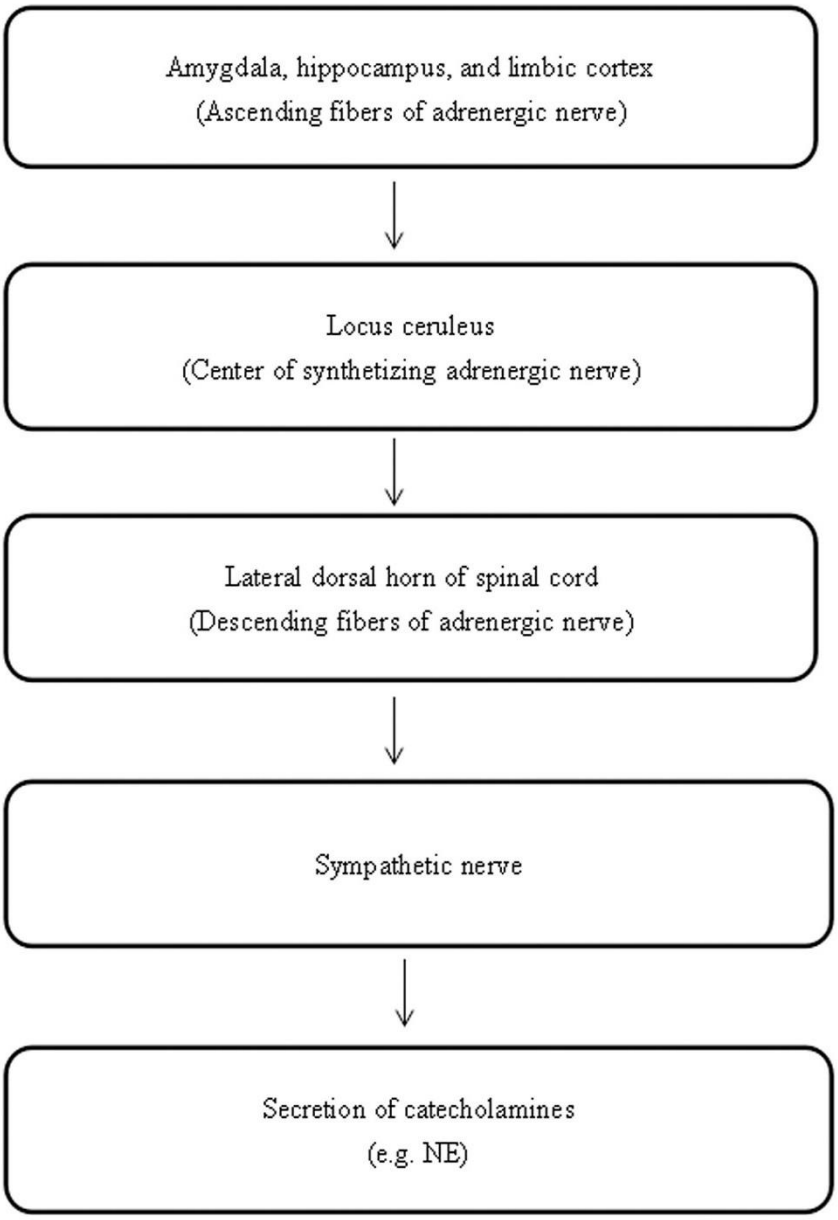

Figure 2.3 Neuropathways associated with the LC/NE system.

Increasing clinical trials support the association between liver diseases and the lack of ANS regulation (Guang Xin et al., 2005). Jin (2000) reported a positive correlation between increased sympathetic tone activity and the excess type of liver dysfunction, such as loss of appetite and a wiry pulse, along with a negative correlation between increased parasympathetic tone activity and the deficiency type of liver dysfunction, such as a weak pulse. Yuan et al. (2004) suggested that the NE level is higher in patients with depression compared to healthy people. Because results on NE levels in patients with depression are contradictory, experimental studies to explore this monoamine transmitter concentration in depressed patients would be a promising direction for further research.

2.4.2 HPA axis

In addition to the LC/NE system, the regulation of the HPA axis may be implicated in depression when liver dysfunction exists. The hypothalamus plays a role in the physiology of depression by increasing the activity of the HPA axis (Benca et al., 1992). The significance of the HPA axis in mediating physical manifestations of psychological stress has been well-documented (Nestler et al., 2002; Steiger, 2007). The activity of the HPA axis is mainly related to the operation of CRH from the parvocellular neurons of the paraventricular nucleus of the hypothalamus (Gu et al., 2018; Steiger, 2007). The secretion of CRH stimulates the release of adrenocorticotropic hormone (ACTH), secreting cortisol in humans and corticosterone in rats from the anterior pituitary. Most neuroendocrine studies of patients with clinical depression have reported elevated cortisol secretion and ACTH due to the impairment in the negative feedback system of cortisol to the HPA (Tsang & Fung, 2008; Figure 2.4).

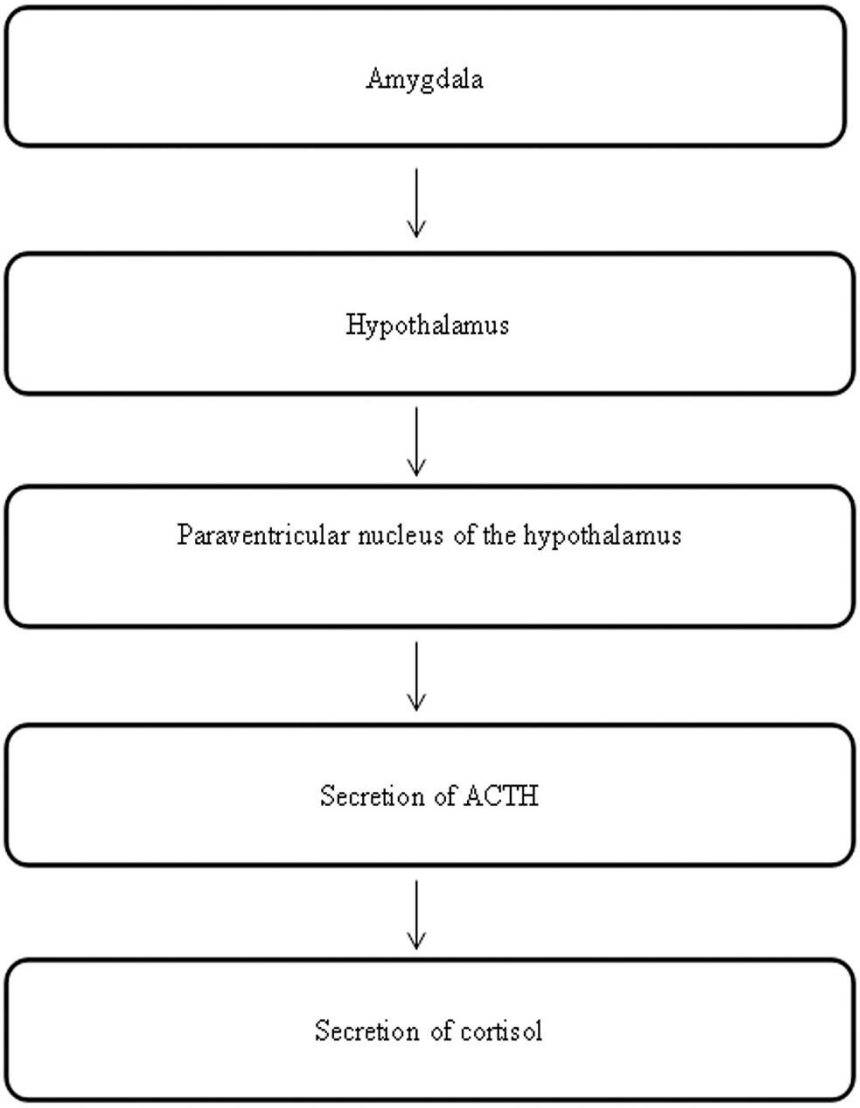

Figure 2.4 Neuropathways associated with the HPA axis.

In addition, the body state called “flight or flight” can be caused by elevated cortisol levels (Wang et al., 2017). Since the negative feedback of the HPA axis and cortisol is impaired, a higher level of HPA axis activity leads to reduced vagal modulation or excessive activation of sympathetic neurons, resulting in physiological activation, such as increased heart rate, peripheral vasoconstriction, elevated body temperature, and increased body metabolic rate (Bonnet & Arand, 2003; Kales, 1984; Kales et al., 1987; Vgontzas et al., 2001). This suggests that depression is closely related to the over-secretion of ACTH and cortisol.

2.4.3 ANS dysregulation

Apart from the function of regulating emotions in the liver, the digestive function of the spleen and stomach depends on the movement of liver Qi in TCM theory. If dysfunction exists in the liver, digestive activities are impaired. People may exhibit the symptoms of belching, sour regurgitation, and nausea or vomiting. Lastly, the flow of bile is affected by liver function. If dysfunction of the liver occurs, the flow of bile may stagnate, leading to a bitter taste in the mouth, belching, or jaundice, and resulting in sleep disturbance. An experimental study found that ANS dysfunction could be one of the reasons for emotional disturbance and functional dyspepsia (Vgontzas et al., 2001). Moreover, studies have shown a correlation between the symptoms of stagnation of liver Qi, deficiency of bile secretion, and intestinal malabsorption (Jin et al., 1985; Yue & Tian, 1995; Figure 2.5).

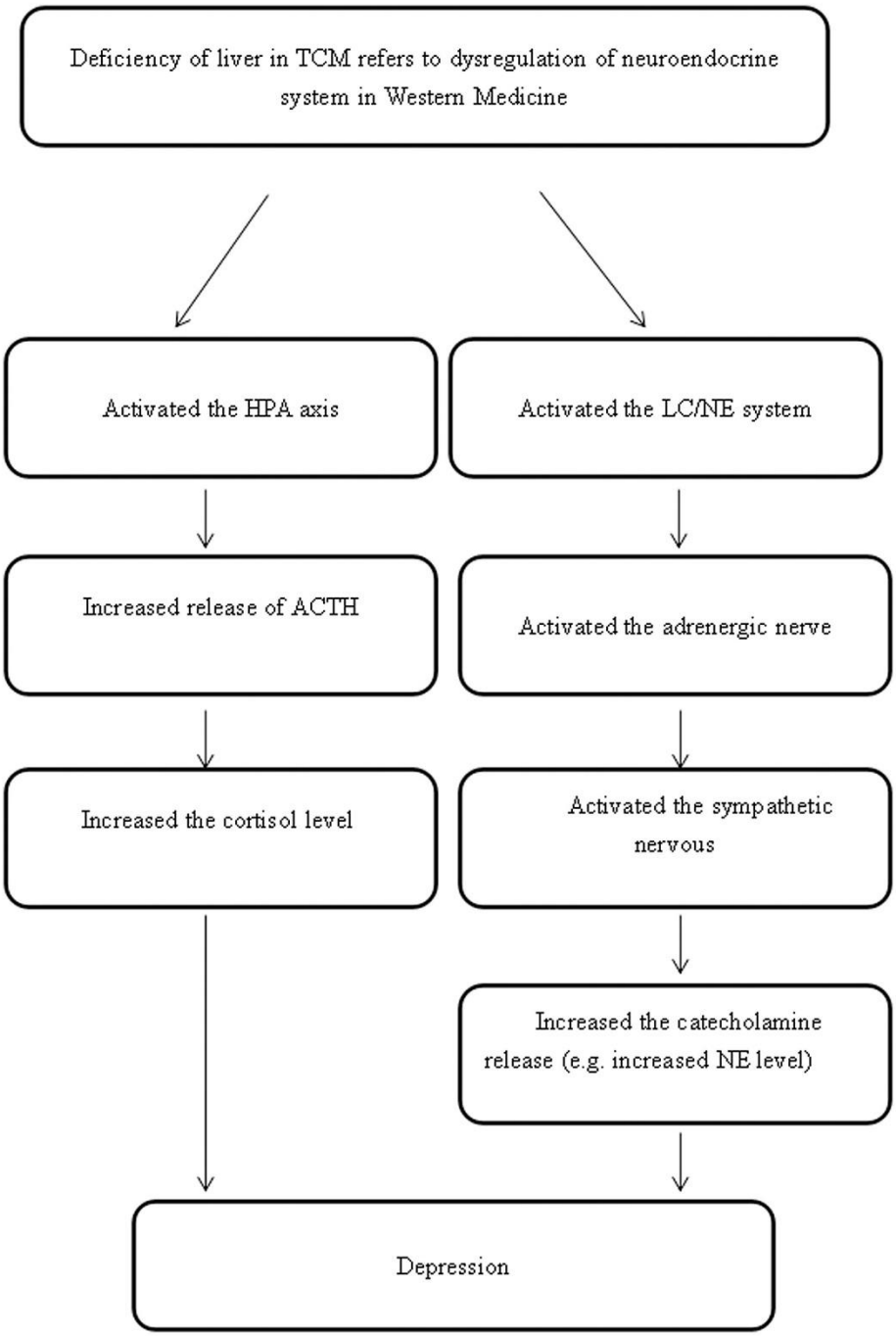

Figure 2.5 Hypothesized pathological pathways linking liver dysfunction and depression.

2.4.4 Tryptophan and serotonin deficiencies

The spleen is an abdominal organ that is involved in the production and removal of blood cells. It is a part of the immune system, according to Western medicine. However, the definition of the spleen in TCM theory is different, with a broader implication than in Western medicine. It refers not only to the organ itself but also to the functions of digestion (including the pancreas and small intestine) regarding depression (Yu, 2013).

The primary function of the spleen is to aid the stomach in the digestion of food by transporting and transforming nutrients from food and water, absorbing the nourishment, and separating the usable part of food and water from the unusable part (Giovanni, 1989). Once food and water are ingested, the spleen and stomach work closely together in digesting, extracting, and transporting the essence from food and water to the body. When the spleen is working properly, digestion is normal and a person has a good appetite, normal absorption, an adequate energy supply, and regular bowel movements (Giovanni, 1989). Because the liver has the function of assisting the digestive functions of the spleen and stomach, if it does not function properly, this affects the spleen function, resulting in poor appetite, indigestion, and abdominal distension. In five-element terms, this corresponds to "Wood overacting on Earth."

Previous research aligns with our postulation. Patients with dysfunction of the spleen have shown a low concentration of urine amylase, an insufficient concentration of serum gastrin, and a low frequency of peristalsis of the stomach (Jia et al., 1999; Tao et al., 2005; Zhang, 2006). A review showed that compared to patients with only one gastrointestinal disease, patients with comorbid gastrointestinal diseases were more likely to experience anxiety, depression, and insomnia, with pathogeneses of visceral hypersensitivity, altered gastrointestinal disease motility, infection, and

stressful early life events (Yue & Tian, 1995). Lindgren et al. (2012) reported that depression was related to the symptoms of poor appetite, heartburn, diarrhea, bloating, constipation, and epigastralgia in pilots. Moreover, tryptophan, which is an indispensable amino acid and a precursor of serotonin and melatonin, which are thought to regulate mood, is taken from food (Zhang, 2006). The intake of tryptophan influences the regulation of emotional state by influencing serotonin synthesis, and this could be considered an effective therapy for treating depression (Hartmann, 1982; Lieberman, 2003; Shaw et al., 2002). If a lack of food intake is related to a deficiency in tryptophan and eventually serotonin, emotional changes such as depression could occur, which parallels the findings from previous studies (Birdsall, 1998; Le Floc'h et al., 2011; Lieberman, 2003; Sainio et al., 1996; Yao et al., 2011). These studies provide preliminary evidence to support the postulation that the stagnation of liver Qi and spleen deficiency in depressed people, in terms of TCM theory, may parallel the abnormal digestive functions in patients with depression based on the Western medical viewpoint (2.6).

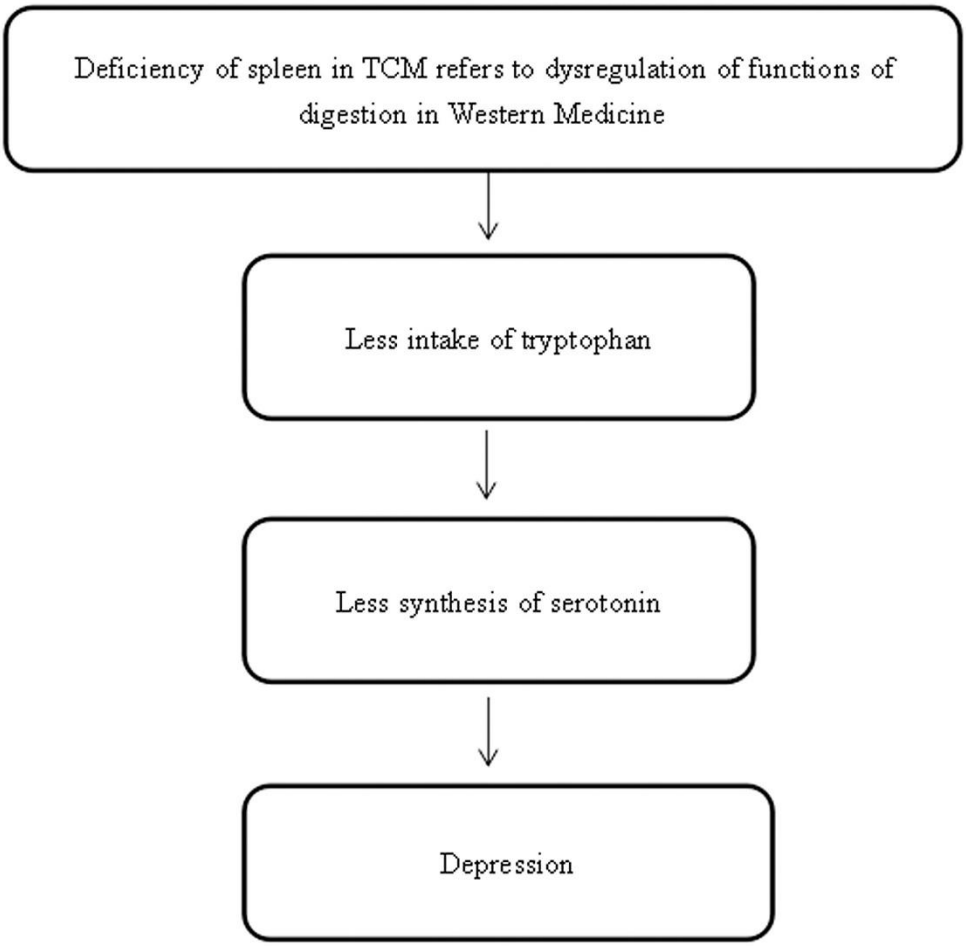

Figure 2.6 Hypothesized pathological neuropathways linked with spleen dysfunction and depression.

2.4.5 Hypoactivation in the frontal cortex

The heart is a muscular organ that pumps blood throughout the body through the circulatory system, which provides oxygen and nutrients and removes metabolic waste. However, the function of the heart is more diversified in TCM than in Western medicine. The heart is responsible for the circulation of blood and the regulation of mental activities (Giovanni, 1989; Guang Xin et al., 2005; Zhang, 2004). According to TCM, the main functions of the heart are to govern the circulation of blood, control the blood vessels, manifest the complexion, and store the Shen, which implies consciousness, mental functions, emotion, and vitality (Giovanni, 1989; Ross, 1985; Guang Xin et al., 2005; Zhang, 2004).

In TCM theory, a healthy heart is essential for supplying blood to all tissues in the body. With heart dysfunction, the circulation of blood is insufficient, and the four limbs may be cold. People might exhibit the symptoms of a lower body temperature and a white or purple complexion (Giovanni, 1989). Additionally, storing Shen, which can be translated as “spirit” or “mind,” is a part of the heart’s functions. Shen highlights the whole emotional, mental, and spiritual aspects of a person. In this sense, Shen not only indicates the heart, but also encompasses the emotional, mental, and spiritual phenomena of all organs. If dysfunction of the heart occurs, the blood is insufficient to nourish the Shen, and a person will have difficulty in maintaining a good memory and good mental health; thus, they may suffer from depression. Furthermore, the heart is in charge of controlling blood vessels. The function of storing Shen depends on adequate nourishment from the heart blood. Therefore, a mutual relationship exists between the functions of controlling blood vessels and storing mind. Because the blood is the root of Shen, if the heart blood is sufficient, the mind is peaceful and happy, and the pulse becomes regular and normal. Conversely, if

the heart blood is deficient, insufficient blood exists to root the mind, which results in mental restlessness, depression, palpitations, and a weak or irregular pulse.

Increasing studies support this ancient theory, showing that, compared with healthy people, patients with depression associated with deficiency of the heart and spleen have lower brain activity in the left frontal cortex region (Feng et al., 2005; Wang, Wang, et al., 2008; Xie, 2007). These findings are in line with those of Western medicine that major depression is related to decreased activity in the left hemisphere relative to the right hemisphere and a decline in the activity of the left frontal cortex in people suffering from depression compared to healthy people. Clinical studies have reported that depression is related to altered resting-state activity in the PFC, and growing findings from functional and structural imaging studies show that depression is associated with volume reduction in the left subgenual PFC region (Botteron et al., 2002; Drevets et al., 1997; Öngür et al., 1998; Wang, LeBar, et al., 2008; Ye et al., 2012). This is because the orbitofrontal cortex (OFC) is involved in cognitive processing and decision-making, and the main function of the PFC is to extract the relevant information about a cognitive experience to modulate emotion and behavior changes (Feng et al., 2005). Moreover, studies have reported that the body temperature in depressed people was lower than in healthy people (Lin et al., 2011; Zhe, 2004). This may result from autonomic response dysfunction mediated by central adrenergic activation (Hamer et al., 2007; Hughes et al., 2006; Shinba et al., 2008; Figure 2.7, 2.8).

