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Acupuncture and the Brain

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Changzhen Gong and Wei Liu

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PREFACE

Over the last hundred years, advances in scientific technology have produced marvelous 3-dimensional maps of brain anatomy and function, provided insights into brain chemistry and the role of neurotransmitters, and traced complex feedback loops between the brain and every area of the body. Yet even these truly remarkable discoveries have only begun to reveal the mysteries of the brain, which remains the most complex and intricate organ known to man.

Within this context, acupuncture and Chinese medicine offer a unique perspective on comprehending the brain's workings. It can be said that traditional Chinese medicine "maps" of the external and internal meridian system represent a vehicle for understanding the workings of the human body that is as sophisticated as a modern anatomy chart. It is now widely appreciated that, at a functional level, acupuncture is a highly effective modality in the treatment of neurological disorders. We have visualized this recognition as a "journey" that acupuncture has taken from its ancient roots to the laboratories and research centers of current neurology research.

Applications of Acupuncture to Neurological Conditions: Acupuncture and the Brain synthesizes groundbreaking work being done in neurobiology, illustrating acupuncture's remarkable journey. It provides a comprehensive overview of the classical foundations and modern advancements of acupuncture in the field of neuroscience. Functional magnetic resonance imaging (fMRI), along with other neuroimaging technologies like EEG, MEG, SPECT, fNIRS, and PET have enabled researchers to directly trace the effects of acupuncture needling on the brain and revolutionized our understanding of how acupuncture impacts the brain and nervous system. We have been fascinated by these fMRI studies over the last two decades, leading us to collect all the published studies we could find for inclusion in this book.

Applications of Acupuncture to Neurological Conditions: Acupuncture and the Brain not only highlights acupuncture's historical significance but also showcases its ability to evolve and align with the dynamic and ever-expanding knowledge of neuroscience. It is my hope that this book will serve as a testament to acupuncture's enduring relevance and its potential to offer unique therapeutic insights and treatments for brain-related ailments in a way that bridges the gap between ancient wisdom and modern scientific understanding.

Over the years, we have experienced several synchronous events which spurred and solidified my interest in this subject. In January 1999, the first cohort of students enrolled in the school we founded – the American Academy of Acupuncture and Oriental Medicine. At the end of 1998, *Lancet* published a commentary on acupuncture called "The West Gets the Point" by Dora T. Hsu and David L. Diehl. This commentary discusses the historical roots of acupuncture dating back 3000 years and the increasing acceptance of acupuncture in Western medicine due to physiological and neurobiological research. It highlights the importance of proper research methodology and the most recent acupuncture study with fMRI, especially in blinded prospective studies, when evaluating acupuncture's effectiveness. The essay cites the Consensus Development Conference held by the US National Institutes of Health in 1997, where experts concluded that acupuncture was effective treatment for several medical conditions including postoperative and chemotherapy-associated nausea and vomiting, and notes that 1998 also saw research using single–photon–emission computerized tomography and fMRI technology to examine the effect of body acupuncture on brain physiology. The piece also mentions recent research grants awarded for acupuncture studies and the existence of professional acupuncture societies for physicians. The *Lancet* article concluded by stating that the future of acupuncture lay in increased funding for clinical research, translating Chinese research, and expanding its inclusion in health insurance plans. For the next twenty years, we made sure to distribute this short essay to our students.

In 2007 our son, Dan Gong, was pursuing a bachelor's degree in neurobiology at Harvard and was interested in some research experience. Friends introduced him to Shan Baoci, a principal researcher at the Key Laboratory of Nuclear Analysis Techniques, Institute of High Energy Physics, Chinese Academy of Sciences in Beijing. Dan was able to spend part of his summer break at the Beijing lab for fMRI research as Dr. Shan's research team investigated the specificity of acupuncture points on different meridians. The study focused on stimulating four acupuncture points on two different meridians and examined their characteristic responses in the human brain. The acupoints Taichong (LR3) and Zhongdu (LR6) on the Liver meridian and Zusanli (ST36) and Xiangu (ST43) on the Stomach meridian were studied, along with two nearby sham acupuncture points. Their results revealed that real acupoints consistently activated specific areas of the brain, such as the bilateral primary somatosensory area and the ipsilateral cerebellum. The study suggests that different acupoints on the same meridian may activate similar brain areas, and that commonly-used clinical acupuncture points might influence a broader range of cortical areas compared to less commonly-used ones. Their research was published in the July 2008 issue of the *Journal of Alternative and Complementary Medicine*. Dr. Gong was fortunate enough to visit their lab several times and witness their moments of excitement when their research produced tangible evidence.

Applications of Acupuncture to Neurological Conditions: Acupuncture and the Brain is a testament to the convergence of millennia-old wisdom and the innovations of contemporary science. It offers a comprehensive understanding of how acupuncture impacts the brain and the broader implications for healthcare. As we embark on this journey, we are bound to gain a deeper appreciation for the profound and intricate relationship between acupuncture and the brain, with far-reaching implications for both traditional medicine and the modern medical landscape.

CHAPTER ONE

ACUPUNCTURE AND THE BRAIN

All medical systems employ two basic ways of looking at the body: the structure or morphology of the body, and the function or physiology of the body. Any systematic way of looking at the structure or function of a living organism can be called a "map" of that organism. Beginning 3,000 years ago, Chinese medicine practitioners found a way to explain how the body works by mapping an interconnected network of channels, or meridians, which carry vital energy throughout the structure of the body. Meridian pathways flow along the surface of the body, and also connect all the internal organs to each other and to the surface meridians. The ancient Chinese mapmakers of the human body also noted specific places on the superficial meridians where the body's energy could be accessed for therapeutic results: the acupuncture points.

There are approximately 365 classical acupuncture points along the meridian system, and each acupuncture point is given an individual name, such as Tianzhu ("celestial pillar") or Shenmen ("spirit's gate"). These names often sound poetic to western ears, but they are essentially practical: they denote either the location or the therapeutic function of the point. In this way, Chinese scholars and practitioners plotted a memorable landscape of the body which creates associative patterns in the acupuncturist's mind and provides a subtle and dynamic context for achieving therapeutic results.

In the West, physicians began by diagramming various components of the body: the bones of the skeleton, the internal organs, the circulatory system, etc. As medical science progressed, attention focused on the mechanisms of physiology, such as hormones, neurotransmitters, the immune system, and genetics. Understanding the human brain and how it works has been a goal of scientists and medical researchers for several hundred years, but it has only been in the last few decades that significant breakthroughs in unraveling the mystery of the brain have been made. Electrodes placed on brain tissues gave early researchers clues as to the function of various brain structures. Analysis of chemicals such as dopamine and serotonin provided evidence of the function of neurotransmitters. Computerized axial tomography (CAT) scans showed the anatomical structures of the brain in detail. Most recently, functional magnetic resonance imaging (fMRI) technology has made it possible to view the brain in action. Functional magnetic resonance imaging relies on the paramagnetic properties of oxygenated and deoxygenated hemoglobin to see images of changing blood flow in the brain associated with neural activity. This allows images to be generated that reflect which brain structures are activated by different types of stimulation.

Applications of Acupuncture to Neurological Conditions: Acupuncture and the Brain presents an intriguing fusion of classical acupuncture with cutting-edge advancements in medical technology, particularly functional magnetic resonance imaging (fMRI). This work emphasizes the clinical application of two key acupuncture methodologies – classical acupuncture and scalp acupuncture – in the treatment of various brain disorders. Additionally, it explores how fMRI, a revolutionary tool in neuroimaging, is being employed to deepen our understanding of acupuncture's effects on the brain.

Classical acupuncture has been widely used for centuries to treat a plethora of health issues, including neurological and psychiatric conditions. Scalp acupuncture, a more recent development, specifically targets areas on the scalp to influence brain function directly. These techniques have shown promise in the management of a range of brain disorders, offering a unique approach to neurological rehabilitation.

In this context, fMRI serves as a bridge between these traditional practices and modern neuroscience. By providing detailed images of brain activity before and after acupuncture treatments, fMRI allows researchers and practitioners to visualize and understand the neural changes and mechanisms underlying acupuncture's therapeutic effects. This integration of traditional acupuncture methods with advanced neuroimaging technology not only validates ancient practices but also opens new avenues for treating complex brain disorders. Throughout the book, we explore the synergistic relationship between these acupuncture techniques and fMRI, highlighting their potential in advancing the treatment and understanding of brain-related conditions.

Acupuncture research, like acupuncture practice, provides us with a treasure trove of information and useful results. The millennia-old meridian and acupoint maps of the body are being decoded by cutting-edge technology. As scientists continue to explore the many landscapes of the human body, acupuncture practitioners may someday witness the seamless convergence of an ancient healing art into modern medicine.

Since the 1990's, scientists have been using fMRI technology to observe the brain's response to acupuncture stimulation. This line of research has connected the structural/functional landscape of acupuncture points with the structural/functional landscape of the brain. Visible links have been established between acupoints with specific therapeutic functions and areas of the brain which correspond to these functions. A study done by Li, *et al.*[1], found a connection between analgesic acupuncture points and pain-related brain structures. Stimulation of acupoints Hegu (LI4) and Shousanli (LI10) on the arm, and acupoints Xuanzhong (GB39) and Yanglingquan (GB34) on the leg, which are often used to relieve painful musculo-skeletal conditions, showed activation over the right and left premotor areas of the brain. This study supported the existence of sensorimotor-implicated acupoints which, when stimulated, activate sensory and motor cortices of the brain. Siedentopf, *et al.*[2], found that applying laser acupuncture to Zhiyin (BL67), which is used for ophthalmic disorders, activates the cuneus and medial occipital gyrus areas of the brain, which are related to visual function.

fMRI technology opens lines of research not only into the effect of stimulating specific acupoints, but also the effect that various needling techniques can produce in the brain. Acupuncture needling techniques such as needle rotation, deep vs. shallow needling, and duration of acupuncture are being investigated, as well as the effect of electrical acupuncture *vs*. manual acupuncture. A study by Napadow, *et al.*[3], compared stimulation of Zusanli (ST36) with manual acupuncture, low-frequency electroacupuncture, and high-frequency electroacupuncture. Both manual acupuncture and electroacupuncture at Zusanli (ST36) activated the anterior insula and deactivated limbic and paralimbic brain structures including the amygdala and hippocampus. However, only electroacupuncture activated the anterior middle cingulated cortex, and only low-frequency electroacupuncture activated the pontine raphe area.

Another intriguing aspect of fMRI research is the discovery of functional network connectivity in the brain, and the fact that stimulation of acupoints can activate this connectivity. Functional connectivity describes the interdependence of regions of the brain which are functionally related and connected. The research team of Fang, *et al.*[4], investigated the effect of using combinations of acupoints on brain function. They found that using the classic point combination of Hegu (LI4), Zusanli (ST36), Taichong (LR3), Xingjian (LR2), and Neiting (ST44) resulted in modulation of the brain's limbic-paralimbic-neocortical network. The research team of Hui, *et al.*[5], discovered that needling Zusanli (ST36) modulated neural activity at multiple levels of the cerebro-cerebellar and limbic system.

The primary purpose of acupuncture is to treat health conditions and disease. Therefore, a major avenue of fMRI research involves studying brain response to acupuncture which is being applied to address specific health problems. For example, a study by Napadow, *et al.*[6], established functional connectivity between the hypothalamus and the amygdala in response to stimulation of Hegu (LI4) for carpal tunnel syndrome. Ongoing fMRI research into the effect of acupuncture stimulation on health conditions and pathologies includes studies on spastic cerebral palsy, Alzheimer's disease, visual impairment, cervical spinal cord injury, stroke, vascular dementia, addictions, repetitive strain injury, musculoskeletal disease, and on and on.

Following this introductory chapter, *Applications of Acupuncture to Neurological Conditions: Acupuncture and the Brain* presents nine carefully-researched chapters, each of which examines a specific facet of acupuncture's interaction with brain health and function. Chapters Two through Ten systematically explore the convergence of ancient acupuncture techniques with contemporary neuroscientific insights, with an emphasis on the insights gained through the use of functional magnetic resonance imaging (fMRI). The chapters are arranged to offer a progressive understanding, starting from the fundamental principles of acupuncture applied to brain disorders and advancing towards more complex applications and the latest research findings.