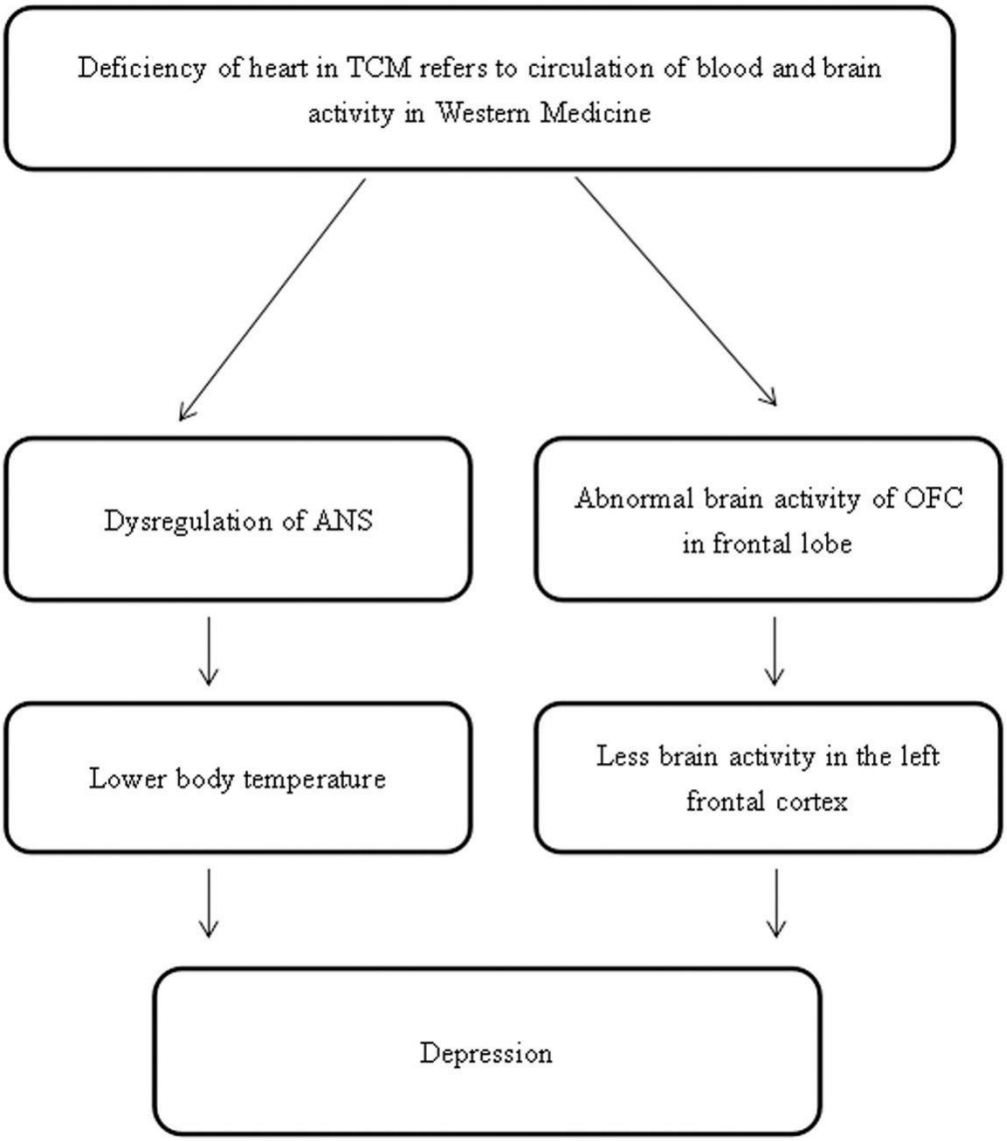

Figure 2.7 Hypothesized pathological neuropathways linking heart dysfunction and depression.

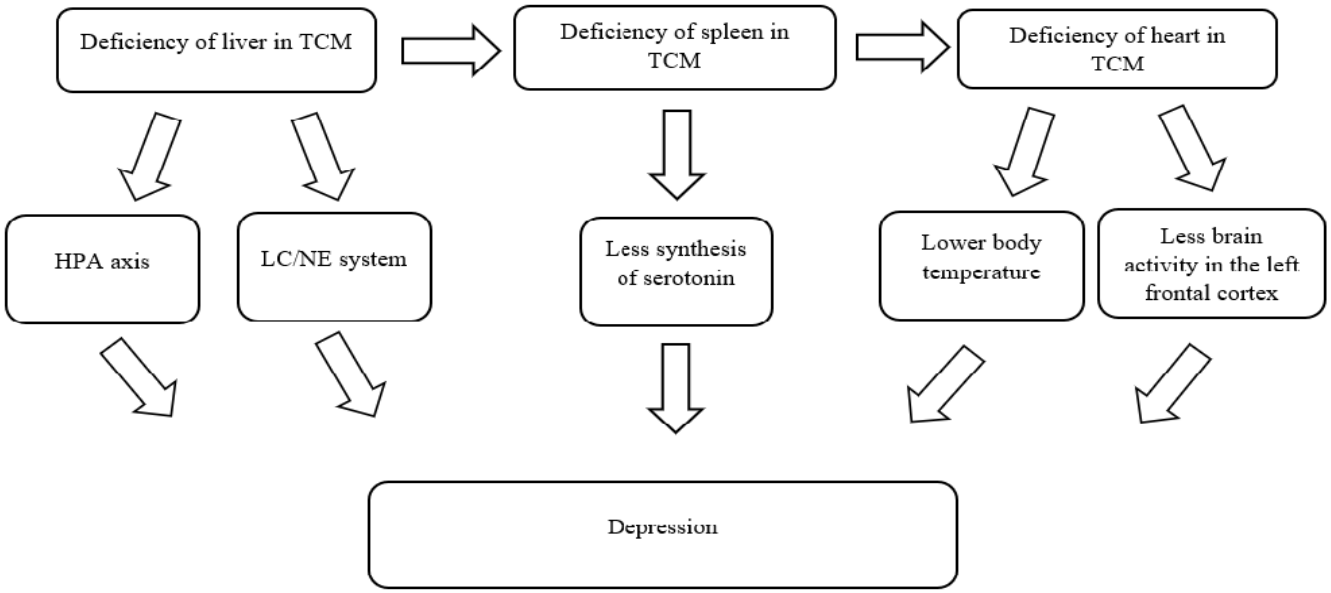

Figure 2.8 Summary of hypothesized pathological pathways of depression with an attempt to integrating Eastern and Western medicine disease concepts.

2.5 Summary and way forward

These two different systems of medicine have been used in parallel for approximately 200 years. TCM is mainly based on observation and experience. In contrast, Western medicine basically relies on scientific investigation. Recent studies in Western medicine have suggested that the dysregulation of neurotransmitters could be one of the most vital causes of depression, whereas the classical texts of TCM state that the dysregulation of liver Qi is the main cause of depression.

Interest in the neuroscientific investigation of TCM for depression has increased dramatically in the past few decades. Because the investigation of TCM using neuroscience theories and methodologies is a relatively new field of research, limited studies are available in the literature. Knowledge of the mechanism that underlies TCM for depression is still in its infancy. However, emerging evidence suggests that TCM theory might be illustrated by the changes in neurotransmitters, brain structure and function, and neuroendocrine factors found in people with depression.

Therefore, we propose the following postulations linked to the liver, spleen, and heart. In terms of TCM theory, (1) liver function may be explained by the HPA axis and LC/NE system, (2) spleen function may correspond to the digestive system, and (3) heart function may refer to the circulation of the blood and the regulation of brain activity. Further study using longitudinal designs and larger sample sizes is recommended to advance our understanding of the mechanism of TCM for treating patients with depression. Moreover, studies applying the integrated approach of East meets West and a rigorous research design are strongly recommended.

CHAPTER 3

The neuroscience of non-pharmacological traditional Chinese therapy for major depressive disorder: A systematic review and meta-analysis

This chapter summarizes the current non-pharmacological traditional Chinese therapies for patients with MDD. The therapeutic effects of acupuncture might be attributable to three plausible pathways: the HPA axis, the locus coeruleus (LC) immunity pathway, and the negative feedback loop of the hippocampus.

3.1 Introduction

MDD is a common and serious mental illness. The prevalent hectic life and work rhythm is associated with an increase in this mental illness (Ferrari et al., 2013; Organization, 2012). It affects more than 350 million people, especially those who reside in industrialized and urban areas. The incidence of MDD is around 6% in the general population (Andrade et al., 2003), with a lifetime rate reaching 16% (Kessler et al., 1994; Lee et al., 2007). The symptoms of MDD vary from fatigue, depressed mood, emotional disturbance, poor appetite, sleeping problems, cognitive impairment, and feelings of worthlessness or excessive guilt to suicidal thoughts. Individuals with MDD who experience these symptoms have a reduced quality of life, and MDD places a heavy economic burden on their families and society (Ted, 2000a). Thus, MDD has been targeted as one of the most serious health issues faced by industrialized societies and requiring more urgent attention.

In the past two decades, antidepressant medication (e.g., selective serotonin reuptake inhibitors; SSRIs) has been used for MDD as a mainstream treatment (Fountoulakis & Möller, 2011). Significant effects on reducing levels of depression are widely accepted, but these pharmacological treatments have adverse effects (e.g., nausea and vomiting), particularly in long-term users (Fountoulakis & Möller, 2011). Beyond this medication, cognitive behavioral therapy (CBT) and counseling are alternative methods for treating MDD (Wright et al., 2019). Notably, these nonpharmacological treatments are costly, time-intensive, and not suitable for all individuals with MDD (Bach et al., 2017; Renn & Areán, 2017; Zhou et al., 2017). Therefore, we must explore other methods for treating MDD, such as nonpharmacological traditional Chinese therapy (NTCT).

NTCT originated in ancient China (Jiang, 2005). Mind–body therapies such as

Tai Chi, Qigong, and acupuncture are core parts of NTCT, which emphasize the integration of mind (brain) and body in practice. Recent years have seen increasing worldwide interest in the clinical application of NTCT in treating depression, and beneficial effects have been observed in some studies (Cheng et al., 2016; Luo et al., 1998). Beyond this, imaging studies have investigated the potential neuromechanism of beneficial effects of NTCT for MDD (Wang et al., 2016; Wang et al., 2017). To date, no systematic review has been undertaken to synthesize the existing literature on this topic. Thus, this systematic review and meta-analysis aimed to summarize the neural basis for the clinical evidence of the effectiveness of NTCT in patients with MDD and propose some plausible pathological pathways of depression based on NTCT.

3.2 Methods

This systematic review was registered by the authors in the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42017080937).

3.2.1 Information sources

This systematic review with meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two independent reviewers (Ye and Cheung) served as the systematic reviewers of the following databases: PubMed, Embase, China National Knowledge Infrastructure (CNKI), SPORTDiscus, Scopus, and PsycINFO, from their inception to October 2018. The following main keywords were used in the systematic search: depression, major depressive disorder, affective disorder, neuroscience, neuroimag*, neurotransmitter, complementary therapies, traditional Chinese, mind–body therapies, and Qigong). The reference sections of relevant articles were also reviewed by the

authors. The languages were restricted to English and Chinese.

3.2.2 Study selection and eligibility criteria

The titles and abstracts of all the articles obtained through the search were independently screened by the two reviewers. Studies were included if they (1) focused on a kind of NTCT (e.g., acupuncture, acupressure, auricular therapy, massage, Qigong, moxibustion, or Tai Chi); (2) involved patients diagnosed with MDD based on any valid and clinical diagnostic criteria (Zhang et al., 2018); (3) recruited adults (aged above 18); (4) had a control group; (5) targeted outcomes using depression scales with at least one neuroscience measurement, including electroencephalography (EEG), functional magnetic resonance imaging (fMRI), magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional near-infrared spectroscopy (fNIRS) but were not limited to biomarkers such as blood, saliva, and urine samples; (6) were full papers written in English or Chinese; and (7) were published in peer-reviewed journals. Studies were excluded if (1) the full text was not available; (2) they had a focus on children (under the age of 18); (3) they had a focus on pharmacological treatments; (4) they used outcome measures without depression scales or neuroscience assessments; and (5) they were literature or systematic reviews. Any disagreement between the reviewers was resolved by discussion under the supervision of the corresponding author, who is an experienced researcher in integrative medicine.

3.2.3 Data extraction and management

The data extracted from selected studies included the characteristics of the population, diagnoses, interventions, study design, and outcomes. A consensus was reached via discussion if disagreement occurred between the two reviewers.

3.2.4 Study quality assessment

The 11-item PEDro scale was used to measure the methodological quality of the clinical studies (Lee & Lim, 2017; Yang et al., 2015). This involves the eligibility criteria, randomization, concealed allocation, similar baseline, blinding of participants, blinding of therapists, blinding of assessors, key outcome measures from more than 85% of the subjects, intention-to-treat, between-group differences, and both point measures and measures of variability. The maximum total score was 10 because the first item (eligibility criteria) did not contribute to the total. Points were awarded when a criterion was clearly satisfied (Liye Zou et al., 2018).

3.2.5 Data analysis

The meta-analysis on depressive outcomes was conducted through Review Manager (version 5.3, Nordic Cochrane Centre, Copenhagen, Denmark). The mean changes in depressive outcomes between the baseline and posttreatment measurements were computed for both the experimental and control groups in eligible studies. The effect size of each study was reported by the mean differences of change scores. When the 95% confidence interval (CI) did not include 0 or the *p*-value was less than 0.05, the CI and statistical significance were reported. The standardized weighted mean difference (SMD) method was used to obtain the pooled estimates of effect size for studies that reported the same outcome by different scales. The homogeneity of the included studies was assessed by the Chi-squared (I^2) test. The publication bias was assessed by funnel plot, along with Egger's regression test.

3.3 Results

3.3.1 Search selection

The electronic and manual searches resulted in 1,522 records in total. Forty-three full-text articles were obtained using the predetermined selection criteria, generating

12 articles with 894 participants. A total of eight articles were finally selected for the meta-analysis. The detailed process for article selection is shown in Figure 3.1.

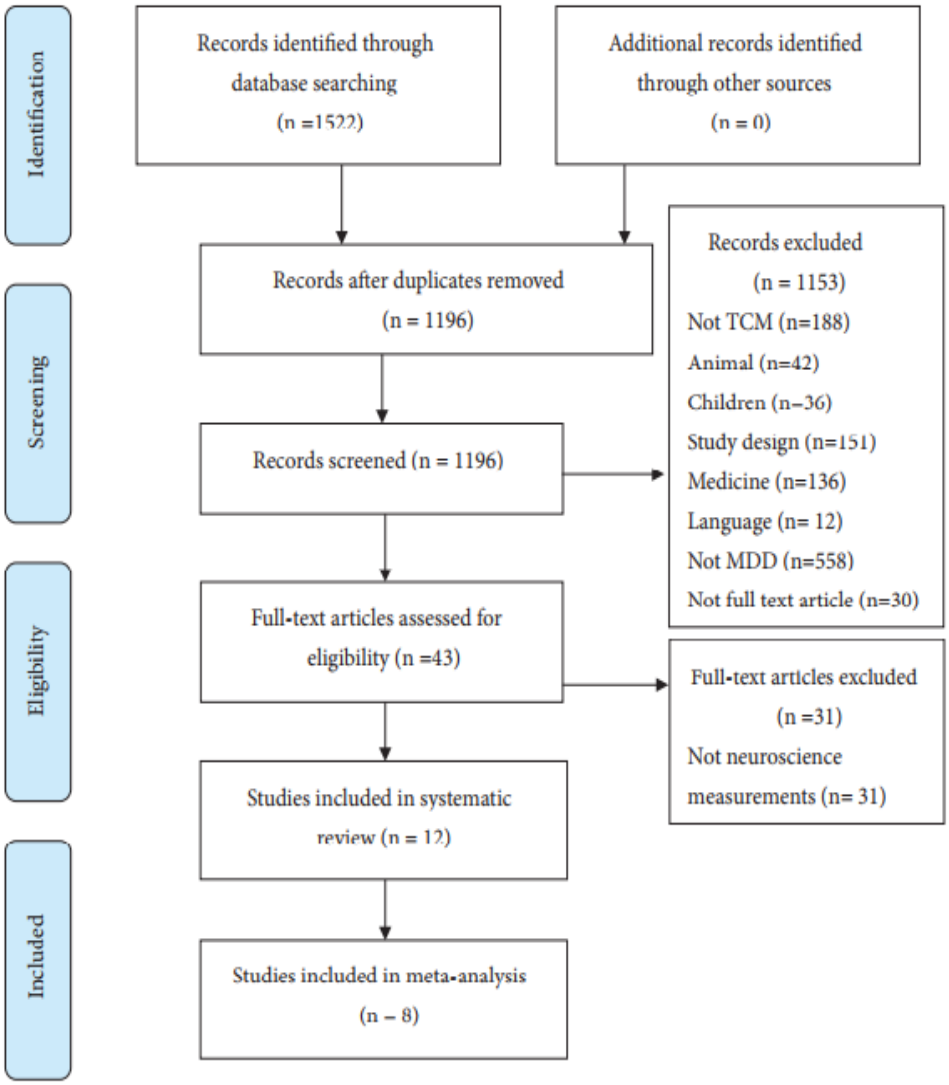

Figure 3.1 PRISMA flow chart of study selection process.

3.3.2 Study characteristics

The studies included 265 male and 597 female participants with an age range of 31.80 years to 80.65 years. The sample size in these studies ranged from 36 to 125. The place of studies conducted was mainly mainland China (n=6, 50%; Liu et al., 2015; Wang et al., 2016; Wang et al., 2017; Zhu et al., 2018; Zhu et al., 2017; Zhuo, 2017). Additionally, three studies were conducted in Hong Kong (Chan et al., 2013; Song et al., 2007; Tsang et al., 2013), and one study was published in each of Canada (Song et al., 2009), Mexico (Vázquez et al., 2011), and the USA (Lavretsky et al., 2011). Nine of the 12 trials were published in English-language journals, and three were published in Chinese-language journals. Nine of these selected articles used an RCT design, and three used a clinical control trial (CCT) design. Table 3.1 summarizes the details of the included studies.

Table 3.1 Characteristics of included studies

Source	Study design	No. of participants	Intervention group	Treatment duration	Control group	Treatment duration	Depression diagnostic criteria	Assessment
Song et al., 2007	CCT	120	N=30 Acupuncture + Fluoxetine	Acupuncture 45min/ Weekday, 6w	Con1 (n=30): fluoxetine Con2 (n=30): Sham acupuncture + placebo Con3 (n=30): No intervention (health control)	Con1: daily, 6w Con2: daily, 6w	DSM-IV	HAMD G protein in platelets Gαs 45 Gαi Gαq
Tsang et al, 2013	RCT	38	N=21, Eight Section Broads	Eight Section Broads 45min/ session, 3 times/w, 12w	Con (n=17): Newspaper reading	45min/ session, 3 times/w, 12w	DSM-IV	GDS HRSD 5-HT Cortisol (salivary)
Lian et al, 2017	CCT	96	N=48 Acupuncture + Chinese herbs	Acupuncture: 4-5 times/w + Chinese herbs daily, 6w	Con (n=48): Western medicine	daily, 6w	CCMD-3	HAMD 5-HT
Lavretsky et al, 2011	RCT	73	N=36 Tai chi + Escitalopram	Tai chi 2hrs/weekly + 10mg/daily, intensity gradually increased, 10w	Con (n=37): Health education + Escitalopram	2 hrs/weekly + 10mg/daily, intensity gradually increased, 10w	DSM-IV	HRSD CRP
Chan et al, 2013	RCT	50	N=17 DMBI+ medication,	DMBI 90min/session, weekly, 10 sessions	Con1 (n=17): CBT+ medication, Con2(n=16): Medication	Con1: 90min/session, weekly, 10 sessions Con2: daily	DSM-IV	PDS via BDI-II EEG (frontal α asymmetry) Hemispheric θ coherence (inter/intra)

Source	Study design	No. of participants	Intervention group	Treatment duration	Control group	Treatment duration	Depression diagnostic criteria	Assessment
Song et al, 2009	CCT	125	N=31 Electro-acupuncture + placebo capsules	Acupuncture 45min/session, 3 times/w + 20mg/daily, 6 w	Con1(n=32): Fluoxetine + sham electro-acupuncture Con2 (n=32): sham electro-acupuncture + placebo capsules Con3 (n=30): No intervention (health control)	Con1: 20mg/daily +Acupuncture 45min/session, 3 times/w, 6w Con2: Acupuncture 3 times/w + 20mg/daily, 6w	DSM-IV	HRSD IL-lß TNF-a IFN-λ IL-4 IL-10
Vazquez et al, 2011	RCT	42	N=23 Electro-acupuncture with low frequency (4Hz)	Acupuncture 30min/session, twice/w, 6 w	Con (n=19): Sham electro-acupuncture with low frequency (4Hz) Non-therapeutic point	30min/session, twice/w, 6 w	DSM-IV	CRS SCL-90 Cortisol (salivary)
Wang et al, 2016	RCT	36	N=18 Acupuncture + fluoxetine	Acupuncture 20min/session for first 3 days, 3 days/session for the rest of 8w, +20mg/daily, 8 w	Con (n=18): Sham acupuncture + fluoxetine The same acupoints (no needle inserted)	20min/session for first 3 days, 3 days/session for the rest of 8 weeks, +20mg/daily, 8w	ICD-10	MADRS SDS fMRI rsFC

Source	Study design	No. of participants	Intervention group	Treatment duration	Control group	Treatment duration	Depression diagnostic criteria	Assessment
Wang et al, 2017	RCT	36	N=18 Acupuncture + fluoxetine	Acupuncture 20min/session for first 3 days, 3 days/session for the rest of 8w, +20mg/daily, 8 w	Con (n=18): Sham acupuncture + fluoxetine The same acupoints (no needle inserted)	20min/session for first 3 days, 3 days/session for the rest of 8w, +20mg/daily, 8w	ICD-10	MADRS SDS fMRI rsFC
Liu et al, 2015	RCT	120	N=60 Acupuncture + medication	Acupuncture 30min/session, alternate day, + 20-50mg, 1-2 times/daily, intensity gradually increased, 6w	Con (n=60): Medication	20-50mg, 1-2 times/daily, intensity gradually increased, 6w	ICD-10	MADRS 5-HT IL-lß IL -6 IL-4 IL-10
Zhu et al, 2018	RCT	65	N=33 Acupuncture + SSRIs	Acupuncture 30min/session, 5 times/w + daily SSRIs, 6w	Con (n=32): Western medicine	daily, 6w	CCMD-3	HAMD HRV SDNN HF LF
Zhu et al, 2017	RCT	61	N=30 Acupuncture +SSRIs	Acupuncture 30min/session, 5 times/w + daily SSRIs, 6w	Con (n=31): Western medicine	daily, 6w	CCMD-3	HAMD IL-6 TNF-α

Abbreviations. Con: control group; SSRI: selective serotonin reuptake inhibitors; HAMD: Hamilton depression rating scale; GDS: geriatric depression scale; HRSD: Hamilton rating scale for depression; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th version; CCMD: Chinese Classification of Mental Disorders; ICD-10: the International Classification of Diseases, 10th revision; CRP: C reactive protein; 5-HT: serotonin; MADRS: Montgomery-Asberg depression rating scale; SDS: self-rating depression scale; IL: interleukin; TNF-α: tumor necrosis factor-α; IFN-λ: interferon-λ; rsFC: resting-state functional connectivity; fMRI: functional magnetic resonance imaging; DMBI: Dejian mind-body intervention; CBT: cognitive behavioral therapy; PDS: percentage of subjects reducing depressive syndrome; CRS: the Carroll rating scale; SCL-90: psychiatric symptom checklist; HRV: heart rate variability; SDNN: standard deviation of normal to normal R-R intervals; HF: high frequency; LF: low frequency.