Chapter Two delves into the intricate neural interplay initiated by acupuncture, exploring how the activation of specific sensory neurons and various brain regions contributes to acupuncture's pain-relieving and health-promoting effects. Acupuncture has been esteemed for centuries for its ability to mitigate pain and enhance overall well-being. Despite its ancient origins, the understanding of how acupuncture achieves these effects is still evolving. Scientific investigations have begun to unravel the complex neural pathways involved in acupuncture's therapeutic action. These studies reveal that acupuncture's influence goes far beyond simple local stimulation, affecting deep structures within the central nervous system. By examining the journey of acupuncture signals from the point of needle insertion to their ultimate impact on the brain, this chapter aims to shed light on the sophisticated mechanisms underlying acupuncture's remarkable therapeutic potential. The contents of this chapter have become the foundation of any science-based writings about acupuncture, even though the cited studies focus primarily on pain management.

Chapter Three explores the multifaceted aspects of scalp acupuncture, including its origins, development, and the diverse styles which evolved over time. Scalp acupuncture, a relatively modern addition to the traditional acupuncture repertoire, emerged in the 1970s, representing a fusion of ancient Chinese medical theory with contemporary neuroanatomy and neurophysiology. It has been extensively applied to brain disorders. Various eminent practitioners have contributed to this evolution, creating styles like Jiao's, Fang's, and Zhu's, each with its unique focus, needling techniques, and therapeutic applications. The practice of scalp acupuncture is rooted in the traditional Chinese belief that the scalp mirrors the entire body, with specific areas corresponding to different organs and functions. This has led to its evolution from traditional practice, integrating classical acupuncture principles with modern insights into the nervous system and brain function. The therapeutic efficacy of scalp acupuncture, supported by clinical studies, spans a wide range of conditions from chronic pain and neurological disorders to mental health issues, highlighting its increasing recognition and relevance in modern healthcare. The development of the International Standardized Scalp Acupuncture system marks a significant milestone in global recognition and standardization, providing a consistent framework for practitioners worldwide and enhancing the integration of this practice with other medical approaches.

Chapter Four "Acupuncture for Brain Disorders I" examines the role of acupuncture in treating a variety of psychiatric disorders, such as major depression, schizophrenia, bipolar disorder, obsessive-compulsive disorder, and others. These conditions, affecting people across all demographics, diminish an individual's ability to cope with daily life. Acupuncture, rooted in traditional Chinese medicine, is gaining acceptance as a safe and effective treatment option. This approach is said to harmonize the body's energies and regulate various hormonal and neurochemical balances, showing particular promise when combined with psychotherapy and herbal treatments. Clinical studies from around the world support acupuncture's positive effects on psychiatric conditions, particularly in managing symptoms like insomnia, depression, and anxiety. This chapter provides an in-depth Chinese medicine perspective on these disorders, supported by recent clinical studies, and highlights the need for more well-designed research in this field.

Chapter Five "Acupuncture for Brain Disorders II" is a continuation of Chapter Four and sets the stage for a comprehensive examination of how acupuncture is applied in the treatment of various complex neurological conditions. This chapter covers autism spectrum disorder (ASD), stroke, Parkinson's disease, Alzheimer's disease, and epilepsy. A common thread across these conditions is the intricate interplay between the brain and neurological function. Each section explores the unique challenges presented by these disorders, the nuances of applying acupuncture in each specific disorder, and the emerging recognition of acupuncture as a therapeutic modality with the potential to mitigate symptoms. Acupuncture is presented as a multifaceted approach to brain disorders and considered in both its historical context and current clinical applications.

In Chapter Six, we consider the fascinating intersection of acupuncture and advanced neuroimaging technologies like EEG, MEG, SPECT, fNIRS, and PET. These tools have revolutionized our understanding of how acupuncture impacts the brain and nervous system, providing insights into its potential therapeutic mechanisms. The chapter delves into how different neuroimaging techniques, each with its unique strengths, contribute to a multi-dimensional understanding of acupuncture's effects. Technologies like EEG and MEG offer real-time insights into brain activity, revealing the intricate dance of neural rhythms in response to acupuncture. SPECT and PET scans go a step further, illustrating changes in cerebral blood flow and metabolic activity, which are key indicators of acupuncture's influence on brain function. These imaging methods have shed light on acupuncture's role in treating a spectrum of neurological and psychiatric conditions, from epilepsy to stroke rehabilitation. By understanding the neural correlates of acupuncture, we gain a clearer picture of its potential in enhancing brain health and function. This chapter not only highlights the intersection of traditional Chinese medicine and modern neuroimaging but also indicates the direction of future research and clinical applications of acupuncture in the realm of neurology.

Chapter Seven deals with functional magnetic resonance imaging (fMRI) and its application to acupuncture research. fMRI, a revolutionary tool, provides a window into the brain's activity by tracking changes in blood flow, offering insights into how acupuncture stimulates specific cerebral regions and influences overall neural function. The chapter details a spectrum of fMRI studies which have been conducted to understand acupuncture's influence on brain structures and functions. It highlights the diverse ways acupuncture affects the brain, from altering blood flow and neuronal signaling to influencing functional connectivity and pathological changes during stimulation. These studies not only corroborate the holistic effects of acupuncture but also reveal its point-specific impacts on the brain, contributing to a better understanding of how this traditional practice induces profound physiological and mental changes. Through detailed examination of various research findings, the chapter illuminates the correspondence between specific acupuncture points and activated or deactivated brain structures, enhancing our understanding of acupuncture's mechanisms. This exploration provides invaluable insights into the synergy between brain and body changes induced by acupuncture, making a compelling case for its integration into modern medical practices. As the knowledge base expands, the potential applications and benefits of acupuncture continue to grow, opening new horizons in both clinical practice and research.