The duration of the NTCT varied from six to 12 weeks. Of the trials, only two used a follow-up assessment, at eight weeks and four weeks, respectively (Lavretsky et al., 2011; Tsang et al., 2013). The major intervention in the selected trials was acupuncture (n=9). Seven of the nine acupuncture trials reported that the duration of the intervention was six weeks (Liu et al., 2015; Song et al., 2009; Song et al., 2007; Vázquez et al., 2011; Zhu et al., 2018; Zhuet al., 2017; Zhuo, 2017), and two reported that it was eight weeks (Wang et al., 2016; Wang et al., 2017). Only three studies reported using Tai Chi or Qigong as an intervention (Chan et al., 2013; Lavretsky et al., 2011; Tsang et al., 2013). The studies measured the effects of NTCT on depressive symptoms (n=12; Chan et al., 2013; Lavretsky et al., 2011; Liu et al., 2015; Song et al., 2009; Song et al., 2007; Tsang et al., 2013; Vázquez et al., 2011; Wang et al., 2016; Wang et al., 2017; Zhu et al., 2018; Zhu et al., 2017; Zhuo, 2017), cortisol (n=2; Tsang et al., 2013; Vázquez et al., 2011), 5-HT (n=3; Liu et al., 2015; Tsang et al., 2013; Zhuo, 2017), G-protein (n=1; Song et al., 2007), cytokine (n=3; Liu et al., 2015; Song et al., 2009; Zhu et al., 2017), brain functional connectivity (n=2; Wang et al., 2016; Wang et al., 2017), brain activity (n=1; Chan et al., 2013), CRP (n=1; Lavretsky et al., 2011), and HRV (n=1; Zhu et al., 2018). Three trials found that in the groups using acupuncture with medication or Tai Chi with medication, the adverse effects caused by medication were significantly reduced (Lavretsky et al., 2011; Liu et al., 2015; Zhuo, 2017). None reported any serious adverse events.

3.3.3 Quality assessment of studies

As rated by the PEDro scale, the sum scores of the selected trials ranged from 5 to 8, suggesting fair to high study quality. Allocation concealment was not used in three quarters of the eligible studies (Song et al., 2009; Song et al., 2007; Tsang et al., 2013; Vázquez et al., 2011; Wang et al., 2016; Wang et al., 2017; Zhu et al., 2018; Zhu et al., 2017; Zhuo, 2017). More than half of the selected studies did not explicitly indicate the blinding of assessors, therapists, or participants (Lavretsky et al., 2011; Liu et al., 2015; Song et al., 2007; Tsang et al., 2013; Vázquez et al., 2011; Wang et al., 2016; Wang et al., 2017; Zhu et al., 2018; Zhu et al., 2017; Zhuo, 2017) or intention-to-treatment technique (Chan et al., 2013; Liu et al., 2015; Song et al., 2009; Vázquez et al., 2011; Wang et al., 2016; Wang et al., 2017; Zhu et al., 2018). The study quality of all eligible trials is presented in Table 3.2.

Table 3.2 PEDro quality scale results of included studies

Source	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	PEDro
Song et al, 2007	1	0	1	0	0	1	1	1	1	1	7/10
Tsang et al, 2013	1	0	1	0	0	1	1	1	1	1	7/10
Lian et al, 2017	0	0	1	0	0	0	1	1	1	1	5/10
Lavretsky et al, 2011	1	1	1	1	0	1	0	1	1	1	8/10
Chan et al, 2013	1	1	1	1	1	1	0	0	1	1	8/10
Song et al, 2009	1	0	1	1	1	1	1	0	1	1	8/10
Vazquez et al, 2011	1	0	1	0	0	0	1	0	1	1	5/10
Wang et al, 2016	1	0	1	1	0	0	0	0	1	1	5/10
Wang et al, 2017	1	0	1	1	0	0	0	0	1	1	5/10
Liu et al, 2015	1	1	1	0	0	0	1	0	1	1	6/10
Zhu et al, 2018	1	0	1	0	0	1	1	0	1	1	6/10
Zhu et al, 2017	1	0	1	0	0	0	1	1	1	1	6/10

Note. Item 1: randomization; Item 2: concealed allocation; Item 3: similar baseline; Item 4: blinding of participants; Item 5: blinding of therapists; Item 6: blinding of assessors; Item 7: key outcome measures from more than 85% of subjects; Item 8: intention-to-treat; Item 9: between group difference; Item 10: point measures and measures of variability; 1: explicitly described and present in details; 0: absent, inadequately described, or unclear.

3.3.4 Effects of acupuncture

The indicators of outcome variables in the included studies included the Hamilton Rating Scale for Depression (HRSD/HAMD), the Montgomery–Asberg Depression Rating Scale (MADRS), the Carroll Rating Scale for Depression (CRS), and the Self-Rated Depression Scale (SDS). The most used depressive scale in these studies was the HRSD/HAMD (n=5; Song et al., 2009; Song et al., 2007; Zhu et al., 2018; Zhu et al., 2017; Zhuo, 2017). Two trials that estimated the effects of acupuncture on MADRS were included (Liu et al., 2015; Wang et al., 2016).

We did not include one study in our meta-analysis because of a problem of duplication with the dependent samples (Wang et al., 2017). To detect the consistency of the effects of acupuncture interventions on depressive symptoms, a sensitivity analysis was conducted by removing two trials with outlying effect sizes (SMD=-4.05, SMD=-2.35; Vázquez et al., 2011; Zhuo, 2017) based on the funnel plot and Egger's regression test (intercept=-10.333, p=0.09; Figure 3.2). After removing the outliers for further analysis, no significant difference was found using Egger's regression test (intercept=-2.144, p=0.67).

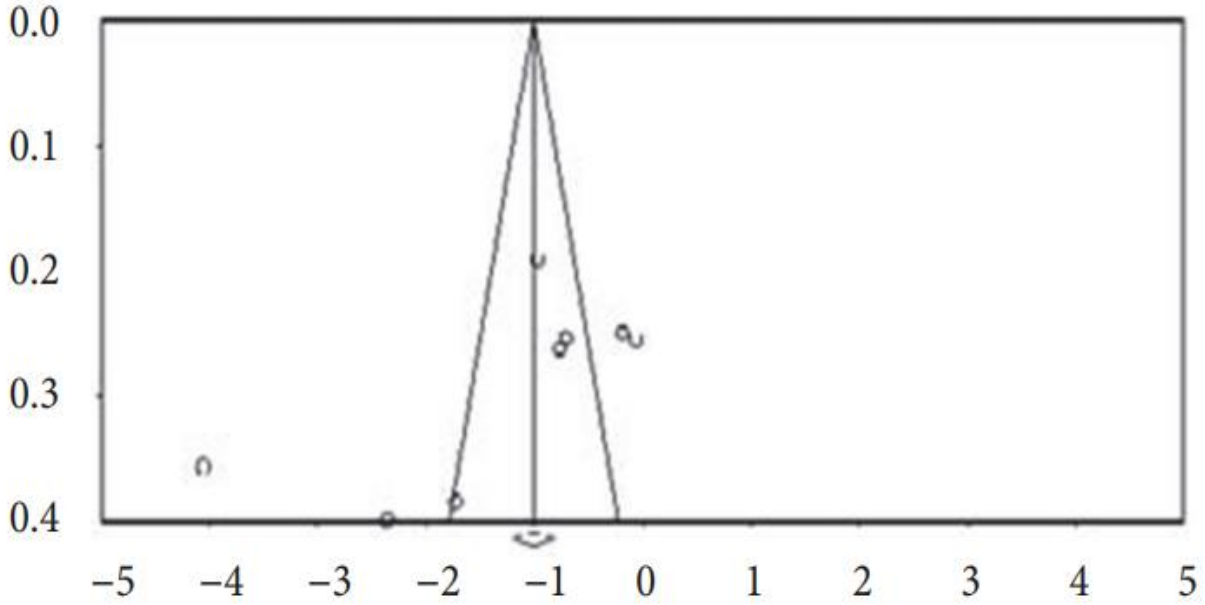

Figure 3.2 Funnel plot of publication bias of included studies.

A total of six studies were included in this meta-analysis (Liu et al., 2015; Song et al., 2009; Song et al., 2007; Wang et al., 2016; Zhu et al., 2018; Zhu et al., 2017). A significant improvement was found in reducing depressive symptoms (SMD -0.69, 95% CI -1.09 to -0.28, p=0.002, I^2=73%, p<0.0008; Figure 3.3) with the measurement of depression scales compared to the medication group over time after the acupuncture-medication intervention.

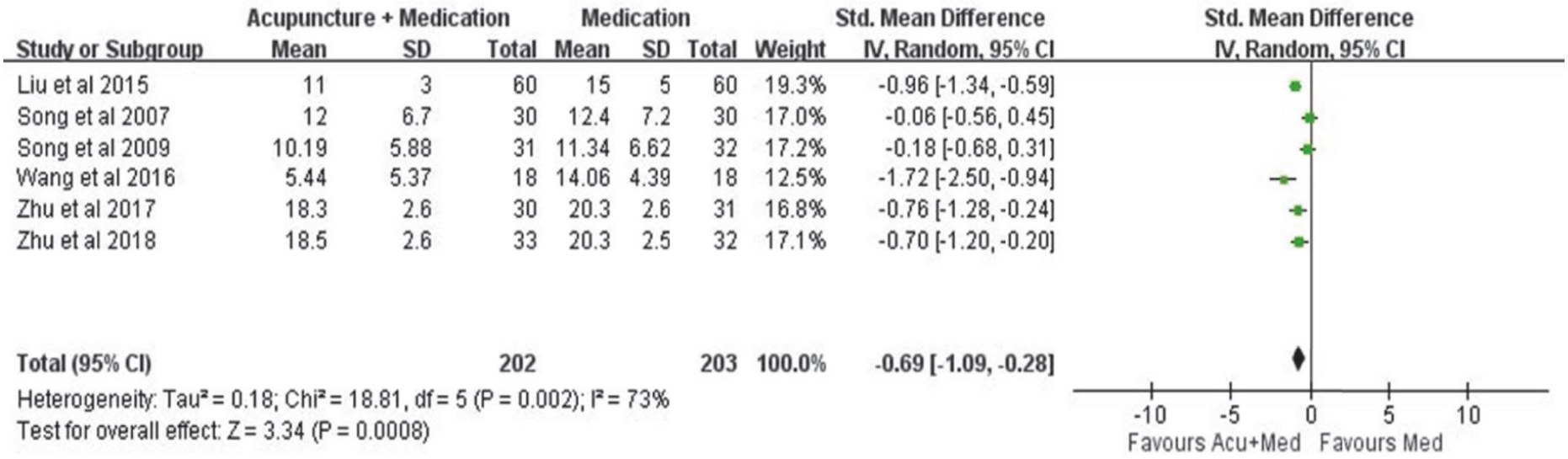

Figure 3.3 Effects of acupuncture intervention on depressive symptoms.

Three trials investigated the treatment effects using the measurement of 5-HT (Liu et al., 2015; Tsang et al., 2013; Zhuo, 2017), and two showed significant benefits in the acupuncture and medication intervention group compared to the medication control group (Liu et al., 2015; Zhuo, 2017). Song et al. (2007) reported that the intensity of the Gα protein in depressive patients was higher than in the healthy controls, but no significant changes were found after acupuncture treatment, even if the severity was considerably relieved. Vázquez et al. (2011) reported a significant improvement in cortisol levels, standard deviation of normal-to-normal R-R intervals (SDNN), and high frequency (HF) in the acupuncture and medication group, whereas a reduction of low frequency (LF) in the same group was found by Zhu et al. (2018).

Three trials reported the concentration of cytokines: interleukin-Iß (IL-Iß), interleukin-4 (IL-4), interleukin-10 (IL-10), interleukin-6 (IL-6), interferon-λ (IFN-λ), and tumor necrosis factor-α (TNF-*α*; Liu et al., 2015; Song et al., 2009; Zhu et al., 2017). Two trials reported that IL-6 increased after six weeks of an acupuncture and medication intervention compared to the medication group (Liu et al., 2015; Zhu et al., 2017). One trial reported an increase in the concentration of TNF-α (Song et al., 2009), and another showed a contradictory result, reporting a decreased concentration of TNF-α after six weeks of an acupuncture and medication intervention (Zhu et al., 2017). No change was found in IL-4 or IL-10 after the six-week intervention (Liu et al., 2015; Song et al., 2009). The details of the outcomes are summarized in Tables 3.1 and 3.3.

Table 3.3 Summary of neurophysiological outcomes in included studies

	5-HT	Gα protein	Cortisol	C reactive protein	TNF-α	IL-lß	IFN-λ	IL-4	IL-10	IL -6	EEG	Neuroimaging outcome	HRV
Song et al., 2007		v											
Tsang et al, 2013	v		v										
Lian et al, 2017	v												
Lavretsky et al, 2011				v									
Chan et al, 2013											v		
Song et al, 2009					v	v	v	v	v				
Vazquez et al, 2011			v										
Wang et al, 2016												v	
Wang et al, 2017												v	
Liu et al, 2015	v					v		v	v	v			
Zhu et al, 2018													v
Zhu et al, 2017					v					v			

Two out of the nine trials involved neuroimaging outcomes based on acupuncture techniques. Wang et al. (2017) compared the changes in resting-state functional connectivity (rsFC) in the ventral and dorsal striatal areas with the cortical cortices as well as the striatum seeds and the occipital regions between real and sham acupuncture groups. A significant increase was found after an eight-week intervention. Another study by Wang et al. (2016) emphasized the increased rsFC between the left amygdala and the subgenual anterior cingulate cortex (sgACC)/pregenual anterior cingulate cortex (pgACC), as well as between the right amygdala and left parahippocampus (Para)/putamen (Pu; Tables 3.1 and 3.3).

3.3.5 Effects of Tai Chi and Qigong

The indicator of depressive outcome variables in two of these three trials was the HRSD (Lavretsky et al., 2011; Tsang et al., 2013). Another trial measured the change in the number of MDD patients in each group according to the BDI-II scale (Chan et al., 2013). All the studies suggested a significant improvement in depressive symptoms in patients with MDD after Tai Chi and Qigong interventions.

Lavretsky et al. (2011) showed a reduction in C-reactive protein (CRP) after Tai Chi exercise compared to the health education group. Tsang et al. (2013) found no statistical difference in cortisol levels after Baduanjin exercise compared to the newspaper reading group. Chan et al. (2013) demonstrated that the Chan-based Dejian mind–body intervention (DMBI) significantly improved the frontal α asymmetry and intra- and inter-hemispheric θ coherence in front-posterior and posterior brain regions. However, these positive findings were not found in either CBT or waitlist groups.

3.4 Discussion

TCM has been practiced for over 2,000 years. Reporting the effects of NTCT and proposing possible mechanisms that may help to strengthen the scientific basis of TCM are important. Considering the different ways of approaching diseases, we did not include studies using traditional Chinese herbs in this review. We searched empirical studies published in both English and Chinese because TCM was traditionally performed in ancient China.

This is the first systematic review and meta-analysis synthesizing the effects of NTCT on MDD. We found that acupuncture may have positive effects on the treatment of MDD. This finding suggests that mixed-intervention approaches may be optimal for the treatment of MDD. However, the evidence on whether this

intervention is effective on cytokines, brain connectivity, brain structure, endocrine factors, HRV, or neurotransmitters is insufficient. Because the three studies that described exercise interventions were based on Tai Chi and Qigong, we may not have sufficient evidence to propose plausible pathways based on mind–body exercise in the current review.

Although previous studies have suggested that patients with MDD might benefit from acupuncture interventions (Kou et al., 2017; MacPherson et al., 2017), the potential mechanism by which acupuncture works on MDD remains elusive. Three plausible pathological mechanisms may explain how the body responds to acupuncture interventions in patients with depression. First, the feedback from the HPA axis could be considered the most important mechanism. The activity of the HPA axis is mainly related to the operation of CRH from the parvocellular neurons of the paraventricular nucleus of the hypothalamus (Steiger, 2007). The secretion of CRH stimulates the release of adrenocorticotropic hormone (ACTH), and the increased level of ACTH stimulates the release of glucocorticoid by the adrenal cortex, leading to an increase in the concentration of cortisol. The increased cortisol level has been widely suggested to be closely related to the severity of depressive symptoms (Dziurkowska et al., 2013; Plotsky et al., 1998; Suzuki & Tobe, 2017). The available evidence suggests that the level of cortisol decreases in patients with depression after acupuncture interventions. Thus, the dysregulation of the HPA axis can be considered a central pathophysiological process caused by depression (Rhebergen et al., 2015; Ye, Cai, et al., 2019).

Second, the LC and immunity pathway could be one of the pathological reasons for depression (Herbert & Cohen, 1993). The LC is the center for synthetizing the adrenergic nerve. The ascending fibers of the adrenergic nerve are mainly projected to the amygdala, hippocampus, and limbic cortex, which are responsible for emotional changes, memory, and behavior changes. The descending fibers of the adrenergic nerve are mainly projected to the lateral dorsal horn of the spinal cord, which corresponds to the regulation of activity of the sympathetic nerve and secretion of catecholamines including N and NE. An activated amygdala may stimulate the release of CRH, which increases the activity of the sympathetic nerve via the mediating lateral dorsal horn of the spinal cord. Once the sympathetic nerve is activated, the adrenaline medulla releases NE and E due to the activated adrenal gland. Thus, a

positive bidirectional feedback loop exists between CRH and the sympathetic nerve (Damjanov, 2009; Ye, Cai, et al., 2019).

Furthermore, the characteristics of the inflammatory responses are based on a complex interaction between pro- and anti-inflammatory cytokines. NE and E modulate the release of pro- and anti-inflammatory cytokines through α- and β-adrenoceptors (Haskó & Szabó, 1998). A positive relationship between NE and TNF has been found, and both catecholamines of NE and E have been found to stimulate the release of IL-6 via immune cells (Bertini et al., 1993; Chrousos, 2000; Spengler et al., 1994). When a stressful situation occurs, adrenergic agents may increase due to the activation of the sympathetic nerve. This may lead to an increase in proinflammatory cytokines such as TNF, IL-1ß, and IL-6 (Won & Kim, 2016). The positive association between MDD and proinflammatory cytokines and the negative relationship between anti-inflammatory cytokines such as IL-10 and IL-4 have been reported in previous studies (Dhabhar et al., 2009; Strike et al., 2004; Wright et al., 2005).

Moreover, the changes in cytokines may produce behavioral changes through changes in levels of indoleamine 2,3-dioxygenase (IDO), which leads to a reduction of tryptophan (Felger & Lotrich, 2013). Because tryptophan is a precursor of 5-HT, its depletion leads to a reduction of 5-HT. Previous findings that the level of 5-HT significantly decreased in patients with depression compared to healthy controls support this finding (Liu et al., 2015). The findings from our review are also in line with this conclusion. Because the mechanism between depression and the immune system is still unclear, more studies are needed to explore underlying pathways.

Third, the negative feedback loop of the hippocampus has recently received intensive attention in studies on depression. Glucocorticoid receptors in the hippocampus are widely reported by researchers, and studies have found that the released glucocorticoid triggers negative feedback with the hippocampus, which leads to a decreased number of neuronal cells and eventually the hypoactivity of the hippocampus (Campbell et al., 2004; Wang & Yan, 1991). Current findings using neuroimaging measurements support this possible pathway. Duan et al. (2011) found statistical improvement in the ratio of N-acetyl-aspartate/creatine (NAA/Cr) in the hippocampus after acupuncture interventions compared to pretreatment, which indicated that acupuncture may improve depressive symptoms by decreasing the level

of cortisol and activating the activity of the hippocampus (Figure 3.4). Although neuroimaging studies show some beneficial effects in patients with depression after acupuncture interventions, valid conclusions cannot yet be drawn due to the small number of available studies. Further studies are needed to assess the changes in brain function through neuroimaging techniques.

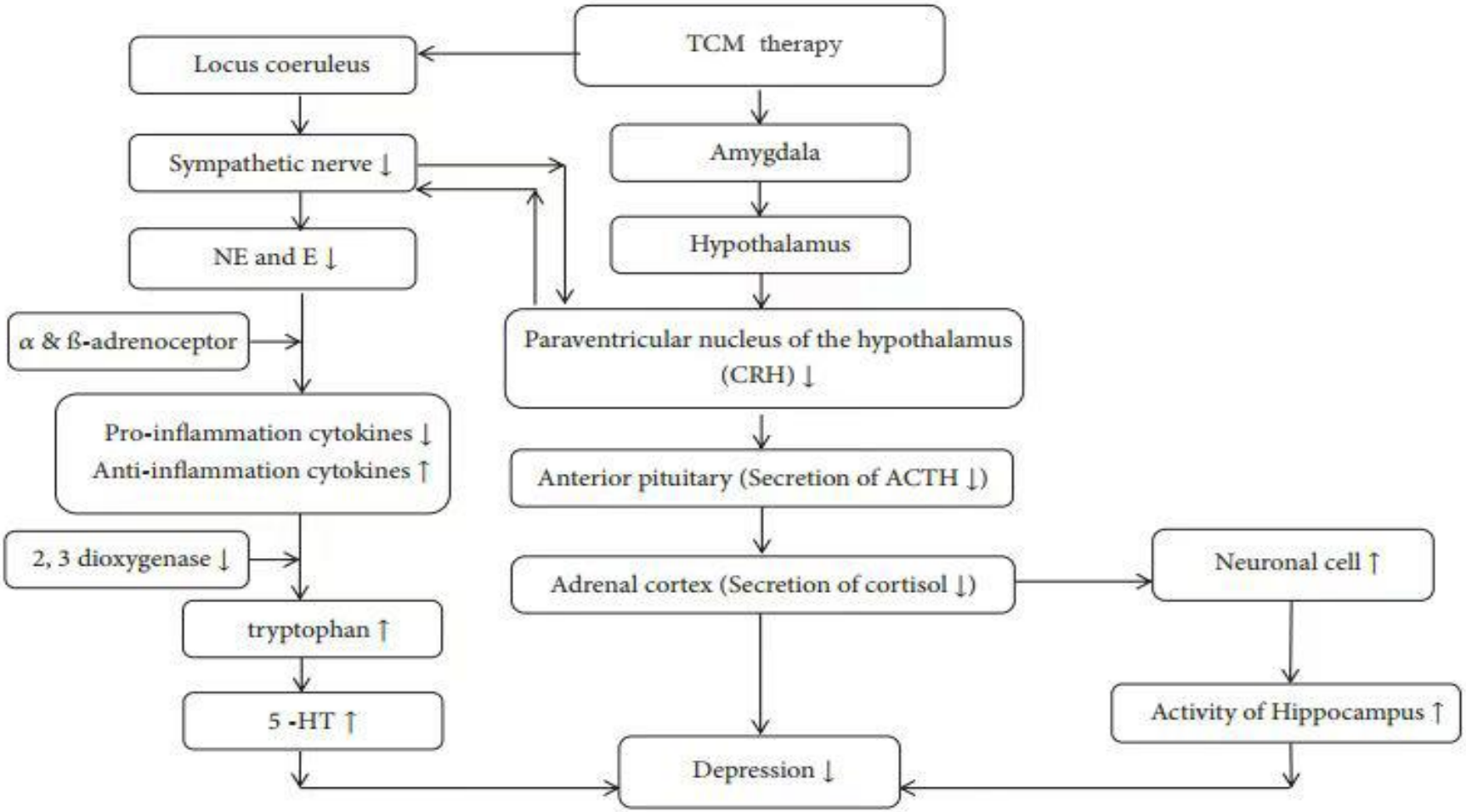

Figure 3.4 Hypothetical models associated with HPA axis, LC–immunity, and negative feedback loop of hippocampus.

3.4.1 Study limitations

This systematic review and meta-analysis have several limitations. First, due to the great variation in neuroscience outcomes across eligible studies and the minimal number of studies with each outcome, a meta-analysis to synthesize the neurological effects in MDD was not performed. Second, most of the selected studies used inadequate allocation concealment. Participants knew whether they were in the experiment or control groups, even though a randomization procedure was used. Such insufficient concealment might generate subjectivity and expectation biases. Third, blinding of the intervention was absent in many studies. This might have led to overestimation of the treatment benefits of NTCT for MDD. Future studies may ask patients not to disclose the treatment protocol to others to minimize these biases. Fourth, because only two studies reported a follow-up period, a meta-analysis to investigate the long-term effects of NTCT for MDD was not conducted. Fifth, the publication language was limited to Chinese and English. We may have missed studies published in journals in other languages. Sixth, this systematic review and meta-analysis aimed to summarize the neural basis of NTCT and propose plausible mechanisms of NTCT for MDD. We did not include "Yu" syndrome in the selection criteria because few studies have mentioned TCM diagnoses, neuroscience outcomes, and NTCT. Thus, the hypothetical neurophysiological pathways of "Yu" syndrome cannot be understood from this systematic review. Further experimental studies may explore the mechanisms of TCM therapy on depression based on TCM-based organ function. Last, this systemic review only recruited studies measuring depressive syndromes by questionnaires and neurophysiological assessments. The results should be cautiously interpreted because this may affect the representativeness and limit the generalizability.

3.5 Conclusion

This systematic review and meta-analysis have demonstrated that acupuncture and medication interventions produce more benefits than medication for improving depressive symptoms. The mechanisms by which acupuncture leads to positive responses for MDD might be based on three hypothetical pathways: the HPA axis, the LC–immunity pathway, and the negative feedback loop of the hippocampus. Few peer-reviewed articles reported on the neurological effects of NTCT in either Chinese or English before 2007.

CHAPTER 4

Theoretical framework for Chapters 5 and 6

This chapter presents an overall theoretical framework for this PhD study, consisting of two main parts. The methodological details and results are presented in Chapters 5 and 6, respectively. Chapter 5 is a cross-sectional study aiming to test the hypothesized pathological pathways linking TCM-based liver function and depression. Chapter 6 is a pilot RCT, aiming to investigate the efficacy of Baduanjin exercise in adults with MDD and support the East meets West model regarding TCM-based liver function with the application of Baduanjin as an intervention. The findings of these two chapters provide a better understanding of the pathology of depression based on integrated Eastern and Western approaches.

4.1 Theoretical background of this study

Summarizing from the earlier chapters, depression is a common mental illness characterized by a loss of interest and energy and a depressed mood, with an estimated 5.0% of adults affected worldwide (Bueno-Antequera & Munguía-Izquierdo, 2020; World Health Organization, 2021). The pathology of depression in Western medicine may refer to various factors including neuroendocrine elements, neurotransmitters, and GE interaction. On the other hand, the etiology of depression in TCM may relate to the Zang Fu (臟腑) theory, indicating the imbalance of Qi and Blood in different organs. These are two different medical systems for interpreting the concept of depression. Compared to Western medicine, TCM lacks scientific evidence to support its theory, even if it has evolved over thousands of years in China, because it mainly focuses on clinical practice. This lack of scientific evidence may lead to skepticism, criticism, and even rejection of TCM (Ted, 2000b).

The relationships between depression, the HPA axis, and the LC/NE system have been documented by experimental studies. One of the most consistent biological findings in psychiatry is the link between an altered activity of the HPA axis and depression (Juruena et al., 2018). Belvederi Murri et al. (2014) highlighted that a high degree of dysregulation of HPA axis activity was associated with depression. The activity of the HPA axis is mainly related to the operation of CRH from the hypothalamus (Gu et al., 2018; Steiger, 2007). The secretion of CRH stimulates the release of ACTH and cortisol. Thus, patients with depression have increased levels of cortisol and ACTH due to the impairment of the negative feedback system of the HPA axis. Moreover, NE is derived from the LC, which has been found to have a close link with depression (Schmidt et al., 2019). Increased CRH may stimulate sympathetic nerve activity by mediating the lateral dorsal horn of the spinal cord. Once the sympathetic nerve is activated, increased NE is found due to the activated adrenal gland. Thus, patients with depression may experience increased activities of sympathetic nerves and NE levels (Ye, Cai, et al., 2019).

Interestingly, studies with traditional Chinese therapies have found that the symptoms of abnormally increased TCM-based liver Qi were closely correlated with dysregulation of the ANS (Yue & Tian, 1995) and an increased level of NE (Spiegelhalder et al., 2011; Wei et al., 2012). Furthermore, excessive activation of sympathetic neurons and vagal modulation may result from the impairment of the

negative feedback of the HPA axis and increased levels of cortisol. Increasing clinical studies have reported the relationship between TCM-based liver dysfunction and the dysregulation of ANS (Guang Xin et al., 2005; Guang Xin et al., 2005). However, the TCM-based theoretical approach to liver function in depression still lacks empirical evidence. Therefore, we proposed two plausible neurophysiological pathways regarding the HPA axis and LC/NE system to interpret TCM-based liver function, as described in Chapter 2. However, these theoretical models still must be tested by experimental studies. More clinical trials are required to verify these possible pathways.

MDD is one of the most common mental disorders leading to morbidity and mortality in recent years (Marwaha et al., 2023). Psychotherapy and pharmacotherapy are the mainstream treatments for MDD worldwide. However, these treatments may have long-term adverse effects and require time and money. Therefore, an adjuvant therapy with a low cost and fewer adverse effects is required for individuals with MDD.

Baduanjin exercise is a moderate-intense Chinese mind–body exercise that has been practiced for over 2,000 years (Xia et al., 2019). The essence of this exercise is the integration of natural breathing, mind, and physical movements. Previous experimental studies have found that Baduanjin exercise had beneficial effects on improving depressive symptoms (Lee et al., 2019; Tsang et al., 2003; Tsang et al., 2013; Tsang et al., 2002; Zhang et al., 2021) and cortisol levels (Tsang et al., 2013). However, these studies recruited patients with depression whose primary diagnosis was physical illness. Few studies have investigated the effects of Baduanjin exercise in patients with MDD, and few have explored the mechanisms of Baduanjin exercise.

This doctorate thesis aims to fill the knowledge gap between TCM-based liver function and neurophysiological biomarkers in depression. Chapter 5 reports the first main part, which is a cross-sectional study of 100 individuals with depression. Its purpose was to test the hypothesized pathological pathways linking TCM-based liver dysfunctions and depression proposed in Chapter 2. The aims of the second main part of this study are presented in Chapter 6. Because the efficacy of Baduanjin for MDD remains elusive, this aimed to investigate the effects of Badaunjin on MDD and support the pathological models with the application of Baduanjin exercise as an intervention. This is a pioneering study examining the pathology of depression

regarding TCM-based liver function through Western scientific approaches. The findings of this study can provide more evidence to support the application of the Zang Fu (臟腑) theory of depression. Additionally, results from this study can contribute to a better understanding of the pathologies of depression based on an integration of Eastern and Western approaches. Finally, these findings deliver more evidence-based practice for health professionals using Baduanjin exercise as an intervention for patients with MDD and provide a reference for synthesized rehabilitation treatment plans in clinical practice.

CHAPTER 5

The relationship between liver function and neurophysiological factors in depressed individuals: A cross-sectional study

This chapter reports the first main part of this PhD study, which aims to test two pathways linking TCM liver-based function and depression among 100 depressed individuals using path analysis. The findings of this chapter support the hypothetical model of the relationship between HPA axis (pathway from cortisol to ACTH) and depression.

5.1 Introduction

5.1.1 Study background

Depression is a common psychiatric disorder characterized by a loss of interest and energy as well as a depressed mood, which causes much disability and mortality worldwide (Bueno-Antequera & Munguía-Izquierdo, 2020). Compared to healthy individuals, depressed individuals may experience worse quality of life, sleep disorders, fluctuations in body weight, and a reduced life expectancy, which creates a heavy economic burden. Given the increasing rates of depression, developing a better understanding of this illness, together with efforts to prevent it and reduce the growing economic burden that results from it, have been recognized as public health priorities.

TCM has been applied in clinical practice for more than 2,000 years in China (Xu et al., 2013). In contrast to Western medicine, TCM adopts a holistic approach as its theoretical foundation, which has evolved based on accumulated clinical experience (Wang et al., 2018). Worldwide, more than 200 million patients have received TCM therapies, including acupuncture, massage, and Chinese herbs (Ye, Cai, et al., 2019). Previous systematic reviews have suggested that TCM therapies significantly improved depressive symptoms (Armour et al., 2019; Li et al., 2020; Smith et al., 2018; Wang et al., 2013; Wang et al., 2017; Wang et al., 2019). Although the efficacy of TCM is established, its mechanisms are still unknown to scientific communities because it is mainly based on clinical practice instead of solid scientific evidence. Therefore, more research is urgently needed to evaluate the mechanisms of TCM according to modern scientific approaches.

Two hypothesized pathological pathways linking TCM-based liver function and depression were proposed in our prior theoretical review (Ye, Cai, et al., 2019). Based on TCM theory, liver function is first affected when an emotional change occurs. By contrast, Western medicine suggests that depression has a profound relationship with neurotransmitters, such as norepinephrine, epinephrine, and serotonin. The previous theoretical review suggested that plausible mechanisms of depression exist in TCM according to the Western medical approach (Ye, Cai, et al., 2019). However, no experimental study supports this theory.

5.1.2 Aim and hypotheses

This study aimed to test the plausible pathways linking TCM-based liver function

to depression based on the integration of Eastern and Western medicine while also obtaining a deeper understanding of depression (Figure 5.1). The specific hypotheses were:

1) A significant relationship exists between cortisol, ACTH, and TCM-based liver function in participants with depression.
2) A significant relationship exists between NE, the LF/HF ratio, and TCM-based liver function in participants with depression.
3) The TCM-based liver function in depression can be predicted by ACTH and cortisol.
4) The TCM-based liver function in depression can be predicted by NE and LF/HF.

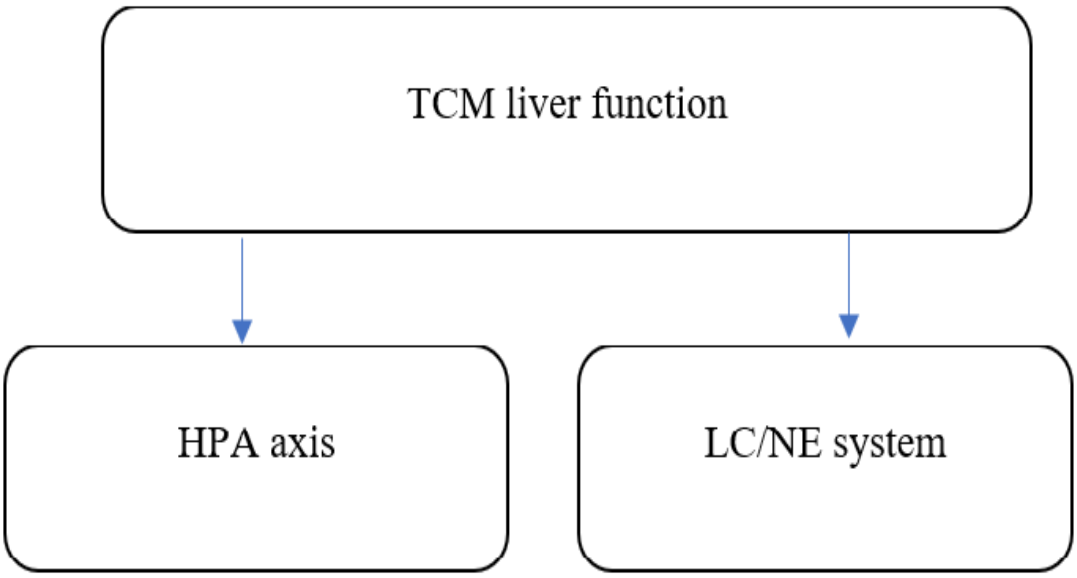

Figure 5.1 Hypothesized model to interpret TCM liver function.

5.2 Materials and methods

5.2.1 Participants and sample size

Potential participants were invited to join this research study by a member of the research team from the Rehabilitation Hospital in Fujian, China, between October 2020 and October 2021. A qualified research assistant who received diagnostic training from a certified clinical psychiatrist and a TCM practitioner explained the research and conducted an initial screening for those who showed an interest in participating. The criteria for inclusion in the study were: (1) age between 18 and 65 years, (2) a current episode of depression diagnosed by a psychiatrist based on the DSM-5 criteria, (3) symptoms of liver Qi stagnation diagnosed by the International Medicine of Traditional Chinese Medicine, (4) a baseline score of 12 or higher on the $HRSD_{17}$ (Yeung et al., 2012), (5) a score of 20 or higher on the Montreal Cognitive Assessment (MoCA), and (6) willingness to give consent by signing a written informed consent form. Participants were excluded if they fit any of the following criteria: (1) a primary diagnosis of an illness other than depression, (2) pregnancy or lactation, (3) substance use or drug dependence, or (4) acute suicidal or violent behavior. All eligible participants were asked to sign their informed consent forms, which were formulated according to the Declaration of Helsinki. This study was approved by the local research ethics committee (approval number: 2020YJS-003-01), and the trial was registered in the Chinese Clinical Trial Registry (ChiCTR1900027222).

The calculation of the sample size was based on the rule that for each parameter, 20 subjects are recommended (Kline et al., 1998). Therefore, a total of 100 participants were needed for this study.

5.2.2 Data collection procedures

Participants' demographic and anthropometric data—including their age, gender, education, height, body weight, and marital status—were recorded after the informed consent form had been signed. After recording their personal information, eligible participants were asked to abstain from coffee, tea, and alcohol for 24 hours before 9 a.m. on the day of measurement. Blood samples were obtained each day for one week after the initial screening by a certified phlebotomist, and HRV was measured at the same time interval on the same day as the blood samples were taken. All testing was conducted in a quiet laboratory setting to minimize distraction.

5.2.3 Outcome measurements

5.2.3.1 Liver function in TCM

The severity of liver Qi stagnation was assessed according to *Guiding Principles of Clinical Research on New Drugs of Traditional Chinese Medicine* (Zheng, 2002). The symptoms were described as follows: (1) major symptoms, including mental depression, frustration, pessimism, feeling world-weary, and sighing often; (2) secondary symptoms, including poor memory, insomnia, irritability, belching, hiccups, restlessness, pain, abdominal distension, and a foreign body sensation in the throat; (3) a coating on the tongue, such as a pink tongue with a thin white coating; and (4) a pulse sign, such as a wiry pulse. The major symptom items were rated on a seven-point scale ranging from 0 to 6, and the secondary symptom items were rated on a four-point scale ranging from 0 to 3. The higher the total score, the more severe the liver Qi stagnation. The Internal Consistency is 0.764 (α=0.764).

5.2.3.2 Neurophysiological biomarkers

NE, ACTH, and cortisol levels were collected between 9 and 11 a.m. from participants. A 5-ml tube with EDTA-Na_2 was used to collect whole blood from a vein in the cubital fossa, which was then centrifuged for 15 minutes at 1,000 x g at 40 ºC. After 30 minutes, the isolated plasma was collected, and the plasma sample was then stored at -20 °C until analysis. When the plasma was ready to process, it was thawed, and enzyme-linked immunosorbent assay (ELISA) kits (Elabscience Biotechnology Co. Ltd, Wuhan, China) were used to determine the concentrations of NE, ACTH, and cortisol. The NE assay had a sensitivity of 0.19 ng/mL, with intra-assay and inter-assay variance of less than 10%. The ACTH assay had a sensitivity of 9.38 pg/mL, with intra-assay and inter-assay variance of less than 7%. The cortisol assay had a sensitivity of 2.92 ng/mL, with intra-assay and inter-assay variance of less than 9%. All measurements were taken in line with the manufacturer instructions.

5.2.3.3 Heart rate variability

The participants were instructed to sit in a chair for a rest period of 15 minutes at a room temperature of 26 ºC before measurement and were told to relax and breathe normally during measurement. HRV data were acquired using a battery-operated portable HRV device (Check MyHeart™, Daily Care Biomedical, Taiwan; Boos et al., 2017). Data were obtained from a five-minute ECG with a sampling rate of

250/sec. Two electrodes were placed on both sides of the inner forearms. The raw ECG data was exported to a PC using a USB cable for subsequent analysis (Gifford et al., 2018). Frequency-domain analysis was performed using the non-detrend method of FFT. A ratio from LF to HF was selected since this represents sympathovagal balance or sympathetic modulations (Camm et al., 1996). The participants received 100 HKD in compensation for travel expenses after completing all of the assessments.

5.3 Data analysis

Descriptive analyses were used for the demographic data, and frequency analyses were employed for the enumeration data. Continuous variables were described using the mean and standard deviation (SD). The Shapiro–Wilk test was used to test data normality for each outcome variable. Log10 transformation was performed to meet the assumptions of normality if the variables did not follow the normal distribution. The Pearson correlation coefficients of cortisol, ACTH, NE, HRV, and TCM-based liver function were investigated. Statistical analyses were performed using SPSS version 25.0 (SPSS Inc, USA).