Chapter Eight presents a focused examination of how various acupuncture needling techniques influence brain activity, as revealed through functional magnetic resonance imaging (fMRI). It delves into the impact of different methods such as reinforcing, rotating, and electrostimulation, highlighting their distinct effects on the brain. Key topics include comparisons between low and high-frequency electrostimulation, the nuances of acupressure *versus* acupuncture, and the implications of needle depth and duration. Additionally, the chapter provides insight into the phenomenon of 'deqi', a unique acupuncture sensation, exploring its neural correlates and significance in treatment efficacy. This chapter underscores the importance of needling techniques in acupuncture's clinical effectiveness, offering valuable insights for its integration into modern medical practices.

Chapter Nine investigates how functional connectivity in the brain is facilitated by acupuncture, as revealed through functional magnetic resonance imaging (fMRI). This chapter investigates the complex interactions between various brain regions during acupuncture treatments, focusing on how acupuncture affects functional networks within the brain. It examines key aspects [of connectivity] such as the endogenous analgesia functional network, limbic and paralimbic system responses, and the modulation of sensorimotor brain networks. The chapter also discusses the specific neural pathways involved in acupuncture's pain relief mechanisms and explores the differences between the effects of actual acupuncture and sham-acupuncture procedures. Advanced imaging techniques shed light on the nuanced ways acupuncture influences brain activity and connectivity, contributing to our understanding of its therapeutic effects.

Chapter Ten explores acupuncture's effects on various pathological states using functional magnetic resonance imaging (fMRI). The cutting-edge research described in this chapter examines how acupuncture influences brain functionality in conditions ranging from stroke and Alzheimer's disease to carpal tunnel syndrome, depression, and more. fMRI studies reveal how acupuncture potentially aids motor function recovery in stroke patients, enhances cognitive abilities in aphasic individuals post-stroke, and impacts brain functioning in Alzheimer's disease. Significant alterations in brain activation patterns and connectivity documented by fMRI offer new insights into the ways acupuncture might modify pathological states and shed light on the complex mechanisms behind acupuncture's therapeutic potential in treating a wide array of challenging health conditions.

In conclusion, Chapter Eleven presents an intriguing list of possibilities for the application of acupuncture brain mapping and offers readers an inspiring vision of the ways in which acupuncture and modern neuroscience can join forces as collaborative partners: "The integration of acupuncture and neuroscience can foster closer collaboration between acupuncturists, neuroscientists, and healthcare professionals. Such collaboration can lead to innovative research projects, holistic patient care, and a broader perspective on health and healing."

CHAPTER TWO

NEURAL PATHWAYS TO THE BRAIN

Acupuncture has long been revered for its remarkable ability to alleviate pain and promote well-being. While the precise mechanisms underlying its therapeutic effects remain elusive, a growing body of scientific evidence suggests that acupuncture's impact extends far beyond local stimulation, reaching the depths of the central nervous system (CNS). This intricate neural circuitry, spanning from the peripheral points of acupuncture needles to the pinnacle of the brain, orchestrates a symphony of physiological changes that contribute to acupuncture's therapeutic benefits.

At the heart of this neural pathway lies the activation of specialized sensory neurons, known as nociceptors. These sentinels of our body, primarily responsible for detecting pain, are also exquisitely sensitive to acupuncture's mechanical stimulation. Upon needle insertion, nociceptors fire a barrage of electrical signals, relaying information about the needling site along ascending neural pathways that culminate in the brain.

As this neural cascade ascends, it encounters a network of interconnected brain regions, each playing a distinct role in processing and modulating the incoming sensory information. The thalamus, a gateway to higher brain centers, acts as a relay station, integrating signals from various sensory modalities, including pain. The periaqueductal gray (PAG), a pivotal hub in the brain's pain-modulating circuitry, receives input from the thalamus and orchestrates the release of endogenous opioids, the body's natural painkillers. These potent analgesics, released in response to acupuncture stimulation, dampen the transmission of pain signals, providing relief from discomfort and inflammation.

The neural journey of acupuncture extends beyond pain modulation, influencing a myriad of physiological processes that contribute to overall well-being. The limbic system, the seat of emotions and memories, is also engaged by acupuncture, potentially explaining its ability to alleviate anxiety, depression, and stress. The hypothalamus, a master regulator of the autonomic nervous system, receives signals from the limbic system and other brain regions, influencing heart rate, blood pressure, and other physiological parameters. This modulation of the autonomic nervous system contributes to acupuncture's ability to promote relaxation, reduce stress hormones, and enhance immune function.

The neural pathways of acupuncture extend beyond the confines of the CNS, influencing peripheral biological processes. Acupuncture has been shown to modulate the release of neurotransmitters, such as serotonin and dopamine, which play a role in mood regulation and pain perception. Additionally, acupuncture can stimulate the release of endorphins, enkephalins, and other endogenous opioids, not only in the brain but also in peripheral tissues, further enhancing pain relief and promoting healing.

While the intricate neural circuitry underlying acupuncture's therapeutic effects is still being unraveled, the accumulated evidence provides a compelling narrative of a complex interplay between peripheral stimulation, neural pathways, and central brain modulation. Acupuncture's ability to influence a wide range of physiological processes, from pain relief to emotional well-being, can be attributed to its engagement of diverse neural networks, each contributing to a symphony of healing.

When acupuncture acts on the body, the most rapid and direct reaction is the impact on the nervous system, which is manifested as the release and transmission of nerve signals. Acupuncture analgesia is the most popular field of acupuncture research. Current studies have shown that acupuncture signals inhibit pain signals at multiple levels and links of the nervous system. Peripheral acupuncture signals are transmitted to the center through the receptors in the depth of acupoints and the excitation of nerve endings. After entering the spinal cord, the afferent impulse caused by acupuncture mainly crosses the ventral lateral tract of the contralateral spinal cord. At the spinal cord level, acupuncture signals travel along the afferent nerve into the spinal cord, interacting with the nociceptive signals coming from the site of pain. This inhibition mainly follows the dorsal lateral spinal tract down to the dorsal horn of the spinal cord. At the brain stem level, acupuncture signals enter the giant cell nucleus of the medullary reticular structure along the ventral lateral cord, causing changes in unit discharge of the nucleus mass. The response caused by the nociceptive stimulus can also reach the giant cell nucleus and interact with each other, resulting in the inhibition of the nociceptive stimulus. At the thalamic level, acupuncture signals can inhibit the special form of discharge response caused by nociceptive stimuli in the medial thalamic nucleus, especially in the parafascicular nucleus and the central lateral nucleus. Other relevant pain modulation structures, such as the head of caudate nucleus, central thalamic nucleus, central gray matter of midbrain, raphe nucleus, and limbic system including hippocampus, cingulate gyrus, septum, amygdala, and hypothalamus, can also modulate nociceptive responses. At the cerebral cortex level, its downward modulation effect on acupuncture analgesia is mainly manifested in two aspects. The one is the regulation of nociceptive stimuli. The second is the downward adjustment of acupuncture analgesic effect. Although the research on the mechanism of acupuncture analgesia needs to be further deepened, the conclusive evidence established so far is sufficient to show that the mechanism of acupuncture analgesia is related to the regulation and participation of the anti-pain system in the central nervous system.