Figure 5.2 depicts the hypothesized model exploring both the direct and indirect effects of neurophysiological biomarkers on the severity of TCM-based liver dysfunction in depressed patients using path analysis. Maximum-likelihood estimation was used to test the fit of the hypothesized model. The variables and the direction of the relationship were based on an earlier study (Ye, Cai, et al., 2019). Chi-square (χ^2), the root mean square error of approximation (RMSEA), the normed fit index (NFI), and the comparative fit index (CFI) were selected to evaluate the goodness of fit of the model. A value of 0.08 or below for RMSEA was considered an adequate fit (Arewasikporn et al., 2018), and a value of 0.9 or above for both CFI and NFI was regarded as a good fit. A non-significant likelihood ratio of χ^2 and the degree of freedom (df) test suggests a good model fit, but because it is sensitive to sample size, a χ^2/df ratio of 3 or less indicates an acceptable fit (Cui et al., 2019; Lu et al., 2019). The path model was applied using the statistical software IBM SPSS AMOS version 25.0. The level of statistical significance was set at $p<0.05$.

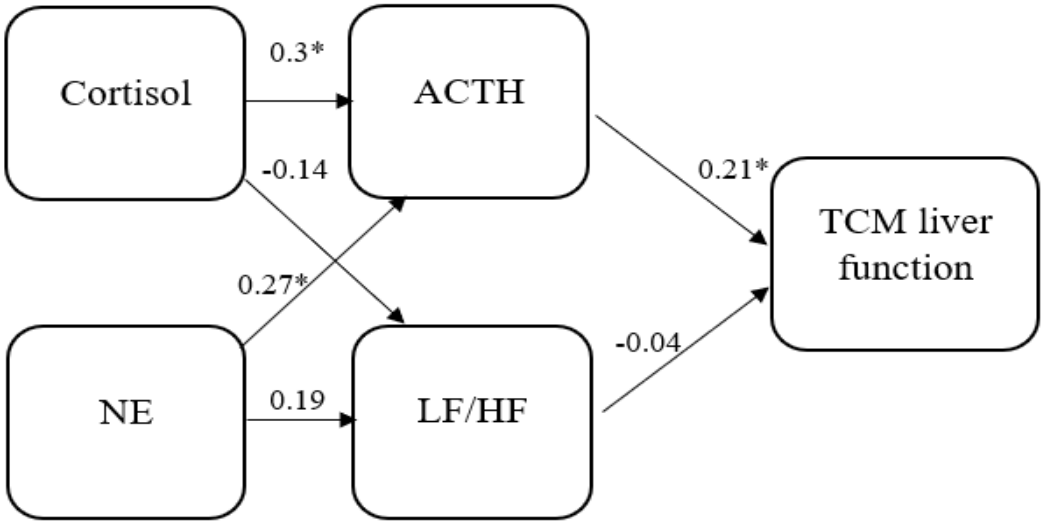

Figure 5.2 Path analysis model with standardized regression coefficients among 100 participants.

The goodness-of-fit statistics for the hypothetical path model:
χ^2=4.689, df=3, *p*=0.196, χ^2/df=1.563, CFI=0.947, NFI=0.888, and RMSEA=0.075.

5.4 Results

5.4.1 Demographic characteristics of participants

Table 5.1 shows the demographic data of the l00 participants. Their mean age, height, and weight were 45.06 ± 14.37 years, 164.20 ± 8.96 cm, and 59.13 ± 9.79 kg, respectively. The majority of the participants were female (70%), and 81% of the participants were married. Approximately 70% of participants were highly educated, having received education for more than 12 years (Rencken et al., 2020).

Table 5.1 Demographic data of participants

Characteristics	Mean	SD
Age, year	45.06	14.37
Gender, n (%)		
Male	30(30%)	
Female	70(70%)	
Height (cm)	164.20	8.96
Weight (kg)	59.13	9.79
Education status, n (%)		
Low (< 9 years)	10 (10%)	
Medium (9-12 years)	20 (20%)	
High (>12 years)	70(70%)	
Marital status, n (%)		
Single	19(19%)	
Married	81(81%)	

5.4.2 Normality of research variables

All of the variables of ACTH, NE, cortisol, and HRV in this study did not meet the assumption of normal distribution. Thus, the log10 transformation was performed for subsequent analysis. The mean and SD for all variables are shown in Table 5.2.

Table 5.2 Pearson correlation between variables

	Cortisol	LF/HF	NE	ACTH	TCM liver function
Cortisol	1.000	-0.140	0.243*	0.302*	-0.002
LF/HF	--	1.000	0.187	0.163	-0.039
NE	--	--	1.000	0.272*	0.136
ACTH	--	--	--	1.000	0.211*
TCM liver function	--	--	--	--	1.000
	Cortisol	LF/HF	NE	ACTH	TCM liver function
Mean	2.489	0.124	0.935	3.116	1.397
SD	0.113	0.427	0.125	0.819	0.080

Notes: LF/HF: Low frequency/high frequency; NE: Norepinephrine; ACTH: Adrenocotocotropic hormone; TCM: Traditional Chinese medicine; *p<0.05; --: Not applicable.

5.2.3 Relationship between neurophysiological biomarkers and TCM-based liver function

The relationship between ACTH and TCM-based liver function was significant (r=0.211, p=0.041). Cortisol was significantly associated with NE (r=0.243, p=0.015) and ACTH (r=0.302, p<0.001). A positive significant relationship was also found between NE and ACTH (r=0.272, p<0.001). The correlational relationships between all variables are shown in Table 5.2.

5.4.4 Fitness of the hypothetical path model

Figure 5.2 presents the results of the path analysis. The goodness of fit of the hypothetical path model was χ^2=4.689, df=3, p=0.196, χ^2/df=1.563, CFI=0.947, NFI=0.888, and RMSEA=0.075. Although one of the indices (NFI=0.888) was unsatisfactory and did not fulfill the basic requirement (NFI<0.90) in the present study, this model could still be regarded as acceptable because the other indices had already fulfilled the requirements following the implementation of recommendations suggested by the modification indices (Nurul Faziera Khairul Adlee, 2020).

5.4.5 Hypothesis testing and variable effect verification

All of the standardized beta coefficients and the total effect of the variables on TCM-based liver function are depicted in Figure 5.2.

Hypotheses 1 and 3 were supported; cortisol had a significant positive correlation with ACTH (β=0.302, t=3.266, p=0.001), and ACTH had a significant positive relationship with TCM-based liver function (β=0.211, t=2.147, p=0.032; Figure. 5.2). These findings indicate that cortisol partially affected TCM-based liver function through the mediating effect of ACTH. However, hypotheses 2 and 4 were not supported; NE had a marginally significant association with the LF/HF ratio (β=0.187, t=1.840, p=0.066), and no significant relationship existed between the LF/HF ratio and TCM-based liver function (β=-0.039, t=-0.398, p=0.690; Figure 5.2). In addition, a positive significant correlation between NE and ACTH was found (β=0.272, t=2.946, p=0.003). An insignificant relationship was observed between cortisol and the LF/HF ratio (β=0.-140, t=-1.385, p=0.166).

5.5 Discussion

This study tested two neurophysiological pathways based on the integration of Eastern and Western medicine using path analysis. To our knowledge, this is an

innovative study that examines the mechanisms of TCM-based liver function in terms of depression based on an integrated approach of East meets West. The findings supported the hypothetical model of the relationship between TCM-based liver function and the HPA axis (Hypotheses 1 and 3) but not the LC/NE system (Hypotheses 2 and 4). In other words, hypotheses 1 and 3 were supported by the findings of this study. In contrast, hypotheses 2 and 4 were not supported.

The results showed that cortisol and ACTH were positively correlated with TCM-based liver function in individuals with depression. This finding supported the proposed pathways laid out in our prior theoretical review (Ye, Cai, et al., 2019). Previous experimental studies (Veith, 2015, 2016; Zhongying et al., 2002) have suggested that increased cortisol and ACTH were closely linked with more severe depressive symptoms. TCM practitioners widely believe that the Chinese herb Chaihu may target liver function and have an influence on mental illness (Chinese Pharmacopoeia Commission., 2020; Wang et al.,, 2022). Zhong (2006) found that the Shuyu capsule, extracted from Chaihu, significantly improved the levels of cortisol and ACTH in patients with depression, as demonstrated by the HPA axis. Another study by Xu et al. (2019) found that Chaihu significantly reduced the incidence of depressive-like behaviors in rats by regulating the HPA axis. Wei et al. (2019) highlighted that the Chaihu formula statistically improved the HPA axis, which reduced depression in rats. Liver function in TCM has an increasingly evident close link with the HPA axis in depression. Consistent with these findings, our results verify that the links between TCM-based liver function and depression can be interpreted using the HPA axis.

Admittedly, NE was marginally correlated with HRV, and a relationship between HRV and TCM-based liver function was not found in this study. A cross-sectional study by Baumert et al. (2009) reported a somewhat positive relationship between NE and HRV parameters in patients with depression. A randomized controlled study by Davidson et al. (2005) found that antidepressants blocked norepinephrine uptake and also lowered HRV parameters. Another study by Ahrens et al. (2008) highlighted that the central noradrenergic function is closely connected to HRV parameters in patients with major depression. These results support our current findings that a marginally positive relationship existed between HRV and NE. In contrast, our findings on HRV and TCM-based liver function are not supported by previous experimental studies. Shi

et al. (2014) suggested that acupuncture treatments targeting acupoints of the liver, heart, and brain—according to TCM—might significantly improve HRV parameters in patients with depression. Another study by Hu et al. (2018) emphasized that capsules of Shugan Jieyu that target TCM-based liver Qi stagnation significantly improved the standard deviation of NN intervals (SDNN) as well as the LF and HF of the HRV parameters in individuals with depression. Furthermore, Yi et al. (2015) indicated that a decoction of Shugan increased HF in those depressed patients who had a differentiation in the syndrome of liver Qi stagnation. Significantly, LC innervating and receiving information from the spinal cord and different brain areas is at the center of the synthesizing adrenergic nerve in the brain (Suárez-Pereira et al., 2022). Evidence exists that the LC can increase the synthesis of NE and enhance the activity of the sympathetic nerves by activating the HPA axis in stress-related disorders, such as depression and anxiety. Based on TCM, liver dysfunction and depression may have similar clinical symptoms to the increased activity of the sympathetic nerves, such as irritability, increased muscle tension and heart rate, and poor digestion. Moreover, TCM treatments targeting the regulation of the liver can significantly improve depressive symptoms. However, our results did not fully support this view, which may have been caused by the insufficient sample size in this study. Therefore, more studies with a larger sample size will be necessary to examine the relationship between sympathetic nerves and TCM-based liver function.

Interestingly, our results showed a positive correlation between NE and ACTH but a non-significant negative correlation between cortisol and the LF/HF ratio. ACTH plays a vital role in stimulating the adrenal glands to release androgens and increase the secretion of catecholamine, including NE and E (Ottaviani et al., 1999; Valenta et al., 1986). Thus, the relationship between NE and ACTH may provide further insight to interpret TCM-based liver function. Therefore, further studies are needed to analyze this potential pathway.

Yu in TCM may refer to depression (Ng, Chan, Ho, Wong, & Ho, 2006). Liver Qi stagnation is one of the depression types based on TCM theory, according to the internal medicine of TCM. Yu may embrace more syndromes than depression. However, some scholars have suggested that Yu may parallel depression, whereas some disagree. More studies are needed to explore the relationship between TCM liver function and depression.

5.6 Conclusion

Depression is a widespread mental disorder that causes a heavy economic burden on society. TCM and Western medicine have different views on depression. This is the pioneering study to examine the pathology of depression regarding TCM-based liver function through Western scientific approaches. The results of this study may provide some support to the hypothetical model of the relationship between cortisol, ACTH, and TCM liver function.

5.7 Limitations

This study has some limitations. First, the participants were recruited from only one hospital. Thus, the results might not be generalizable to the entire population with depression. Second, the majority of participants were female (70%), which may produce a gender bias. Third, the study involved only a cross-sectional data analysis—that is, the causal relationship between TCM-based liver function and the HPA axis could not be established based on the data from this study. Future studies using a longitudinal design are highly recommended to analyze the causal relationship of variables involved in the pathways of depression based on TCM theory. Fourth, the sample size may not be large enough in this study. Some researchers have recommended that the minimum sample size for path analysis using AMOS software is 200 (Valenzuela & Bachmann, 2017). Therefore, further experimental studies with a larger sample size to analyze the pathological models based on the integration of Eastern and Western medicine are highly recommended. Fifth, data on the validity of the TCM scale were not found. Further studies may consider conducting exploratory factor analysis to measure the quality of this scale. Sixth, biomarkers may be influenced by stress levels, medication, or physical activity, but we did not use these factors as confounding variables in this study. Thus, the results should be cautiously interpreted. Last, the standardized operating procedure to diagnose MDD for inpatients was applied, including taking blood and CT or MRI assessments. However, no standardized instrument exists to diagnose depression for outpatients. Clinical psychiatrists diagnose depression based on clinical symptoms and observation. This study did not apply the Structured Clinical Interview for DSM-5 Disorders (SCID) due to the limited staffing during the pandemic. Further work may include the SCID as a standardized instrument to diagnose depression based on the DSM-5.

CHAPTER 6

The effects of Baduanjin exercise on neurophysiological and TCM-based outcomes in patients with major depressive disorder: A pilot randomized controlled trial

This chapter presents the second main part of the PhD study, which examined the safety and efficacy of a 10-week Baduanjin intervention program in patients with MDD by conducting a pilot RCT. In general, the results of this study suggested that Baduanjin exercise can be considered a safe and efficient intervention for MDD and provided some support to the hypothetical model of the relationships between cortisol, ACTH, and TCM liver function that were proposed and tested in Chapters 2 and 5.

6.1 Introduction

6.1.1 Study background

MDD is a prevalent mental illness worldwide characterized by depressive mood, loss of motivation and energy, and feelings of hopelessness (Abdoli et al., 2022). It is one of the leading causes of disability and has a greater influence on public health than physical diseases such as diabetes and arthritis (Egede, 2008; Ng & Leng, 2018). A cross-sectional study by He (2019) in China showed that the prevalence of depression was more than 40% in individuals with chronic illnesses, and this high incidence was associated with social participation, culture, education, physical functioning, and cognition. Recently, an epidemiological study conducted in 31 provinces across China highlighted that most depressed adults had social impairment and only 9.5% of depressed Chinese people received adequate treatment. Of these, 1.5% received general medication and 2.7% received complementary and alternative medicine treatments (Lu et al., 2021). Removing barriers to the accessibility and acceptability of mental health care is urgently needed for Chinese people with depression (Lu et al., 2021; Yeung et al., 2012).

The mainstay treatment for MDD worldwide is psychotherapy and pharmacotherapy. However, the clinical efficacy of these treatments has received increasing attention (Jakobsen et al., 2017). Pharmacological treatment may cause unwanted effects such as weight gain and sleep disorders. Psychological interventions such as CBT and counseling are time-consuming and labor-intensive, with high professional charges associated (Ferguson, 2001). In China, most adults have little mental health knowledge (Yin et al., 2020). More specifically, some Chinese people diagnosed with depression have cultural barriers to receiving mental health care such as counseling, CBT, and medications (Yeung et al., 2012). When depressed, few Chinese adults are willing to go to hospitals or medical centers to seek help from professional psychiatrists or health professionals for fear of being stigmatized. Therefore, the prevalence of depression among Chinese people is high, but few receive professional treatment. Seeking culturally adapted interventions is imperative for depressed Chinese people, whose numbers have increased rapidly in recent years (He, 2019; Lu et al., 2021; Yeung et al., 2012).

Baduanjin exercise is a mind–body intervention that has been evolving for more than 2,000 years in China and is culturally accepted as beneficial to Chinese health

(Koh, 1982). The essence of this exercise is the synchronized integration between the mind, physical movements, and diaphragmatic breathing. Notably, Baduanjin exercise is less physically and cognitively demanding compared with Tai Chi because it only involves eight separate movements (Chan & Tsang, 2019). Many experimental and observational studies have been conducted to investigate the therapeutic effects of Baduanjin exercise on depression in different age groups, and they have shown beneficial effects in improving depressive symptoms (Lee et al., 2019; Ng et al., 2022; Tsang et al., 2003; Tsang et al., 2013; Tsang et al., 2002; Zhang et al., 2021), cortisol level (Tsang et al., 2013), cognition (Tao et al., 2019; Wang et al., 2021; Yu et al., 2021), and quality of life (Bao et al., 2020). However, the majority of these studies recruited individuals whose primary diagnosis was not depression, and few examined the effects of Baduanjin exercise specifically in patients with MDD. A prior theoretic review proposed that the mechanism of depression might relate to the HPA axis and TCM-based liver function (Ye, Cai, et al., 2019). One of our previous systematic reviews found that Chinese mind–body intervention can reduce MDD symptoms by mediating the HPA axis (Ye, Cheung, et al., 2019). Given that the pathology of depression may be caused by neuroendocrine dysregulation and TCM-based liver dysfunction, whether the functional effects of Baduanjin exercise can modulate the neuroendocrine system and TCM-based liver function remains unclear.

6.1.2 Aim and hypotheses

This is a pioneering RCT to explore the neurophysiological and TCM-based outcomes of Baduanjin exercise in patients with MDD. This study aimed to provide further evidence to support the East meets West model regarding liver function that was tested in Chapter 5, with the application of Baduanjin as an intervention. The findings of this study can contribute to a better understanding of the mechanism of this intervention on MDD using an East meets West approach. Additionally, it can test the possible models that we developed regarding TCM-based liver function and depression in the prior theoretical review. The specific hypotheses are:

1) Participants in the Baduanjin group would report fewer depressive symptoms than those in the control group after the intervention program.
2) Participants in the Baduanjin group would report decreased severity of TCM-based liver function compared to those in the control group after the intervention program.

3) Participants in the Baduanjin group would report decreased ACTH levels compared to those in the control group after the intervention program.
4) Participants in the Baduanjin group would report lower cortisol levels than those in the control group after the intervention program.

6.2 Material and methods

6.2.1 Study design

This clinical trial was designed as a pilot randomized, single-blind, two-arm parallel assignment. We reported the study procedures and results using the CONSORT checklist (Moher et al., 2012). The study was conducted following the Declaration of Helsinki, and the trial was registered in the Chinese Clinical Trial Registry (ChiCTR1900027222).

6.2.2 Study participants

Participants were recruited if they met the following criteria: (1) aged 18 to 65 years (Ferrari et al., 2016), (2) diagnosed with a current episode of MDD by a psychiatrist according to the DSM-5 criteria, (3) a baseline score of 12 or higher on the $HRSD_{17}$ (Ryder et al., 2005; Yeung et al., 2017), (4) diagnosed with symptoms of liver Qi stagnation by the National Key Technology Research and Development Program of China during the *10th Five-Year Plan* (Chen Zheqi, 2005; Wu, 2008), (5) a MoCA score of 20 or higher. Participants were excluded from the study if they fit any of the following criteria: (1) a primary diagnosis other than MDD; (2) pregnancy or lactation; (3) substance use or drug dependence; (4) acute suicidal or violent behavior; (5) current medical illness including diabetes, autoimmune diseases, cardiovascular disease, hypertension, chronic fatigue syndrome, or asthma; (6) regular practice of Baduanjin exercise or any kind of mind–body exercise in the past six months; (7) inability to participate in Baduanjin exercise due to mobility problems. Participants receiving treatment for depression, including antidepressants or psychotherapy, could continue their treatments during this study.

6.2.3 Participant enrolment and randomization

Potential participants with MDD were referred by psychiatrists or occupational therapists from a rehabilitation hospital in Fujian, China, between October 2020 and October 2021. The ethical application of this study was approved by the local research ethics committee (approval number: 2020YJS-003-01).

A qualified research assistant who received diagnostic training from a certified clinical psychiatrist and a TCM practitioner explained the research and conducted an initial screening to determine eligibility. All eligible individuals were randomly assigned to either the experimental Baduanjin exercise group or the control group at a 1:1 ratio using computer-generated numbers. Participants were informed by a research assistant about the group allocation (Baduanjin exercise or control) by phone calls after the baseline assessments. A blinded research assistant conducted all outcome assessments while masked to group allocation. All eligible participants were asked to sign their informed consent forms before joining this study.

6.2.4 Sample size calculation

The sample size was calculated using G*Power3.1 software. To achieve a power of 0.8 and a medium effect size of 0.25 at a 0.05 level of significance, a sample size of 48 was needed. Considering a 20% attrition rate, a sample size of 58 was required for the two groups. This was a pilot study conducted to explore the safety and possible effectiveness of the intervention. The final sample size in this pilot study was calculated at around one third of the total sample size. Therefore, a minimum of 20 participants was needed for the two groups.

6.2.5 Intervention and control protocols

A 10-week group-based Baduanjin training program, administered by a certified Qigong instructor with at least three years of teaching experience, was provided to the MDD patients. It involved two sessions per week, with each session lasting 60 minutes (10 minutes for warm-up and cool-down and 50 minutes for Baduanjin movements). The Baduanjin training regime was in line with the Health Qigong-Baduanjin published by the Health Qigong Management Centre of General Administration of Sport of China (2003). Participants in the Baduanjin exercise group were instructed to attend group-based Baduanjin training for the first two weeks in the hospital. They were asked to practice the Baduanjin exercise at home from weeks 3 to 10. Regular phone calls were given to remind the participants to practice the in-home Badaunjin exercise. To maintain adherence to this Baduanjin exercise program, participants were instructed to record their performance for quality assurance purposes.

Participants in the control group were instructed to keep their lifestyle as usual and received free Baduanjin training classes after they completed the 10-week study

period.

6.2.6 Outcome measures

Outcome measures were assessed at baseline and weeks 5 and 10 by research assistants who were blinded to participants' randomization status. Participants in both groups were required to complete the assessments of $HRSD_{17}$, TCM-based liver function, cortisol, and ACTH.

$HRSD_{17}$: The HRSD is the most common scale for quantifying the severity of symptoms of depression by clinicians. This 17-item scale is rated on a three- or five-point scale and relates to symptoms of depression experienced in the previous week. A higher score indicates more severe symptoms of depression (Brown et al., 2008).

TCM-based liver function: According to the *Guiding Principles of Clinical Research on New Drugs of Traditional Chinese Medicine*, TCM-based liver function is evaluated based on the clinical symptoms, tongue, and pulse (Zheng, 2002). The symptoms are: (1) major symptoms, including mental depression, frustrated expression, pessimism and world-weariness, and sighing often; (2) secondary symptoms, including poor memory, insomnia, irritability, belching, hiccups, restlessness, pain, abdominal distension, and foreign body sensation in the throat; (3) tongue coating, including pink tongue with a thin, white coating; (4) pulse signs (e.g., wiry pulse). The major symptom items are rated on a seven-point scale ranging from 0 to 6, and the secondary symptom items are rated on a four-point scale ranging from 0 to 3. A higher score indicates more severe liver Qi stagnation.

Blood sampling analysis: A blood sample for analyzing cortisol and ACTH was collected in a 5-mL tube with EDTA-Na_2 between 9 and 11 a.m. from eligible participants. Whole blood was centrifuged at 1,000 x g for 15 minutes at 4 ºC for plasma isolation. The plasma was divided into six tubes and stored at -20 ºC for subsequent analysis. ELISA kits (Elabscience Biotechnology Co. Ltd., Wuhan, China) were used to determine the concentrations of ACTH and cortisol. All measurements were performed according to the manufacturer protocol.

6.2.7 Safety measures

Participants were advised to complete a form to verify possible adverse events, changes in health status, and attendance. Adherence and the occurrence of adverse events during the study were evaluated for relevance to the intervention by the research team.

2.8 Data analysis

The participants' demographic data characteristics were presented with descriptive statistics. The Shapiro–Wilk test of normality was performed to check the normal distribution of the data. For each outcome measure, two-way repeated measures analysis of variance (RM ANOVA; group x time) was conducted to detect the interaction effect between group and time. If a significant interaction effect existed, a separate subgroup analysis with post hoc pairwise comparison between any two endpoints with the Bonferroni adjustment was conducted. Changes in outcome measures (delta changes) between five weeks post-intervention and baseline and 10 weeks post-intervention and baseline were calculated to detect the trend changes on all variables for both groups. An intention-to-treat analysis with the last observation carried forward (LOCF) method was used for missing data. All statistical tests were performed using the statistical software SPSS (version 22; SPSS Inc, Chicago, IL, USA), and $p<0.05$ was used to denote statistical significance.

6.3 Results

The demographic characteristics of participants in both groups are presented in Table 6.1. Twenty-seven individuals with MDD were enrolled in this study. The majority were female, with 79% in the Baduanjin exercise group and 69% in the waitlist-control group, respectively. The two groups were comparable in terms of age, sex, height, weight, MoCA score, educational status, and baseline scores on $HRSD_{17}$, TCM-based liver function, cortisol, and ACTH ($p>0.05$; Tables 6.1 and 6.2). Detailed information on the study procedure is shown in Figure 6.1. No adverse events occurred during the 10-week intervention period.

Table 6.1 Baseline characteristics data of participants

Characteristics	BD (n=14)	CG (n=13)	*P*
Age, years	40.45 ± 14.49	44.95 ± 13.77	0.416
Gender, female, %	11 (79)	9 (69)	0.580
Height, cm	163.00 ± 9.70	166.00 ± 10.00	0.437
Weight, kg	57.92 ± 6.87	58.64 ± 11.41	0.720
Education status, n(%)			
High (>12 years)	8(62)	12(86)	0.152
MoCA	24.31 ± 4.17	23.43 ±3.01	0.533
$HRSD_{17}$	1.29 ± 0.10	1.28 ± 0.12	0.711
TCM-based liver function	1.42 ± 0.06	1.37 ± 0.10	0.110
Cortisol	2.44 ± 0.10	2.49 ± 0.13	0.379
ACTH	3.12 ± 0.03	3.12 ± 0.07	0.756

Notes: BD: Baduanjin group; CG: Control group.

Table 6.2 Mean and SD performances of all variables

Variable / Group	Time point Mean ± SD				Condition effect	Time effect	Condition x time effect *p*	*F*	η^2
$HRSD_{17}$	Baseline	*P*	Week 5	Week 10					
BD	1.29 ± 0.10	0.711	2.50 ± 0.53	1.14 ± 0.19	0.670	0.001	0.293	1.259	0.048
CG	1.28 ± 0.12		2.73 ± 0.88	1.19 ± 0.15					
TCM liver function									
BD	1.42 ± 0.06	0.110	1.27 ± 0.13	1.20 ± 0.20	0.542	0.001	0.395	0.890	0.034
CG	1.37 ± 0.10		1.20 ± 0.18	1.24 ± 0.26					
Cortisol									
BD	2.44 ± 0.10	0.379	2.22 ± 0.28	1.98 ± 0.43	0.277	0.001	0.606	0.506	0.020
CG	2.49 ± 0.13		2.31 ± 0.24	2.18 ± 0.64					
ACTH									
BD	3.12 ± 0.03	0.756	2.78 ± 0.46	2.64 ± 0.36	0.062	0.003	0.109	2.322	0.085
CG	3.12 ± 0.07		3.08 ± 0.50	2.98 ± 0.55					

Notes: BD: Baduanjin group; CG: Control group; $HRSD_{17}$: 17–item Hamilton Depression Rating Scale; TCM: Traditional Chinese medicine; ACTH: Adrenocorticotropic hormone.

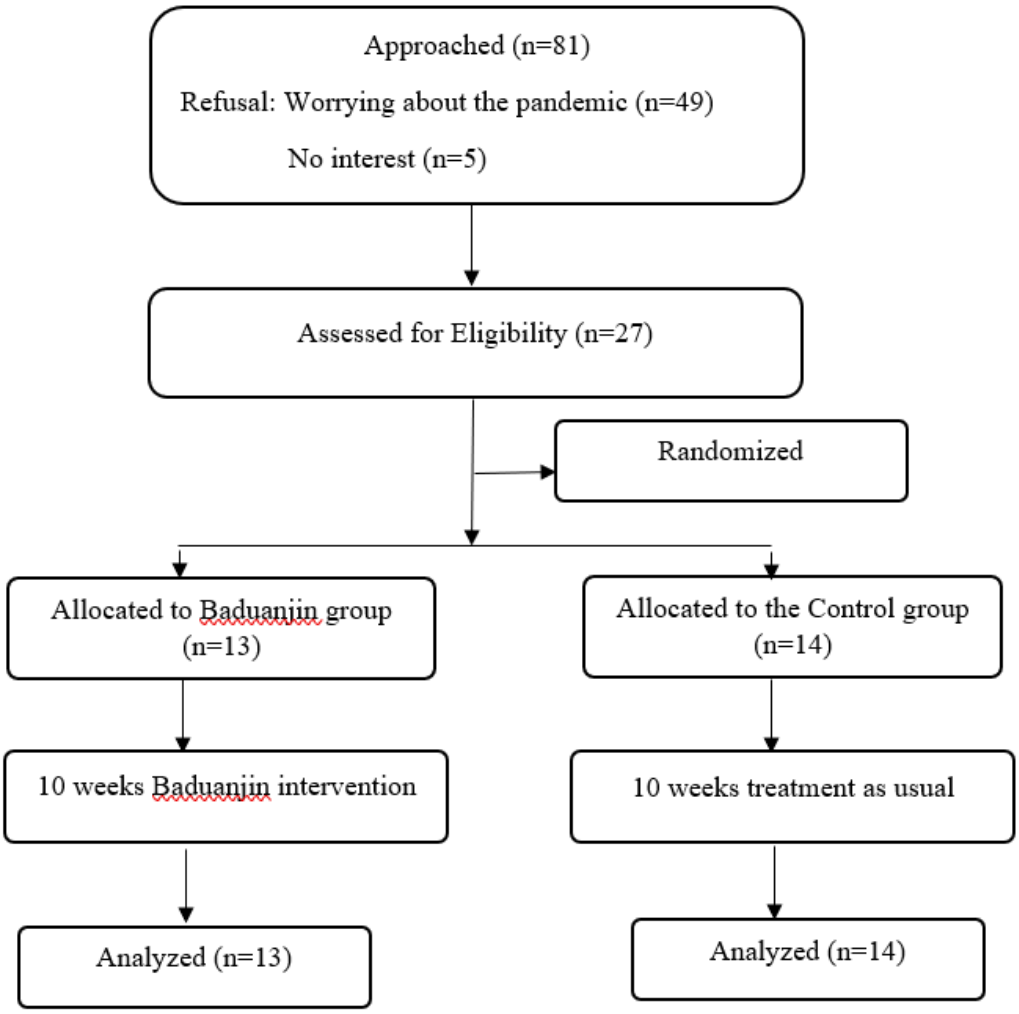

Figure 6.1 Flowchart of this study.

The outcomes of the variables are presented in Table 6.2. Significant time effects for $HRSD_{17}$ (F=22.023, p=0.001, η^2=0.468), TCM-based liver function (F=12.559, p=0.001, η^2=0.334), cortisol (F=11.560, p=0.001, $\eta 2$=0.316), and ACTH (F=6.567, p=0.003, η^2=0.208) were found. Neither group nor interaction effect was found to be significant among all variables after the 10-week Baduanjin intervention (p>0.05).

The results of all outcome variables over time are described in Table 6.3A. The participants in both groups showed significant differences in $HRSD_{17}$, TCM-based liver function, and cortisol at week 5 (all p-values between 0.002 and 0.027) when compared with their baseline scores. However, only ACTH was found to have a significant difference between week 5 and the baseline score in the Baduanjin exercise group (p=0.019). The significant changes in TCM-based liver function (p=0.020) and cortisol (p=0.001) were only found in the Baduanjin exercise group between the week 10 assessment and week 5 measurement. Similarly, significant changes in $HRSD_{17}$ (p=0.003), TCM-based liver function (p=0.002), and cortisol (p=0.001) were found only in the Baduanjin exercise group between week 10 and baseline scores. In addition, significant changes were found in ACTH in the Baduanjin exercise group between week 5 and baseline assessment (p=0.019) as well as between week 10 and baseline assessment (p=0.001). No statistical between-group difference was found in any outcome measure after 10 weeks of the Baduanjin intervention (Table 6.3B).

Table 6.3A Results of all outcome variables over time in both groups.

Variable		Pre vs. 5 weeks post		5 weeks post vs. 10 weeks post		Pre vs. 10 weeks post	
		BD	CG	BD	CG	BD	CG
$HRSD_{17}$	*p*	0.001	0.002	0.693	0.786	0.003	0.001
	95% CI	0.84 to 0.19	0.04 to 0.13	-0.07 to 0.10	-0.04 to 0.05	0.63 to 0.24	0.05 to 0.14
TCM liver	*p*	0.002	0.001	0.020	0.693	0.002	0.084
function	95% CI	0.07 to 0.24	0.08 to 0.25	0.01 to 0.12	-0.20 to 0.13	0.10 to 0.34	-0.02 to 0.30
Cortisol	*p*	0.006	0.027	0.001	0.326	0.001	0.108
	95% CI	0.08 to 0.36	-0.02 to 0.31	0.12 to 0.37	0.14 to -0.16	0.23 to 0.70	-0.08 to 0.69
ACTH	*p*	0.019	0.754	0.191	0.437	0.001	0.344
	95% CI	0.07 to 0.61	-0.23 to 0.31	-0.08 to 0.36	-0.17 to 0.36	0.26 to 0.07	-0.17 to 0.45

Notes: BD: Baduanjin group; CG: Control group; $HRSD_{17}$: 17-Item Hamilton Depression Rating Scale; TCM: Traditional Chinese medicine; ACTH: Adrenocorticotropic hormone.

Table 6.3B Between-group differences over time in all variables.

Variable		5 post	10 post
$HRSD_{17}$	*p*	0.475	0.508
	95% CI	-0.061 to 0.13	-0.09 to 0.18
TCM liver function	*p*	0.284	0.726
	95% CI	-0.19 to 0.06	-0.15 to 0.22
Cortisol	*p*	0.349	0.351
	95% CI	-0.11 to 0.30	-0.23 to 0.63
ACTH	*p*	0.111	0.067
	95% CI	-0.08 to 0.69	-0.03 to 0.72

Notes: $HRSD_{17}$: 17-Item Hamilton Depression Rating Scale; TCM: Traditional Chinese medicine; ACTH: Adrenocorticotropic hormone.

A trend of improvement was observed in $HRSD_{17}$, TCM-based liver function, cortisol, and ACTH in the Baduanjin exercise group based on the delta change calculation. Although all the changes were found to be non-significant, the results of this calculation showed improvements of -0.153 for $HRSD_{17}$, -0.220 for TCM-based liver function, -0.478 for ACTH, and -0.466 for cortisol in the Baduanjin exercise group between the week 10 assessment and baseline scores. The detailed changes in different variables are summarized in Table 6.4 and Figure 6.2.

Table 6.4 Changes between different time points in all variables for both groups

Variables	5 week-pre	*p* 95% CI	10 week-pre	*p* 95% CI
$HRSD_{17}$				
BD	-0.136 ± 0.088	0.141	-0.153 ± 0.148	0.188
CG	-0.086 ± 0.084	-0.02 to 0.12	-0.092 ± 0.075	-0.03 to 0.15
TCM liver function				
BD	-0.154 ± 0.140	0.804	-0.220 ± 0.200	0.381
CG	-0.168 ± 0.147	-0.13 to 0.10	-0.137 ± 0.274	-0.11 to 0.27
Cortisol				
BD	-0.220 ± 0.236	0.571	-0.466 ± 0.396	0.462
CG	-0.166 ± 0.250	-0.14 to 0.25	-0.307 ± 0.664	-0.28 to 0.60
ACTH				
BD	-0.340 ±0.453	0.107	-0.478 ± 0.363	0.066
CG	-0.041 ± 0.474	-0.07 to 0.67	-0.139 ± 0.531	-0.02 to 0.70

Notes: BD: Baduanjin group; CG: Control group; $HRSD_{17}$: 17-Item Hamilton Depression Rating Scale; TCM: Traditional Chinese medicine; ACTH: Adrenocorticotropic hormone.

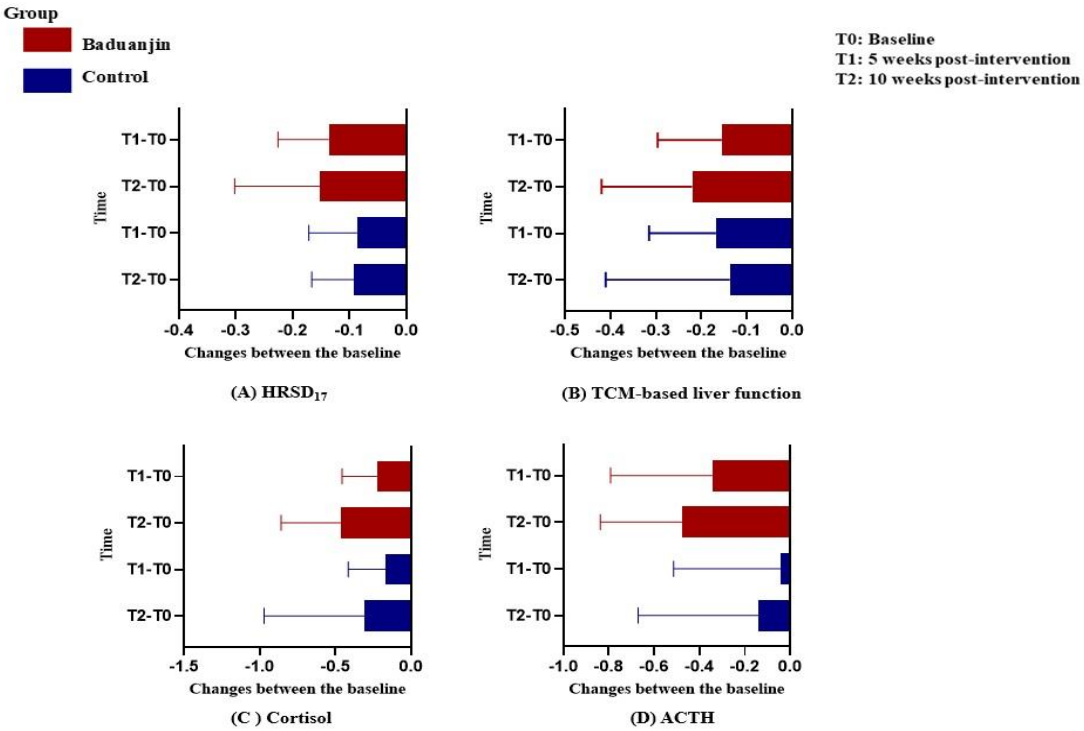

Figure 6.2 Delta changes of all variables between baseline in both groups.

6.4 Discussion

This pilot RCT provides preliminary information on the influence of a culturally relevant intervention: Baduanjin exercise for patients with MDD. The results of this study showed the efficacy of this intervention for MDD by means of neurophysiological and TCM-based outcomes. Despite the marginally significant result for the between-group difference in ACTH after 10 weeks of the Baduanjin intervention, improvement trends in line with the hypotheses were clearly observed in all outcome measurements in the Baduanjin exercise group. These findings can thus be regarded as very preliminary evidence in support of Hypotheses 1 to 4 set at the beginning of this chapter. Hypothesis 1 stated that participants in the Baduanjin group would have lower depressive symptoms than those in the control group after the intervention program. Hypothesis 2 stated that participants in the Baduanjin group would have decreased severity of TCM-based liver function compared to those in the control group. Hypothesis 3 stated that participants in the Baduanjin group would have decreased ACTH levels compared to those in the control group. Hypothesis 4 stated that participants in the Baduanjin group would have lower cortisol levels than those in the control group after the 10-week Baduanjin intervention program. In short, our findings suggest that Baduanjin exercise may have positive impacts on a certain proportion of Chinese adults with mild to moderate symptoms of depression.

Participants in the Baduanjin exercise group demonstrated significant improvements in $HRSD_{17}$, TCM-based liver function, cortisol, and ACTH after five weeks of the Baduanjin intervention. This suggests that a minimum of five weeks of Baduanjin training may trigger an initial response to the psychological measurement, neurophysiological biomarkers, and TCM-based liver function in participants with MDD. Furthermore, significant improvements were found in $HRSD_{17}$, TCM-based liver function, cortisol, and ACTH in the Baduanjin exercise group after the 10-week intervention program compared with the baseline. This study has demonstrated that patients with MDD can benefit from a 10-week Baduanjin exercise regime (two sessions per week, 60 minutes per session), which is supported by the findings of previous systematic reviews investigating the effects of the mind–body intervention on depression (An et al., 2019; Jing et al., 2018; Kong et al., 2022; Luo et al., 2022; Zhang et al., 2021; Zou, Yeung, et al., 2018). A prior theoretic review proposed that TCM-based liver function in depression can be understood from the Western

perspective considering the HPA axis (Ye, Cai, et al., 2019), and the results of a cross-sectional study tested this plausible assumption (Ye et al., 2022). The findings of this pilot study have provided very preliminary support to this theoretical speculation. This suggests that Baduanjin exercise may have a beneficial effect on MDD. Wang et al. (2021) found that an eight-week Baduanjin intervention could significantly improve the depressive symptoms and concentrations of cortisol, NE, and 5-HT in college students with depressive mood. Another study conducted by Tsang et al. (2013) highlighted that a 12-week Baduanjin exercise program significantly reduced the depressive symptoms and concentration of cortisol in depressed elderly people. Notably, the beneficial effects of Baduanjin exercise on depression may be achieved by various mechanisms, such as the activation of anti-inflammatory effects, the ANS, neurogenesis, and neuroplasticity. An experimental study conducted by An et al. (2019) showed that regular practice of Baduanjin exercise could modulate the expression of non-coding RNAs. Because microRNA has been increasingly proposed to have a close link with the pathogenesis of depression, exploring more mechanisms in the future is valuable, especially for the molecular-based pathology of depression.

Although no statistical between-group difference was found after 10 weeks of Baduanjin intervention, trends toward improved $HRSD_{17}$, TCM-based liver function, cortisol, and ACTH after the Baduanjin training were clearly observed. The participants in the Baduanjin exercise group generally had greater improvement than those in the control group. Future full-scale studies are required to investigate the full training effects.

Recruitment in this study was affected by the COVID-19 pandemic. The main reason for refusal to join this study was concern about the pandemic (refusal due to the pandemic: 49 out of 81; no interest: 5 out of 81). Given the hospital management measures, we normally recruited the participants from the wards. This helped guarantee that patients would stay in the hospital for at least two weeks and comply with our supervision.

Program safety is important for health promotion in different populations. No adverse events related to the intervention were reported throughout the study period, which was in accordance with the previous observations (Fang et al., 2021; Wang et al., 2021; Zou, Wang, et al., 2018). Summarizing all of the findings and observations, Baduanjin exercise is recommended as a safe and effective therapy for MDD patients.

6.5 Conclusion

A 10-week Baduanjin intervention program (two sessions per week, with each session lasting 60 minutes) is safe and effective for adults with MDD. Baduanjin exercise may improve the depressive symptoms and severity of TCM-based liver function. This pilot RCT offers a promising perspective for understanding the positive effects of Baduanjin on MDD based on an East meets West approach. Future studies with full-scale RCTs and follow-up assessments will be needed to provide the definitive long-term effects of this intervention.