Through the use of acupuncture techniques to reduce or relieve pain, acupuncture analgesia is the result of the interaction of two different afferent sensory transmission. Acupuncture analgesia can be regarded as such an interaction, the result of the interaction and integration of different sensory afferents in the central nervous system. In other words, pain relief effect is caused by the interaction of nerve impulses from the pain source and nerve impulses from the acupoints within the central nervous system [1]. Pain is considered a “nociceptive stimulus”. There are nociceptive receptors all over the body in the skin and some deep tissues. When the body is stimulated by pain, information from these receptors passes through a complex and orderly pathway to the higher center, resulting in pain perception. The acupuncture process can stimulate many receptors in the body to form acupuncture signals. Similar to the pain information, acupuncture signals can also be transmitted step by step through nerve pathways and form a certain analgesic effect. At all levels of the central nervous system from low to high, acupuncture signals may play a role in inhibiting the transmission of injury information, thus playing a role in analgesia [2]. In this chapter, the neural pathways of acupuncture analgesia are comprehensively analyzed and reviewed, based on the integration of the most recent research.

1. Peripheral Afferent Pathway of Acupuncture Signal

Acupuncture signals are transmitted to the center through the receptors in the depth of acupuncture points and the excitement of nerve endings. Studies have shown that the types of nerve fibers excited by acupuncture, including afferent fibers, are divided into four categories. The class I (Aα) is the afferent fiber of muscle spindle and tendon organs. The class II (Aβ) is the afferent fiber of the skin's mechanoreceptor. The class III (Aδ) is the afferent fiber of skin pain, temperature sensation and deep pressure sensation of muscle. The class IV (C) is the afferent fiber without myeloid pain, temperature and pressure perception. It is generally believed that the acupuncture intensity that patients can accept is mainly Aβ (II) and Aδ (III) fiber excitation. Therefore, acupuncture is the use of weak stimulation to achieve the purpose of analgesia. However, some studies have also shown that the introduction of class C fibers plays an important role in acupuncture analgesia. Animal experiments showed that the analgesic range caused by low-intensity electroacupuncture (non-injurious stimulation) was small, while the analgesic range caused by high-intensity electroacupuncture (injurious stimulation) was large. If acupuncture stimulation achieves the intensity of exciting class C fibers, it may inhibit the introduction of another injurious stimulus in the way of one injurious stimulus, so as to achieve the purpose of analgesia. After needle is inserted into the acupoint in acupuncture, pressure, friction and tension can be generated between the needle body and the surrounding tissues through lifting and thrusting, and twisting methods and other needle manipulations. Therefore, the physical signals of mechanics form [3]. The skin, subcutaneous tissue and muscle at acupoints contain a wealth of receptors, including mechanoreceptors for mechanical stimulation, such as muscle spindle, tactile corpuscles, ring corpuscles and so on. The physical stimulation of acupuncture can directly activate these mechanosensitive receptors and cause nerve excitation. Weimin Li *et al.* [4] recorded nerve electrical signals induced by acupuncture in the branches of sciatic nerve and dorsal root nerve of spinal cord in rats by means of lifting and thrusting, and twisting needle manipulations. Peng, *et al.* [5] found that acupuncture at Hegu (LI4) and Neiguan (PC6) could produce better analgesic effect in the neck region, and the electrophysiological changes caused by it were manifested as increased excitability. Therefore, the nerve of Neiguan (PC6) acupoint and nerve of the neck region may belong to homologous nerve. These induced electrical signals are basically consistent with the frequency of acupuncture stimulation, indicating that the mechanical force signal of acupuncture directly induces nerve discharge. Lu, *et al.* [6] analyzed the nerve fibers that induced discharge and showed that they were mainly class II fibers, which were equivalent to Aβ fibers and mainly transmitted touch and pressure sensation. Lu, *et al.* [7] found that acupuncture at Zusanli (ST36) acupoint had a significant inhibitory effect on the pain model with jaw movement response as the index. The analgesic impulse of acupuncture from Zusanli (ST36) acupoint caused this response was mainly transmitted by Aβ afferent fibers of peroneal nerve. Sufficient amount of Aβ fiber activity was an important factor in producing significant analgesic effects. Inhibitory effect of Aβ crude fibers which transmitted analgesic impulses acted on Aδ and C fine fibers which transmitted pain impulses.

However, the amount of stimulation commonly used in clinical practice is not too strong stimulation that patients can tolerate. Chen *et al.* [8] observed the analgesic effect of acupuncture stimulation at Chengshan (BL57) acupoint with different intensity and different levels on inflammatory pain of musculus gastrocnemius, and analyzed the analgesic characteristics of hot moxibustion stimulation (Moxa), electro acupuncture (EA) and transcutaneous electrical acupoint stimulation (TEAS) and their relationship with sensory afference. It was found that the analgesic effect of Moxa and EA were achieved by activating skin C fiber and muscle A fiber, respectively. Moreover, the sensory afferent mediating of TEAS analgesia was mainly muscle A fiber. Duanmu, *et al.* [9] observed the analgesic effects of electroacupuncture (EA) and transcutaneous electrical acupoint stimulation (TEAS) on muscular inflammatory pain model rats, and discussed the role of different afferent nerve fibers activating deep and shallow local acupoints of pain source in acupuncture analgesia. It was found that TEAS with threshold of C fiber (Tc) intensity at the local pain source Liangqiu (ST34) and EA with different intensity could alleviate the pain behavior of inflammatory pain model rats and inhibit the myoelectric reflection of C fibers. The analgesic effect was related to the level and intensity of local stimulation at the acupoint. This study also proved that EA activated deep C fibers at the local, contralateral and distant acupoints of the pain source Liangqiu (ST34) had analgesic effects, which might be caused by activating the descending inhibition of the upper center. In order to understand the peripheral process of acupuncture analgesic impulse, Lu [10] analyzed the peripheral afferent pathways and afferent fibers of the analgesic effect of acupuncture at Zusanli (ST36) on awake and unanesthetized rabbits and cats by means of blocking and stimulating them. The results showed that the main afferent fiber of analgesic impulse in acupuncture at Zusanli (ST36) was not Aα or C fiber, but Aβ fiber. Moreover, excitation of sufficient quantities of Aβ fibers could lead to significant analgesic effect, and Aδ fiber could play a part in the analgesic impulse transmission of acupuncture at Zusanli (ST36).

Zhu *et al.* [11] conducted an animal experimental study on the segmental and systemic mechanism of acupuncture analgesia and found that at the same ganglion level, acupuncture had obvious analgesic effect as long as the A fiber of acupoint could be excited. Moreover, the mechanism was that the introduction of coarse fiber inhibited pain-sensitive neurons at the spinal cord level. In the different nerve segment, electrical stimulation sufficient to excite finer Aδ and C fibers could raise the pain threshold. The analgesic effect of acupuncture at this nerve segment might require the participation of the superior spinal center. The analgesic effect of acupuncture is closely related to the intensity of acupuncture. Local acupoint selection only requires weak acupuncture needling manipulation to obtain obvious analgesic effect. However, the remote acupoint selection requires strong acupuncture needling manipulation to be effective.

2. Conduction Pathway of Acupuncture Signal in the Spinal Cord

After entering the spinal cord, the afferent impulse induced by acupuncture mainly crosses the ventral lateral tract of the opposite spinal cord, which is similar to the conduction pathway of pain and warmth. It provides the morphological basis for the interaction between acupuncture signal and pain signal in the afferent process. Acupuncture signals affect the movements of the skin and viscera controlled by the adjacent segments and the afference of pain in the adjacent segments through the segmental connection in the spinal cord. More importantly, the ascending acupuncture signal reaches the brain stem, thalamus, cerebral cortex and other parts, and realizes the analgesic effect by activating the high central part to release the descending inhibitory impulse. This inhibitory impulse mainly travels down the corticospinal tract to the dorsal horn of the spinal cord. In patients with syringomyelia, the lesion involves the anterior spinal cord or the ventral lateral cord, and the segmental pain and warmth sensation on one side disappear. Acupuncture at the corresponding points does not cause obvious needle sensation. However, when the dorsal tract of the spinal cord is damaged, it does not affect the production of needle sensation. The ascending pathway of acupuncture signal after transmission to the spinal cord is mainly in the lateral ventral cord, which is consistent with the pathway of pain and temperature sensation. The evidence is that in the spinal cord patients with pain and temperature impairment, their needle sensation also disappeared. However, in the patients with funiculus posterior damage, the needle sensation still remained [12]. At the same time, Liu, *et al.* [13] have found that acupuncture improved the excitability of the corresponding spinal nerves and accelerated the transmission of signals. It is now well established that there are at least three classes of neurotransmitters that exert analgesic effects from the brain down to the spinal cord, which ware namely 5-hydroxytryptamine (5-HT), norepinephrine

(NE) and endogenous morphine-like substances. 5-hydroxytryptamine (5-HT), norepinephrine (NE), enkephalin and dynorphin in the spinal cord play important roles in acupuncture analgesia respectively [2].

The Integration of Acupuncture Signals and Pain Signals at Different Levels of the Center