6.6 Limitations

We would like to acknowledge some limitations of this study. Firstly, no follow-up assessment was applied after the 10-week intervention, so we could not observe the long-term effects of Baduanjin exercise for patients with MDD. Further studies may include follow-up assessments to understand the long-term effects of Baduanjin exercise. Additionally, participants were instructed to mainly practice Baduanjin exercise at home, and regular phone calls were made to remind them to participate in Baduanjin exercise. This meant difficulties in monitoring their performance even if they indicated their attendance in the phone calls. Future studies may invite their family members to join the study. Thirdly, the gender in this study was imbalanced. The majority of participants were women. The results should be cautiously interpreted because the neuroendocrine biomarker changes are more sensitive in women than men (Busch & Menke, 2019). Fourthly, the results of this study could be partially explained even though participants in the control group did not receive any attention or education training. Notably, the participants in both groups still took their medications during the research period. More investigations applying Baduanjin exercise as the mono-intervention will be taken into consideration. Lastly, participants in the Baduanjin group performed the group-based Baduanjin intervention for at least 2 weeks, while the controls conducted their lifestyles as usual. The nonspecific social gathering effects should be considered. Further studies may consider using group reading techniques as controls to limit the effects of social gathering.

CHAPTER 7

Conclusions, implications, and recommendations

This chapter summarizes the main findings of the study, presents the research and clinical implications, and makes recommendations for further study.

7.1 Conclusions

The purpose of this study was to understand the pathology of depression based on an integrated East meets West approach. The objective has been summarized into three major categories: (1) to construct neurophysiological pathways in terms of depression and TCM-based organ function based on a substantial literature review, (2) to test the plausible pathways constructed by the theoretical review by conducting a cross-sectional study, and (3) to support the plausible pathways linking TCM-based liver function and depression by applying Baduanjin exercise as an intervention.

7.1.1 Construct neurophysiological pathways in terms of depression and TCM-based organ function based on substantial literature review

An extensive theoretical review was carried out in Chapter 2 to propose the plausible neurological pathways linking TCM-based organ function and depression. TCM is mainly based on observation and experience. In contrast, Western medicine relies on scientific investigation and experimentation. From a Western view, the pathologies of depression may relate to the dysregulation of neurotransmitters, disorders of glutamine and λ-amino butyric acid, gene and environment interaction, and cognition. On the other hand, TCM views of the pathologies of depression may refer to Zang Fu: internal organs including the liver, spleen, and heart. Three possible neurophysiological pathways were thus proposed: liver function may be explained by the HPA axis and LC/NE system, spleen function may correspond to the digestive system, and heart function may refer to the circulation of the blood and the regulation of brain activity. Further experimental studies are needed to test these plausible pathways.

7.1.2 Test the hypothetical pathways constructed by theoretical review by conducting a cross-sectional study

A cross-sectional study was conducted to test the hypothetical pathways linking TCM-based liver function and depression. The outcomes of ACTH, cortisol, NE, HRV (LF/HF), and TCM-based liver function scale were applied to test the relationships between the HPA axis, LC/NE system, and TCM-based liver function in depressed adults. Significant relationships were found between cortisol, ACTH, and TCM-based liver function in individuals with depression, which supports the findings in Chapter 2. However, only a marginally significant association was found between NE and LF/HF. Thus, the relationship between the LC/NE system, TCM-based liver

function, and depression may not be established in this study due to the insufficient sample size.

7.1.3 Support the plausible pathways linking TCM-based liver function and depression by applying Baduanjin exercise as an intervention

A pilot RCT was conducted to support the plausible pathway from the HPA axis to TCM-based liver function by applying a 10-week Baduanjin intervention program (two sessions per week, with each session lasting 60 minutes). Baduanjin exercise significantly improved the concentrations of ACTH and cortisol, $HRSD_{17}$, and TCM-based liver function compared with baseline scores. The trends of improvement in HRSD, TCM-based liver function, cortisol, and ACTH were only observed in the Baduanjin exercise group, suggesting that Baduanjin exercise may improve the depressive symptoms, cortisol, ACTH, and severity of TCM-based liver function. This is in line with the findings from Chapters 2 and 5. Based on our findings, we can conclude that Baduanjin exercise is a safe and effective intervention for MDD.

7.2 Implications of the study

7.2.1 Research

Western and Eastern medicine are two different systems of medicine in the world (Tian, 2011). These two systems have been parallel for thousands of years. Many studies have been conducted to investigate the pathologies of depression, based on either the Western or Eastern medicine side. The present study specifically focuses on an East meets West approach to understand the pathology of depression. Few studies have attempted to investigate the TCM-based organ function in depression using advanced technologies. Our study is a pioneering effort to construct the plausible pathways linking depression and TCM-based organ function and test their likelihood. Understanding the pathology of depression is crucial. This study has created a general blueprint for interpreting TCM-based pathology of depression using Western medicine approaches.

In addition, this study updates the existing evidence for practicing Baduanjin exercise in patients with MDD. The efficacy of Baduanjin exercise is demonstrated by improving $HRSD_{17}$, the severity of TCM-based liver function, and concentrations of cortisol and ACTH in our study. Previous studies investigating the effects of Baduanjin exercise have mainly been conducted on patients whose primary diagnosis

was not depression. This study expands the existing literature by using MDD patients as the research population. The findings of this study contribute to the efficacy and mechanisms of Baduanjin exercise in adults with MDD. The HPA axis may be only one plausible mechanism of Baduanjin exercise as a treatment for MDD. Apart from the TCM-based liver function, we proposed several possible neurophysiological pathways that may explain depression. These include the TCM-based spleen and heart functions and depression described in Chapter 2. However, due to time and staffing constraints, we only tested the pathways related to TCM-based liver function. The TCM-based spleen function may refer to the function of digestion, and the TCM-based heart function may correspond to the circulation of the blood and the regulation of brain activity. These hypotheses may need more research efforts to test and validate. Thus, further research along this line to integrate East and West understandings of depression may refer to these untested neurophysiological pathways and apply structured research efforts to evaluate their validity.

Lastly, in Chapter 5, a marginally significant relationship was found in the concentration of NE and LF/HF. NE is derived from catecholamine, and the concentration of NE is involved in the “flight or flight” state, which may closely relate to the dysfunction of TCM-based liver function. This study gives a new insight into the pathology of depression. More experimental studies are highly recommended to investigate the connection between Eastern and Western medicine.

7.2.2 Health professionals and clinical practice

This study has several implications for health professionals and clinical practice. First, the findings provide evidence-based TCM theory for those health professionals and TCM practitioners who apply TCM techniques as therapy. The results of this study help more health professionals to better understand what TCM is.

Second, the findings of this study suggest that Baduanjin exercise is safe for adults with MDD to practice. No adverse event was reported during this study. All participants in the Baduanjin group underwent a 10-week Baduanjin intervention program. Although few studies have focused on the use of Baduanjin exercise for adults with MDD, this finding provides a new intervention option for health professionals.

Third, the results of this study showed that Baduanjin exercise had beneficial effects on individuals with MDD. Participants in the Baduanjin group had lower

depressive symptoms, TCM-based liver function severity, and concentrations of cortisol and ACTH compared with baseline scores. Despite no significant between-group difference being found in the study, the trends towards improvement in $HRSD_{17}$, TCM-based liver function, cortisol, and ACTH were only observed in the Baduanjin exercise group. Health professionals may therefore consider using Baduanjin exercise as an intervention for adults with MDD.

7.3 Recommendations

7.3.1 Research

This study provides new insight into the pathology of depression, based on an integration of Eastern and Western approaches. We would like to recommend these key points:

1) Further studies are strongly recommended to investigate the connection between Eastern and Western medicine systems.
2) More experimental studies are suggested to test the hypothetical pathways linking TCM-based organ function and depression that we constructed in Chapter 2.
3) Further full-scale RCTs with sufficient-intensity intervention programs are highly recommended to detect more definitive effects of Baduanjin exercise.
4) Studies focusing on the investigation of the mechanisms of Baduanjin exercise are also strongly recommended.

7.3.2 Health professionals and clinical practice

The results of this study suggest the following key messages for health professionals:

1) A 10-week Baduanjin exercise program (60 minutes per session, twice per week) is safe for adults with MDD.
2) The effects of taking medications plus Baduanjin exercise may be superior to those of taking medication alone.
3) TCM is not only based on clinical experience but also supported by scientific evidence.

7.4 Limitations of the study

This study has some limitations. First, no medication-free period was applied for the participants, and previous studies have suggested that antidepressants may affect

neuroendocrine biomarker concentrations (Busch & Menke, 2019; Trifu et al., 2020). The reason for the absence of a medication-free period was the research ethics committee's requirements. It was also impossible to require MDD inpatients to abstain from any medication.

Second, the length of the intervention program in this study may not have been sufficient. This was due to the COVID-19 pandemic. Originally, the study planned a 12-week Baduanjin exercise program with a one-month follow-up assessment. Because the pandemic was still ongoing at that time, hospitals postponed the data collection. We revised the intervention protocol to a 10-week Baduanjin exercise program with no follow-up assessment to explore the pilot results of this study.

Third, the sample size was relatively small. Therefore, the generalization power of the results is limited.

Fourth, the gender proportions in this study were imbalanced. The majority of participants were women, who are more sensitive than males to the neuroendocrine biomarker changes. Thus, the results of this study should be cautiously interpreted.

Lastly, this study adopted a hybrid intervention program: participants practiced Baduanjin exercise in the hospital for the first two weeks, and they practiced home-based Baduanjin exercise for the remaining eight weeks. Exercise performance is difficult to monitor when participants practice Baduanjin exercise at home. Further studies may recommend domestic helpers and family members to participate in the exercise.

APPENDICES

Appendix 1A: Ethical approval from the Fujian University of Traditional Chinese Medicine Subsidiary Rehabilitation Hospital's Research Ethics Committee and Institutional Review Board

伦理审查批件

批件号	2020YJS-003-01		
项目名称	中西医结合探讨抑郁症：从中医脏腑到神经科学		
项目来源	香港理工大学博士研究生课题		
研究单位	福建中医药大学附属康复医院		
主要研究者	叶佳佳		
审查类别	初始审查	审查方式	快速审查
审查日期	2020 年 10 月 16 日	审查地点	福建中医药大学附属康复医院
审查委员	汪欣、黄赛娥		
批准文件	临床研究方案 版本号：1.0 版本日期：2020-10-15 知情同意书 版本号：1.0 版本日期：2020-10-15 招募受试者材料 版本号：1.0 版本日期：2020-10-15		
审查意见			
根据国家卫生健康委员会《涉及人的生物医学研究伦理审查办法》、国家中医药管理局《中医药临床研究伦理审查管理规范》、国家食品药品监督管理总局《药物临床试验质量管理规范》及《医疗器械临床试验质量管理规范》、世界医学会《赫尔辛基宣言》、国际医学科学组织委员会《人体生物医学研究国际道德指南》的伦理原则，经本伦理委员会审查，同意按所批准的临床研究方案、知情同意书、招募材料开展本项研究。请遵循 GCP 原则、遵循伦理委员会批准的方案开展临床研究，保护受试者的健康与权利。研究开始前，请申请人完成临床试验注册。研究过程中若变更主要研究者，对临床研究方案、知情同意书、招募材料等的任何修改，请申请人提交修正案审查申请。发生严重不良事件，请申请人及时提交严重不良事件报告。请按照伦理委员会规定的年度/定期跟踪审查频率，申请人在截止日期前 1 个月提交研究进展报告；申办者应当向组长单位伦理委员会提交各中心研究进展的汇总报告；当出现任何可能显著影响试验进行、或增加受试者危险的情况时，请申请人及时向伦理委员会提交书面报告。研究纳入了不符合纳入标准或符合排除标准的受试者，符合中止试验规定而未让受试者退出研究，给予错误治疗或剂量，给予方案禁止的合并用药等没有遵从方案开展研究的情况；或可能对受试者的权益/健康、以及研究的科学性造成不良影响等违背 GCP 原则的情况，请申办者/监查员/研究者提交违背方案报告。申请人暂停或提前终止临床研究，请及时提交暂停/终止研究报告。完成临床研究，请申请人提交研究完成报告。			
年度/定期跟踪审查频率	请于 2021 年 10 月 16 日前一个月提交研究进展报告		
有效期	12 个月		
联系人与联系电话	林艳媚 0591-8852		
主席/副主席签字			
伦理委员会	福建中医药大学附属康复医院伦理委员会（盖章）		
日期	2020 年 10 月 16 日		

Appendix 1B: Ethical approval from the Hong Kong Polytechnic University's Research Committee

Dear Tsang Wing Hong Hector

Please note that the following application for human ethics approval has been approved:

Project Title: An East meets West theory of depression: from "Zang Fu" (臟腑) to neuroscience
Application Number: HSEARS20190826001 (Click here to view the application)
Principal Investigator: Tsang Wing Hong Hector
Department: Department of Rehabilitation Sciences
Approver / Delegate: Yee Kay Yan Benjamin

Human Subjects Ethics Application Review System
(It is a system-generated message. Please do not reply to it)

c.c. Approver / Delegates

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Appendix 2: Research project information sheet – Fujian (Chinese)

知情同意书

尊敬的受试者

我们邀请您参加由福建中医药大学附属康复医院和香港理工大学共同批准开展的"中西医结合探讨抑郁症：从中医脏腑到神经科学"课题研究。本研究将在福建中医药大学附属康复医院开展，估计将有 90 名受试者自愿参加。本研究已经得到福建中医药大学附属康复医院及香港医管局伦理委员会的审查和批准，符合相关法律及赫尔辛基宣言。

抑郁症作为常见的精神疾病之一，严重的影响了患者的生活质量。由于抑郁症的病因病机十分复杂，目前一线治疗主要是以抗抑郁药物为主，但长期使用药物会产生大量的副作用，患者常常为此困恼不已。因此，寻找一种替代疗法十分重要。八段锦是我国传统体育运动项目之一，其动作柔和缓慢，连贯协调，架势平稳舒展，它汇集了我国古代保健体操之精华。八段锦强调重心的虚实转换与动静结合，调整呼吸，动作协调，保持平衡。前期试验证明八段锦可以缓解焦虑抑郁等精神症状且减轻疼痛。但八段锦的起效机制还善未清楚。本研究的目的是探讨抑郁症的起病机理。

本研究受试人群的纳入标准为：1. 年龄：18-65 岁；2. 性别：女性和男性；3. 汉密尔顿抑郁症评分表（$HRSD_{17}$）的基线得分为 12 或更高；4. 中医诊断：肝气郁滞；5. 蒙特利尔认知评估 （MoCA） 20 或更高；6. 自愿同意调查，并愿意签署书面知情同意书。

如果您愿意参加本项研究，您将有 50%的可能性接受以下 1 种治疗方案，研究组在常规治疗的基础上加上八段锦功法治疗 ，对照组治疗只进行常规治疗。研究时长为 10 周。我们会在您接受治疗的 5 周内定期对您进行内分泌及心率变异性的检查，并会在治疗结束后 1 周内对您进行随访。在上述治疗/检查中，内分泌和心率变异性是研究性的检查（即，如果您不参加本研究，就不需要接受该检查/治疗）。

如果您为：1. 孕妇或哺乳期；2. 有药物滥用或药物依赖；3. 急性自杀或暴力行为；4. 过去 6 个月定期进行太极，八段锦或任何各种心身运动；5. 由于行动不便，不能进行八段锦运动的将患者不属于本次研究范畴。

如果在本研究期间出现上述不良事件，应及时通知研究者，他/她将对此作出判断并给与适当的处理和记录。我们将尽全力预防由于本研究可能带来的意

外伤害。可能出现与事件及相应的预防、处理措施如下：由于紧张的缘故，可能不适的症状包括疲劳和头晕，为了尽量减少参与者的不适，参与者将被要求在评估后留在实验室内休息至少 20 分钟。

参加本项研究，您的病情有可能获得改善，本项研究还有助于确定哪种治疗方法可以更安全有效地治疗与您患有相似病情的其他病人。

为了补偿您参加本研究可能给您带来的不便，本研究将支付您参加本项研究期间所做的内分泌及心率变异性的检查费用，并免费教授功法治疗。如果您同时合并其他疾病所需的治疗和检查，以及因治疗无效而改用其他治疗的费用，将不在免费的范围之内。

您的医疗记录将保存在医院，研究者、研究主管部门、伦理委员会将被允许查阅您的医疗记录。任何有关本项研究结果的公开报告将不会披露您的个人身份。我们将在法律允许的范围内，尽一切努力保护您个人医疗资料的隐私。

参加本项研究是完全自愿的，您可以拒绝参加研究，或在研究过程中的任何时间退出本研究，这都不会影响医生对您的治疗。如果出现症状加重情况，您可能被终止参加本研究。如果我们得到影响受试者继续参加试验的信息，我们将及时通知您。

Appendix 3A: Research project information sheet – Hong Kong (English)

The Hong Kong Polytechnic University
Department of Rehabilitation Sciences

Research Project Information Sheet

Project title: An East meets West theory of depression: from "Zang Fu" to neuroscience

Investigator(s): Professor Tsang Wing Hong Hector, Cally Kwong Mei Wan Professor in Psychosocial Health, Chair Professor and Head, Department of Rehabilitation Sciences
Ms Bella Jiajia Ye, Department of Rehabilitation Sciences

Project information:

General Information about Research
This study aims to bridge the knowledge gap to understand TCM theories of depression using modern advanced measures in neuroscience. More specifically, the study will test the hypothesized pathological pathways linking Liver dysfunctions. Therefore, this research will try to understand the differences between TCM and Western Medicine by neurophysiological measures in patients with depression.

Role/Duties of Participants
A total of 90 participants would be recruited for this project. Before participating in the study, research staff will explain the study to you and obtain your written consent.

Participants of this research will be required to undergo a series of tests including blood sample for ACTH, cortisol, and NE as well as TCM diagnosis. This is to know more about their health conditions. Blood sample will be collected from 9:00-11:00am by a licensed phlebotomist.

In the 1st session, participants will receive neurophysiological, psychosocial assessments and TCM diagnosis (about 1 hour). In the 2nd session, participants will receive the same assessments 2 times (post 5 and 10 weeks, respectively) because the baseline data has been collected in the 1st session. Approximately 2 hours are needed for completing assessments in the 2nd session. The total time for participants spending on assessments in 2 sessions is around 3 hours. Comprehensive assessments will be given by a certified TCM practitioner and a well-trained research assistant who is supervised by the senior investigator, and familiar with neurophysiological and psychosocial assessments.

Possible Risks and Discomforts
To the best of the researcher's knowledge, the anticipated risk with this study is minimal. Discomforts may include fatigue and dizziness which may result from being nervous. To minimize discomforts of participants, participants will be asked to stay in the laboratory after having completed the assessment for at least 20 minutes to see if any discomforts happened.

Possible Benefits

Participants will get a full clinical evaluation regarding TCM and Western Medicine thereby knowing and understanding their health conditions. A brief health report will be given to them if needed. It will also provide an efficient treatment protocol to patients with depression.

Knowledge Update

Findings from this study will provide more evidence to support the application of TCM theory on depression. Also, it will help clinical professionals deliver more evidence-based practice using Baduanjin exercise as a TCM intervention in patients with depression.

Appendix 3B: Research project information sheet – Hong Kong (Chinese)

香港理工大學
康復治療科學系

知情同意书

科研題目：中西結合抑鬱症理論研究：從"中醫臟腑"到現代神經科學

科研人員：曾永康教授，鄺美雲社會心理健康教授，講座教授及系主任(康復治療科學系)

紫佳佳女士(康復治療科學系)

研究資料

由於中西醫有不同的理論來解釋抑鬱症的起病因素,本研究旨在通過現代神經科學先進措施接壤知識差距,用現代科學的方式瞭解抑鬱症的中醫理論。 該研究將通過中醫臟腑的"肝"來研究抑鬱症的發病機理,並探討中西醫抑鬱症發病機理的不同。

參加者的角色同義務:

此項研究將會招收共九十位參加者。在參加此項研究之前,研究人員會先向你解釋我們的研究內容及獲取你的書面同意。

本次研究的參與者將被要求接受一系列的測試(包含促腎上腺皮質激素,皮質醇,去甲腎上腺素和中醫診斷)以便更多的瞭解參與者當下的健康狀況。參與者將在早上9:00-11:00之間被抽取血樣本。抽血实验将在持有执照的抽血人员帮助下进行。

第一次基線評估，參與者將獲得約1小时做神經生理學，心理社會評估和中醫診斷。 第二次評估，由於基線資料已經在第一次評估中收集，參與者隨後將進行兩次相同的測試，分別是干預後的第5周及第10周進行測試。 第二次評估大概需要花費2小时。 兩次評估大概需要3小时完成。 全面做測試將由一名合格做中醫醫師同一名訓練有素的研究助理進行，該研究助理熟悉神經生理學和社會心理評估，並會喺高級研究人員做指導下為參與者進行測試。

潛在風險或不適:

研究的預期風險非常小。由於緊張的緣故，可能不適的症狀包括疲勞和頭暈。 為了盡量減少參與者的不適,參與者將被要求在評估後留在實驗室內休息至少 20 分鐘。

潛在得益:

參加者將獲得有關中醫同西醫兩方面的臨床評估,從而更好地了解自己的健康狀況。如需要，參加者也可獲得一份簡明的健康報告。實驗結果將為抑鬱症患者提供更多有效的治療方案。

知識更新

研究結果將提供更多的證據來支持中醫理論在抑鬱症中應用。 此外,它會幫助臨床專業人員使用八段錦鍛煉作為抑鬱症患者的中醫干預手段提供更多的循證醫學實踐。

Appendix 4A: Informed consent form – Fujian (Chinese)

知情同意书：同意签字页

临床研究课题名称：中西医结合探讨抑郁症：从中医脏腑到神经科学

申办者：福建中医药大学附属康复医院

受试者声明：我已经阅读了上述有关本研究的介绍，对参加本研究可能产生的风险和受益充分了解。我自愿参加本研究。

我同意□ 或拒绝□ 除本研究以外的其他研究利用我的医疗记录和病理检查标本。

受试者签名：_____

委托代理人签名：_____ 被委托者与受试者关系：_____

受试者（委托代理人）的联系方式：_____

日期：___ 年___ 月___ 日

研究者声明：我确认已向受试者解释了本研究的详细情况，特别是参加本研究可能产生的风险和受益。

研究者签名：_____ 日期：___ 年___ 月___ 日

研究者的工作电话：_____

福建中医药大学附属康复医院伦理委员会办公室联系电话：0591-88529125。

Appendix 4B: Informed consent form – Hong Kong (English)

The Hong Kong Polytechnic University
Department of Rehabilitation Sciences

Research Project Informed Consent Form

An East meets West theory of depression: from "Zang Fu" to neuroscience

I, _____, have been explained the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name or photograph will not appear on any publications resulted from this study.