3.1 Integration of acupuncture signals and pain signals at the spinal cord level

The primary stage of pain information processing is completed in the spinal cord, in which glial cells play an important role in the occurrence and development of chronic neuropathic pain. Acupuncture signals travel along the afferent nerve into the spinal cord and interact with injurious signals from the site of pain. Somatic primary afferent fibers and visceral primary afferent fibers are mainly concentrated in layers I and V of the dorsal horn of the spinal cord, and also exist in layers III, IV, VII, VIII, and even the dorsal sacral medullary commissure nucleus [14]. The high frequency persistent discharge induced by nociceptive stimuli can be recorded by microelectrodes in the cells of the ridge neck tract or the layer V of the dorsal angle. This kind of pain-sensitive cell discharge can be inhibited by electroacupuncture stimulation at acupoints or electrical stimulation of nerve stems. According to the gate control theory, glial cells in the dorsal horn of the spinal cord act as a kind of gate, controlling peripheral pain signals to the cerebral cortex, and are regulated by coarse fibers (Aβ) and fine fibers (Aδ and C). When the coarse fibers are excited, and the gate closes. Thus., the pain signal cannot reach the brain, and the patient does not feel pain. When the fine fibers are excited, the gate opens and pain signals can be uploaded to the brain, producing pain sensations. Transcutaneous electrical stimulation therapy excites coarse myelinated fibers by high frequency and low intensity electrical stimulation, and inhibits the introduction of fine fibers in the same segment at the spinal cord level to produce analgesia. In clinical practice, Quanlian (SI18) acupoint was used for frontal operation and Futu (LI18) acupoint for thyroid operation. Because the acupoints and the surgical site are in the same or similar segments, the analgesic effect is better. This integration in the same or similar segments may be the physiological basis for local acupoint selection near the pain site. Lin [15] observed the effects of electroacupuncture at Futu (LI18) acupoint on the activity of GABA/Glu receptor /cAMP/CREB signaling pathway in rats with cervical incision pain. It was found that NMDAR2B, mGluR5, cAMP, MAPK and p-CREB in the cervical spinal cord were involved in the generation of cervical incision pain sensitivity. Moreover, electroacupuncture at Futu (LI18), Hegu (LI4) and Neiguan (PC6) could relieve cervical incision pain, and was related to inhibiting the expression of pain-sensitive substances such as NMDAR2B, mGluR5, cAMP, MAPK and p-CREB in the spinal cord. NMDAR2B, mGluR5, cAMP, MAPK and p-CREB in the spinal cord play different roles in the regulation of pain. Qiao, *et al.* [16] found that electroacupuncture at Futu (LI18), Hegu (LI4) and Neiguan (PC6) acupoints could relieve acute cervical incision pain in rats. This effect might be related to the down-regulation of 5-HT 1 AR mRNA expression and up-regulation of 5-5-HT 2 AR mRNA and protein expression in the cervical spinal cord. The expression of P2X4 receptor, and the morphological and ultrastructure relationship between neurons and glial cells in the dorsal horn of lumbar spinal cord of rats with rectocolonic dilated visceral pain were observed by electroacupuncture at Zusanli (ST36) acupoint by Qin, *et al.* [17]. They found that the ultrastructural changes of P2X4 receptor immunoreactive neurons and glial cells in the dorsal horn of the spinal cord might be the morphological basis of analgesia by electroacupuncture. Bing Zhu, *et al.* [18] used class C nerve fiber reflex induced by sural nerve stimulation as an index of nociceptive response, and observed that electroacupuncture with threshold of A fiber (Ta) or threshold of C fiber (Tc) intensity at local points on the same side could produce significant inhibitory effects. However, only the inhibition effect of electroacupuncture with Tc intensity was obvious in the heteroganglia segment. After spinal cord amputation in rats, the inhibitory effect of ectopic segment of electroacupuncture on class C nerve fiber reflex basically disappeared. It showed that the analgesic effect of acupuncture at the same level could be completed at the spinal cord level. In the heteroganglia segment, the descending inhibition of the superior spinal center was required. The trial also indicated that there was an obvious segmental relationship between the incoming information of acupuncture and the incoming information of injury-induced stimulation in the spinal cord. When the acupuncture site and injurious stimulation afferent fibers reached the same or similar spinal segments, the inhibitory effect of acupuncture was more obvious. If the two transmission fibers reached the spinal cord segments that were far apart, the inhibitory effect of acupuncture was weak.

The most important basis for the selective regulation of acupoints is the spinal cord and proximal segment innervation mechanism, which is obtained by means of spinal cord integration and reflexes. After the central process of somatosensory neurons enters the nodal cord, it contacts with the anterior horn motor neurons and lateral horn sympathetic neurons in this segment and 1~2 adjacent segments, which is the basis of spinal reflex activity. Hu, *et al.* [20] observed the intervention effect of electroacupuncture at Zusanli (ST36) and Kunlun (BL60) acupoints on mechanical paw withdrawal threshold (MPWT), thermal paw contraction withdrawal latency (TPWL) and activation of astrocytes and microglia in spinal dorsal horn of complex regional pain syndrome type I (CRPS I) in model rats. It was found that electroacupuncture could effectively inhibit pain sensitization and increase MPWT and TPWL in CRPS I rats model. Moreover, the analgesic mechanism might be related to the significant downregulation of the hyperactivation of astrocytes and microglia in the spinal cord. Nociception is mainly involved in pain modulation to achieve analgesia by inhibiting the production of inflammatory factors by spinal cord glial cells [21]. Yang, *et al.* [22] used the method of combining form and function to observe the exocytosis at the non-synaptic site of the large granular vesicles in the caudal subnucleus of the spinal tract nucleus of trigeminal nerve in rats when the acupuncture time was prolonged and the acupuncture frequency was increased during the pain was induced by formaldehyde. It was found by their trail that the amount of exocytosis of large particle vesicles in the caudal subnucleus of trigeminal spinal tract increased with the extension of acupuncture time. In the process of acupuncture analgesia, the caudal subnucleus of spinal tract nucleus of trigeminal nerve might release its stored chemicals through exocytosis of large particle vesicles at non-synaptic sites, and participated in the inhibition of pain induced by formaldehyde, resulting in an analgesic role. Gamma-aminobutyric acid, opioid peptides and substance P at the spinal cord level are involved in presynaptic and postsynaptic inhibition to varying degrees, resulting in analgesic effect.

3.2 Integration of acupuncture signals and pain signals at brain stem level

The brain stem activates the endogenous analgesic system in nociception, excites the nuclei associated with pain modulation, and activates the descending inhibitory system to modulate the transmission of nociception information [23]. The central gray matter of the brainstem, the tegmental structure of the midbrain, the reticular structure of the midbrain, and the giant cell nucleus of the medullary brain are all associated with pain [24]. Acupuncture signals enter the giant cell nucleus of medullary reticular structure along the ventral lateral cord and cause the change of unit discharge of the nucleus mass. Nociceptive stimuli signals can also reach the giant cell nucleus. These two signals can converge on the same nucleus or even the same cell. Through the interaction, the response caused by the nociceptive stimulus is suppressed by acupuncture signals. Electrophysiological studies have shown that the superior central nucleus of brainstem is involved in acupuncture analgesia, and electrical stimulation of the superior central nucleus has obvious analgesic effect. Electrolysis or chemical destruction of the central superior nucleus with 5, 6-DHT significantly reduced the analgesic effect of acupuncture. It is closely related to habenular nucleus, interpeduncular nucleus, periaqueductal gray matter of midbrain and dorsal raphe nucleus. The participation of the superior central nucleus in acupuncture analgesia may be realized through the "limbic midbrain analgesia circuit" [25]. The periaqueductal gray matter (PAG) is the relay station of the pain regulation system in the brain stem region, which is the core structure of the endogenous analgesic system. Acupuncture information travels up along the lateral spinothalamic cord, receives acupuncture signals to activate the brain stem descending inhibitory system, and exerts synergistic analgesic effect by various neurotransmitters [26]. PAG has a variety of neurotransmitters involved in the analgesic response, among which opioid peptides (enkephalins, endorphins), substance P, 5-HT and so on enhance the analgesic effect. The discharge of pain cells in the medial thalamic nucleus is inhibited by direct stimulation of the tail part of the giant cell nucleus of the medulla. This effect is very similar to the inhibition effect of electroacupuncture at Zusanli (ST36) acupoint. Long latency and long post-discharge responses to nociceptive stimuli are recorded by microelectrodes in the central gray matter of the midbrain, the central fasciculate area of the medial reticular structure of the midbrain and the spinal nucleus of the trigeminal nerve. This response can be inhibited by electroacupuncture at acupoints on the extremities or the face. The emergence and disappearance of inhibition occurs gradually. This may be one of the physiological bases of traditional Chinese medicine to select acupoints far away from pain sites. Liu, *et al.* [27] severed bilateral infraorbital nerves in rats and injected nerve snake venom into bilateral infraorbital nerve sheath to selectively destroy class A fibers. Then, the rat model of visceral pain was induced by intraperitoneal injection of acetic acid, and the electroacupuncture at bilateral Sibai (ST2) acupoints was given. The behavioral changes (writhing response) and the expression of c-fos in the nucleus tractus solitarius (NTS) and paratrigeminal nucleus (PTN) of rats with visceral pain were observed. It was found that the somatosensory afferent of mouth and face might converge and integrate with visceral sensory afferent in NTS after PTN relay, thus producing analgesic effect.