I can contact the Principal investigator, Prof Hector Tsang at telephone 2766 6750 for any questions about this study. If I have complaints related to the investigator(s), I can contact Ms Vangie Chung, Secretary of the Departmental Research Committee, at 2766 4394.

Signature (participant): Date:

Signature (witness): Date:

Investigators:

Professor Tsang Hector
Ms Bella, Jiajia Ye

Appendix 4C: Informed consent form – Hong Kong (Chinese)

香港理工大學
康復治療科學系

研究項目同意書

中西結合抑鬱症理論研究：從“中醫臟腑”到現代神經科學

同意書:

本人，_____ ，自願同意參加這個研究。研究人員已向本人清楚解釋列在所附資料卡上的研究程序。本人明白本人可以在任何時候无理由退出研究。本人的退出將不會導致任何懲罰。本人明瞭參加這個研究的潛在風險。而且，本人知悉本人的個人資料將不會向與這個研究無關的人士披露。本人的名字或照片將不會在這個研究的任何刊物上出現。

有關這個研究的任何問題，本人可以聯絡首席調查員曾永康教授(電話：2766 6750)。如需要投訴，本人可以聯絡部門研究委員會秘書鍾靜妍女士(電話:2766 4329)。本人知悉本人將被给予已簽署的同意書副本。

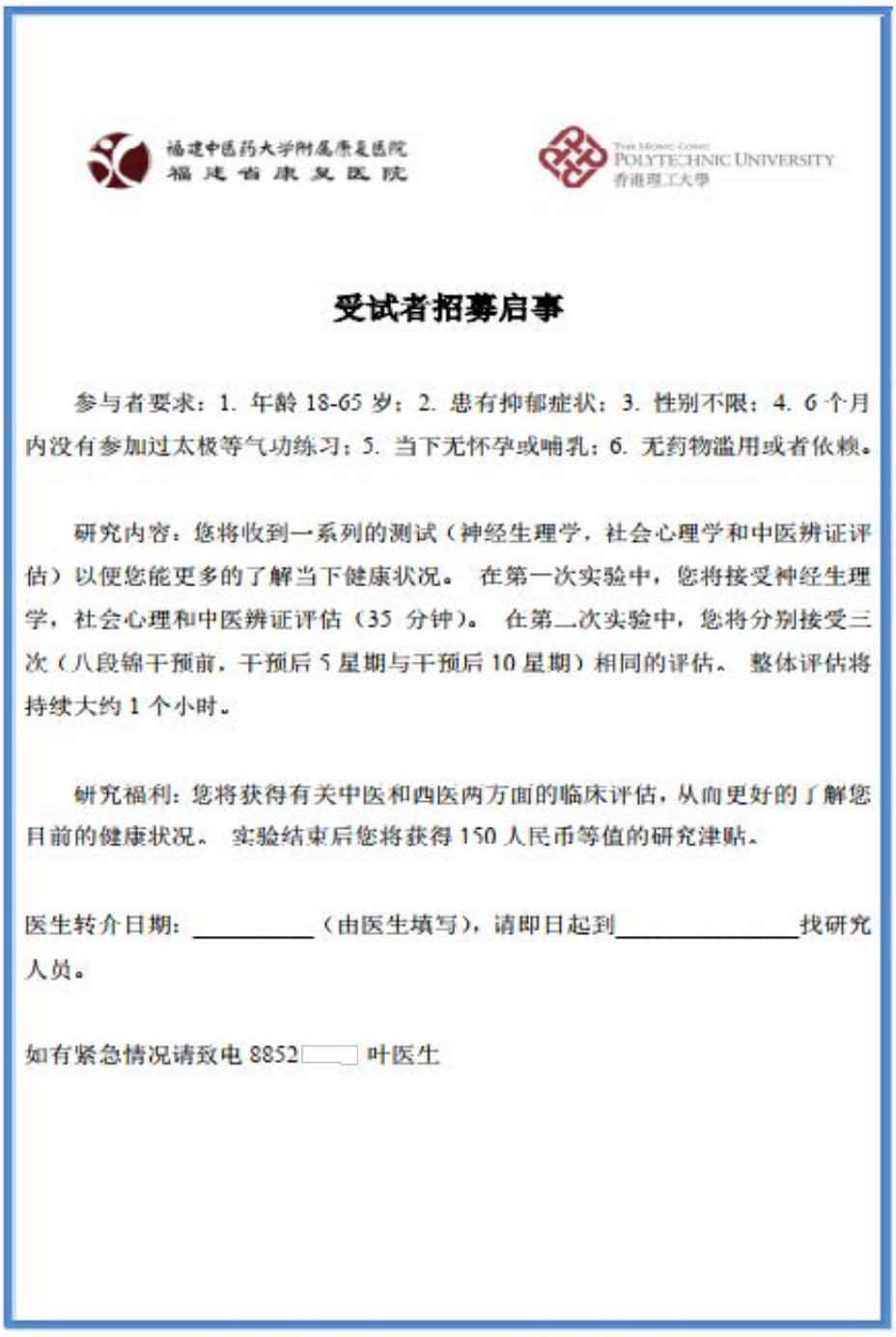
簽名(參加者)：　　日期：

簽名(證人)：　　日期：

調查員:

曾永康教授
葉佳佳女士

Appendix 5: Recruitment poster



福建中医药大学附属康复医院
福建省康复医院

The Hong Kong Polytechnic University
香港理工大學

受试者招募启事

参与者要求：1. 年龄 18-65 岁；2. 患有抑郁症状；3. 性别不限；4. 6 个月内没有参加过太极等气功练习；5. 当下无怀孕或哺乳；6. 无药物滥用或者依赖。

研究内容：您将收到一系列的测试（神经生理学，社会心理学和中医辨证评估）以便您能更多的了解当下健康状况。 在第一次实验中，您将接受神经生理学，社会心理和中医辨证评估（35 分钟）。 在第二次实验中，您将分别接受三次（八段锦干预前，干预后 5 星期与干预后 10 星期）相同的评估。 整体评估将持续大约 1 个小时。

研究福利：您将获得有关中医和西医两方面的临床评估，从而更好的了解您目前的健康状况。 实验结束后您将获得 150 人民币等值的研究津贴。

医生转介日期：_____（由医生填写），请即日起到_____找研究人员。

如有紧急情况请致电 8852 叶医生

Appendix 6: 17-Item Hamilton Rating Scale for Depression ($HRSD_{17}$)

编号:

填表日期: 年 月 日 填表人姓名: 填表人:

□ 填表说明: 本量表共 17 项, 请根据病人情况, 在最适合的项目前打✓。 1-17 项分数总计: 分

1.抑郁情绪 □ 0-无 □ 1-只有问到时才诉述 □ 2-在访谈中自发的描述 □ 3-不用言语也可以从表情, 姿势, 声音或欲哭中流露出这种情绪 □ 4-病人的自发言语和非语言表达 (表情, 动作) 几乎完全表现为这种情绪	6.早醒 □ 0-未出现 □ 1-有早醒, 比平时早醒 1 小时, 但能重新入睡 (应排除平时的习惯) □ 2-早醒后无法重新入睡
2.罪恶感 □ 0-无 □ 1-责备自己, 感觉自己已连累他人 □ 2-认为自己犯了罪, 或反复思考以往的过失和错误 □ 3-认为目前的疾病是对自己错误的惩罚, 或有罪恶妄想 □ 4-罪恶妄想伴有指责或威胁性幻想	7.工作和兴趣 □ 0-无变化 □ 1-提问时才诉说 □ 2-自发地直接或间接表达对活动、工作或学习失去兴趣, 如感到没精打彩, 犹豫不决, 不能坚持或需强迫自己去工作或劳动 □ 3-活动时间减少或成效下降, 住院病人每天参加病房劳动或娱乐不满 3 小时 □ 4-因疾病而停止工作, 住院病者不参加任何活动或者没有他人帮助便不能完成病室日常事务
3.自杀 □ 0-无 □ 1-觉得活着没有意义 □ 2-希望自己已死了或有任何自己可能会死的想法, 但没有考虑到死的方法 □ 3-消极观念 (自杀念头) □ 4-有自杀行为	8.迟缓 (思维和语言缓慢, 注意力难以集中, 主动性减退) □ 0-思维和语言正常 □ 1-精神检查中发现轻度迟缓 □ 2-精神检查中发现明显迟缓 □ 3-精神检查进行困难 □ 4-完全不能回答问题 (木僵)
4.入睡困难 □ 0-无 □ 1-主诉入睡困难, 上床半小时后仍不能入睡 (要注意平时病人的入睡时间) □ 2-主诉每晚均有入睡困难	9.激越 □ 0-未出现异常 □ 1-检查时有些心神不宁 □ 2-明显心神不宁或小动作多 □ 3-不能静坐, 检查中曾起立 □ 4-搓手, 咬手指, 头发, 咬嘴唇
5.睡眠不深 □ 0-无 □ 1-睡眠浅多恶梦 □ 2-半夜 (晚 12 点钟以前) 曾醒来 (不包括上厕所)	10.精神焦虑 □ 0-无异常 □ 1-问及时述说 □ 2-自发的表达 □ 3-表情和言谈流露出明显的忧虑 □ 4-明显惊恐

11. 躯体性焦虑 □ 0-未出现 □ 1-轻度 □ 2-中度，有肯定的上述症状 □ 3-重度，上述症状严重，影响生活或需要处理 □ 4-严重影响生活和活动 生理上的焦虑症状包括口干、腹胀、腹泻、腹绞痛、心悸、头疼、过度换气和叹息、以及尿频和出汗等	17. 自知力 □ 0-知道自己有病，表现为忧郁 □ 1-知道自己有病，但归咎伙食太差、环境问题、工作过忙、病毒感染或需要休息 □ 2-完全否认有病
12. 胃肠道症状 □ 0-未出现 □ 1-食欲减退，但不需他人鼓励便自行进食 □ 2-进食需他人催促或请求和需要应用泻药或助消化药	
13.全身症状 □ 0-未出现 □ 1-四肢，背部或颈部沉重感，背痛，头痛，肌肉酸痛，全身乏力或疲倦 □ 2-症状明显	
14.性症状：指性欲减退，月经紊乱等 □ 0-无异常 □ 1-轻度 □ 2-重度 不能肯定，或该项对被评者不合适（不计入总分）	
15. 疑病 □ 0-无 □ 1-对身体过分关注 □ 2-反复考虑健康问题 □ 3-有疑病妄想，并常因疑病而去就诊 □ 4-伴幻觉的疑病妄想	
16.体重减轻（评估 A 或者 B） A.由病史评估 □ 0-无体重减轻 □ 1-患者主诉可能有体重减轻，或一周内体重减轻超过 0.5 公斤 □ 2-肯定体重减轻，或一周内体重减轻超过 1 公斤	
B. 若每周实际测量体重，则依据实际体重变化来评估 □ 0-于一周内，体重减轻 0.5 公斤以下 □ 1-于一周内，体重减轻 0.5 到 1 公斤之间 □ 2-于一周内，体重减轻 1 公斤以上	

Appendix 7: Traditional Chinese medicine (TCM)-based liver function form

中医肝郁评分表

姓名: **性别:** **年龄:** **填表人:**

肝郁气滞

主症

情志抑郁: 0分:无
2分: 时有发生
4分: 经常发生，但尚能自控
6分: 经常发生，需服药治疗。

委屈欲哭 0分:无
2分: 时有委屈欲哭。
4分: 经常委屈哭泣，尚能控制。
6分: 委屈欲哭，不能控制。

善太息 0分: 无
2分: 偶有太息
4分: 太息时作
6分: 太息频作。

胸胁胀满 0分: 无
2分: 偶有发生，可自行缓解
4分: 每天胸胁胀满小时左右
6分: 持续胸胁胀满。

次症

健忘: 0分: 记忆正常
1 分: 时有忘事
2分: 经常忘事
3分: 经常忘事，影响工作。

失眠: 0分: 正常
1分: 睡眠易醒，或睡而不实。晨醒过早，不影响工作。
2分: 每日睡眠小于小时，难以坚持正常工作

3分：彻夜不眠，难以坚持正常工作。

急躁易怒： 0分：无
1分：情绪急躁
2分：易烦躁发怒

3分：烦躁易怒难以自我控制。

暖气：0分：无
1分：每日3次以下
2分：每日4-9次

3分：每日10次以上。

呃逆： 0分：无
1分：每日3次以下
2分：每日4-9次
3分：每日10次以上

坐卧不安： 0分：无； 2分：坐卧不安。

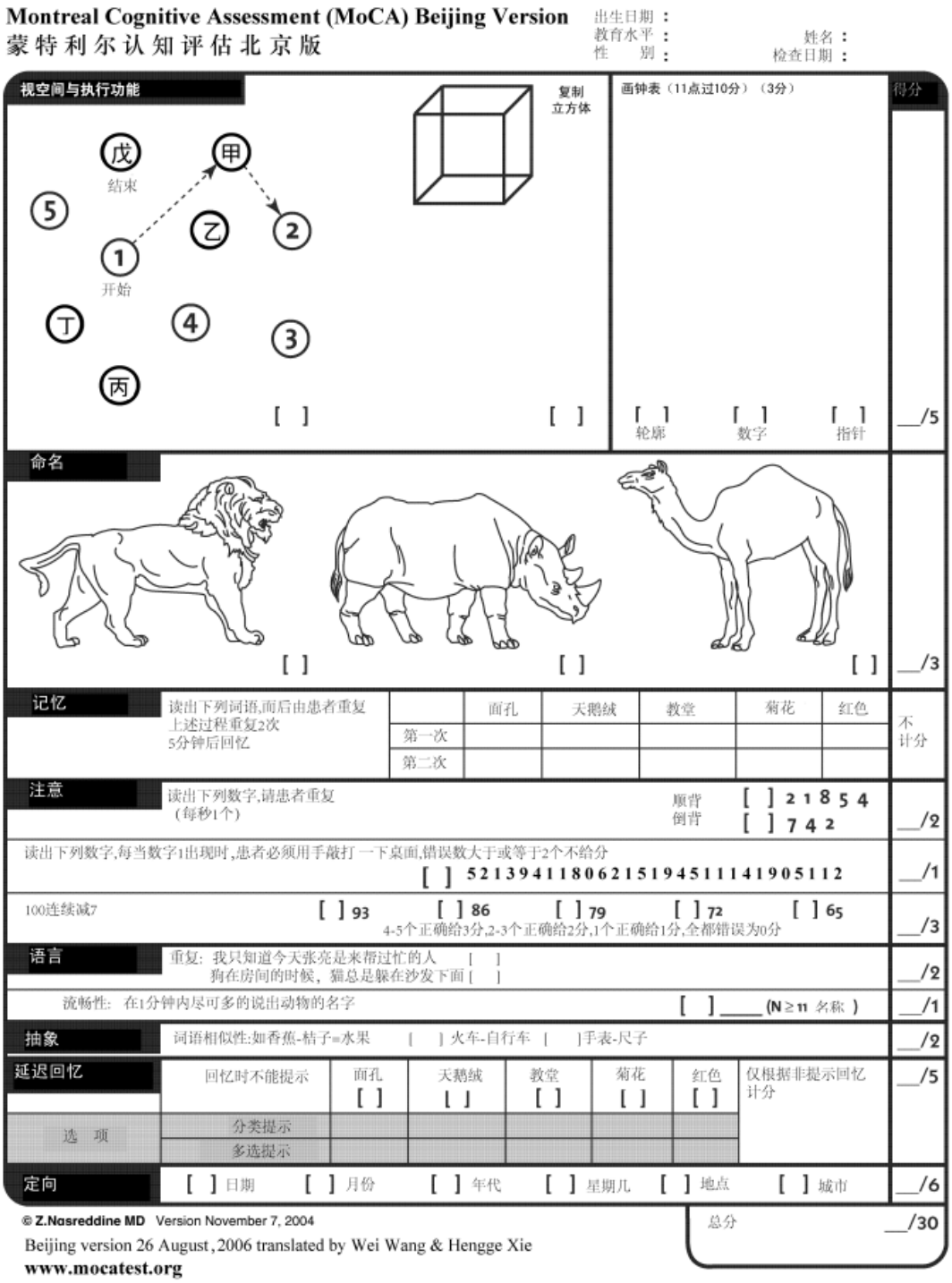
咽部异物感：0分： 无； 2分：有异物感。

身痛： 0分：无； 2分：身痛。

脘闷： 0分：无
1分：偶有发生，可自行缓解
2分：每天脘闷2小时左右
3分：持续不解

总得分：

Appendix 8: Montreal Cognitive Assessment (MoCA) scale



Montreal Cognitive Assessment (MoCA) Beijing Version
蒙特利尔认知评估北京版

出生日期：
教育水平：
性　　别：
姓名：
检查日期：

视空间与执行功能

复制立方体

戊 结束　甲　乙　丙　丁　1 开始　2　3　4　5

[ ]　[ ]

画钟表（11点过10分）（3分）

[ ] 轮廓　[ ] 数字　[ ] 指针

得分 __/5

命名

[ ]　[ ]　[ ]

__/3

记忆

读出下列词语,而后由患者重复
上述过程重复2次
5分钟后回忆

	面孔	天鹅绒	教堂	菊花	红色
第一次					
第二次					

不计分

注意

读出下列数字,请患者重复（每秒1个）

顺背 [ ] 2 1 8 5 4
倒背 [ ] 7 4 2

__/2

读出下列数字,每当数字1出现时,患者必须用手敲打一下桌面,错误数大于或等于2个不给分

[ ] 5 2 1 3 9 4 1 1 8 0 6 2 1 5 1 9 4 5 1 1 1 4 1 9 0 5 1 1 2

__/1

100连续减7

[ ] 93　[ ] 86　[ ] 79　[ ] 72　[ ] 65

4-5个正确给3分,2-3个正确给2分,1个正确给1分,全都错误为0分

__/3

语言

重复：我只知道今天张亮是来帮过忙的人　[ ]
狗在房间的时候，猫总是躲在沙发下面 [ ]

__/2

流畅性：在1分钟内尽可多的说出动物的名字

[ ]____ (N ≥ 11 名称)

__/1

抽象

词语相似性:如香蕉-桔子=水果　[ ] 火车-自行车　[ ]手表-尺子

__/2

延迟回忆

	回忆时不能提示	面孔	天鹅绒	教堂	菊花	红色
		[ ]	[ ]	[ ]	[ ]	[ ]
选项	分类提示					
	多选提示					

仅根据非提示回忆计分

__/5

定向

[ ] 日期　[ ] 月份　[ ] 年代　[ ] 星期几　[ ] 地点　[ ] 城市

__/6

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Beijing version 26 August, 2006 translated by Wei Wang & Hengge Xie
www.mocatest.org

总分 __/30

Appendix 9: MoCA permission

MoCA Test inc.

Copyright Permission To Use The Montreal Cognitive Assessment (MoCA ©)

You are welcome to use MoCA© for non-commercial purposes as you described below with no further permission requirements.

All modifications in any of the details below must be reported to info@mocatest.org, including the addition of a commercial sponsor.

No changes or adaptations to the MoCA© Test and instructions are permitted.

It is mandatory to follow the online MoCA© Training and Certification Program to administer and score MoCA© for clinical, research, and educational use. Training and certification are free for academic researchers involved in an ongoing academic study.

Study Title*:	An East meets West theory of depression: from "Zang Fu" to neuroscience
Study Objectives*:	(1) To construct an East meets West model of depression regarding liver function based on TCM and neurophysiological biomarkers; (2) To test and validate the hypothesized pathological pathways linking liver dysfunctions and depression; (3) To verify the above East Meets West model regarding liver function with the application of Baduanjin as an intervention.
Source of Funding*:	PhD study
Entities Involved Design of the Protocol*:	RCT and cross-sectional study
Name of Principal Investigator*:	Hector Tsang
Institution*:	Department of Rehabilitation Sciences, The Hong Kong Polytechnic University
Country*:	China
Email*:	ye.j.ye@

By signing below, I hereby acknowledge that I have an affirmative duty to report all changes in the above permission request details.

Institution:	The Hong Kong Polytechnic University	**Signature:**	
Name:	Jiajia Ye	**City:**	Hong Kong
Title:	PhD candidate	**Date:**	Mar 11, 2023

Appendix 10. Performance record and adverse event form

参与情况及反馈

填表人姓名：　　表格发放日期：　　表格回收日期：

请练习完在相应空格内打 v，如练习后有不适的症状出现，请在对应空格内写下具体症状及程度。

<table>
<tr><td colspan="6">是否参与八段锦练习
练习后是否有不舒服（例如:头疼，肌肉酸疼，头晕，想吐等症状）</td></tr>
<tr><td>第三周</td><td>是否有不适(轻，中，重)</td><td>第四周</td><td>是否有不适(轻，中，重)</td><td>第五周</td><td>是否有不适(轻，中，重)</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>第六周</td><td>是否有不适(轻，中，重)</td><td>第七周</td><td>是否有不适(轻，中，重)</td><td>第八周</td><td>是否有不适(轻，中，重)</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>第九周</td><td>是否有不适(轻，中，重)</td><td>第十周</td><td>是否有不适(轻，中，重)</td><td colspan="2" rowspan="2">意见和建议</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>

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