3.3 Integration of acupuncture signals and pain signals at thalamic level

Zhang [28] proposed that the thalamus was a key transit station for the transmission of nociceptive information to the cerebral cortex. The structure of the thalamus receiving pain signals is mainly in the medial part of the thalamus. Xu, *et al.* [29] found that when the thalamus was stimulated by exogenous injury, it activated the central nucleus, inhibited the parafascicular nucleus discharge, and blocked the transmission of injury information to the upstream. The dorsal horn of the spinal cord and the medial nucleus of the thalamus are two key structures in the sensory system of pain. In the process of the integration of harmful information, the central nucleus of thalamus and the ventrolateral orbital cortex are involved in the perception and modulation of pain [30]. A special type of discharge response induced by nociceptive stimuli was recorded by microelectrodes in the medial thalamic nucleus group, especially in the parafascicular nucleus and central lateral nucleus. Electroacupuncture at Zusanli (ST36) acupoint could inhibit the discharge of such pain-sensitive cells. The inhibition process occurred slowly, and the inhibition effect was longer after the electroacupuncture was stopped. The experiments of Luo, *et al.* [31] suggested that the inhibition of the discharge of pain-sensitive cells by acupuncture might be affected through the central nucleus of thalamus. Because the stimulation of the central nucleus by 4~8 electrical pulses per second could significantly inhibit the discharge of pain sensitive cells in parafascicular nucleus cells. Sometimes the suppression duration could be as long as 5 minutes. The subcentral nucleus of the thalamus may be a key site for pain transmission and perception [32]. Zhang, *et al.* [33] found that bilateral electrolytic damage to the central nucleus of the thalamus in rats with shallow anesthesia significantly facilitated tail flick reflex, and significantly weakened the inhibitory effect of strong electroacupuncture at Zusanli (ST36) acupoint on reflex. But it had no obvious effect on the action of weak electroacupuncture stimuli. These results suggested that the central subthalamic nucleus might be involved in the modulation of pain perception. Moreover, it played an important role in acupuncture analgesia, especially in the analgesia caused by the introduction of fine fibers [34]. 5-HT and its receptor subtype (5-HT2 receptor) in the hypothalamic nucleus may participate in the analgesic effect of intense electroacupuncture and have a tonic descending inhibitory effect [35]. The electroacupuncture can inhibit the pain discharge of neurons in the ventrolateral nucleus of thalamus [36].

3.4 Integration of acupuncture signals and pain signals at the cerebral cortical level

The cerebral cortex is the highest center of neural activity regulation. Brain imaging has revealed the changes of brain activity induced by nociceptive stimulation during acupuncture. Generally speaking, pain and needle sensation are sensations that enter in the realm of consciousness. In theory, the afferent impulses that transmit these sensations must be projected into the cerebral cortex, where they interact and integrate. There are neurons in the frontal cortex that project directly to the medial lateral nucleus of the thalamus. Electroacupuncture can activate these neurons to regulate the descending of the medial lateral nucleus of the thalamus [37]. Animal experiments have showed that decorticate manipulation had no effect on analgesic effect of acupuncture in rabbits and cats. However, some data showed that the analgesic effect of acupuncture at the acupoint of the affected limb was significantly weakened in brain surgery patients with partial damage or partial resection of one side of the sensory cortex. The research in this area needs to be further deepened. The effect of descending modulation of cerebral cortex on acupuncture analgesia is mainly manifested in two aspects. The one is the regulation of nociceptive stimuli. For example, if the sensorimotor area I is stimulated, its descending fibers inhibit nociceptive function of the parafascicular nucleus of the thalamus by releasing acetylcholine. Another one is the downward adjustment of acupuncture analgesic effect. For example, electroacupuncture stimuli of sensorimotor area II [38] can produce analgesic effects through nucleus accumbens and nucleus habenula exciting the nucleus raphe magnus. If this area is destroyed, the inhibition of electroacupuncture on raphe magnus nucleus is weakened [39]. Wang, *et al.* [40] studied the influence of nucleus habenula on acupuncture analgesia, and pointed out that the activity level of nucleus habenula, as the intermediate station from the limbic structure of forebrain to the brainstem, had a significant influence on the analgesic effect of acupuncture on the pain threshold nucleus. Zhao, *et al.* [41] found that the pain threshold increased when the medial nucleus habenula was excited, while the pain threshold decreased when the lateral nucleus habenula was excited. Aimone, *et al.* [42] found that electrical stimuli of the raphe nucleus inhibited the response of spinal dorsal horn neurons to nociceptive stimuli, and this descending inhibition might be the direct inhibition of the raphe nucleus to spinal cord. In addition, Bowker, *et al.* [43] pointed out that this descending inhibition might also be caused by spinal cord bypass inhibition via dorsal raphe nucleus. Fan, *et al.* [44] found that nucleus raphe magnus WAs an