TCM in post stroke brain remodeling: Research advances

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Abstract: Brain functional remodeling is fundamental to the recovery from stroke and is one of the hot topics in modern brain science research, involving various factors such as neurophysiology, neurochemistry, and neuroimaging. Traditional Chinese Medicine (TCM), with its multi-target and multi-stage effects on the body, has unique advantages in improving neurological functions and promoting brain functional remodeling. Current research mainly focuses on monotherapy with Chinese herbs, compound prescriptions, and acupuncture, among other aspects. This paper summarizes their effects and related mechanisms, aiming to provide theoretical support for the clinical application of TCM in promoting brain function recovery after stroke.

Keywords: Traditional Chinese Medicine, Stroke, Brain Functional Remodeling, Review

1. Introduction

Stroke, also known as cerebrovascular accident, is one of the diseases that severely threaten human health. It is characterized by high incidence, mortality, disability, and recurrence rates in clinical practice. About 3/4 of the surviving patients have varying degrees of functional disorders [1-2], which greatly affects the quality of life and brings a huge burden to families and society. Therefore, improving functional disorders and promoting functional reconstruction is the focus of stroke prevention, treatment, and rehabilitation. In recent years, the theory of brain functional remodeling has become the core mechanism of stroke rehabilitation, and this theory has gradually been recognized. Traditional Chinese Medicine (TCM), acting on the body through multiple targets and links, has unique advantages in improving neurological functions and promoting brain functional remodeling, and has become a hot topic in the study of stroke functional remodeling. This paper reviews and summarizes the relevant research literature on TCM promoting brain functional remodeling in stroke in recent years, in order to provide a theoretical basis for formulating rehabilitation treatment plans in clinical practice.

2. Overview of brain functional remodeling

The plasticity of brain function is an important area of development in recent brain science research. Bathe first proposed the theory of brain plasticity, suggesting that the brain can regain lost functions due to damage through certain learning and training. Neural plasticity is an important basis for functional recovery after brain injury, and its mechanisms are related to factors such as neural structure, neurophysiology, neurochemistry, and neuroimaging [3]. Changes can manifest in many ways, macroscopically they can be seen as changes in brain functions (such as learning and memory functions), mental activities, and behavioral performances, and at the microscopic level, there are changes in the fine structure and function of neuronal synapses and neural circuits, including synaptic morphology and ultrastructure, neurochemical substances (neurotransmitters, receptors, etc.), neurophysiological activities, and changes in brain functional areas and networks [4]. In recent years, with the development of brain science and related scientific and technological advancements, research on brain functional remodeling after stroke has gradually deepened. Existing evidence indicates that the plastic changes in brain neurons are the basis for the recovery of motor function after stroke. Therefore, actively exploring effective rehabilitation methods to promote brain functional remodeling will be more conducive to the functional recovery of stroke patients.

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3. Post-Stroke brain remodeling: Physiochemical factors

Modern research indicates that ischemia of the cerebral cortex or changes in the microenvironment of the surrounding local tissue after stroke can trigger endogenous neural repair. The neural plasticity changes that result are key to functional recovery after stroke. The brain has a certain compensatory repair ability against ischemia-reperfusion injury and can undergo plastic changes through various mechanisms. The factors related to its mechanisms are as follows.

3.1. Synaptic remodeling-related proteins

Synaptophysin, also known as Synaptophysin (SYN), is a calcium-binding glycoprotein closely related to the structure and function of synapses. It is mainly found in the presynaptic vesicle membrane of neurons and is involved in the transport and release of synaptic vesicles. The level of Synaptophysin can accurately reflect the number of synapses and is an important marker for detecting neural development and synaptic density. Studies have found that Synaptophysin is closely related to the formation of synapses; changes in its gene expression and protein content can directly affect the number of interconnected neurons and synapses. When synaptic reconstruction occurs, its expression significantly increases, making SYN considered a marker protein that reflects synaptic activity and neural plasticity [3,5-6]. After cerebral ischemia, synaptic levels mainly undergo plastic changes through increasing in number and altering connection strength. Postsynaptic density is an ultrastructural feature of chemical synapses, participating in synaptic neurotransmission activities. Among them, Postsynaptic density-95 (PSD-95) is a core component of the excitatory glutamate receptor signal transduction system at the postsynaptic site. Its dysregulation is closely related to a variety of neuropsychiatric diseases, making it an important target for current research [7].

Growth associated protein-43 (GAP-43) is a specific phosphoprotein associated with the growth of neuronal axons. Its content is particularly high in growing and regenerating neural tissues, especially within growth cones, and is closely related to neuronal growth and development, axonal regeneration, and synaptic reconstruction [8]. Studies have found that the expression level of GAP-43 in most brain regions is very low in adulthood. When brain tissue is damaged, neurons around the injury mainly compensate functionally through reactive axonal regeneration and collateral sprouting. Concurrently, an upregulation of GAP-43 expression at both the gene and protein levels can be detected in these areas, which gradually declines as the damage is repaired over time. Therefore, GAP-43 has become a preferred molecular probe for neural plasticity research internationally [9].

Microtubule-associated protein-2 (MAP-2) is a phosphoprotein that regulates the assembly and dynamics of tubulin and is mainly found in the soma, dendrites, and dendritic spines of neurons in the brain. It is involved in functions such as the growth of protrusions, cytoplasmic protein transport, and the regulation of neuronal synaptic plasticity [10]. Studies have found that the expression level of MAP-2 in brain tissue decreases after cerebral ischemia, while selectively increases in the ischemic penumbra of the ischemic core area during the early reperfusion phase of neurons. It is therefore believed that MAP-2 may be involved in the reconstruction of damaged neurons in the ischemic penumbra and is one of the early markers reflecting neuronal injury [11].

3.2. Neurotrophic and neuroprotective factors

Brain-derived neurotrophic factor (BDNF) is predominantly found in rich amounts in the cerebral cortex, hippocampus, and other central nervous system areas. It is involved in the growth, development, differentiation, maintenance, and repair of various types of neurons in the central nervous system and offers certain protective effects against ischemic brain damage [12-13]. Nerve growth factor (NGF) is a specific neurotrophic factor that regulates the development, differentiation, growth, regeneration, and functional expression of central and peripheral neurons, fulfilling neurotrophic and neuroprotective functions [14]. Additionally, NGF can promote the formation of new blood vessels by mediating the proliferation and differentiation of endothelial progenitor cells, playing a crucial role in improving blood supply to damaged brain areas and promoting the protection and recovery of neural functions [15]. Neurotrophin-3 (NT-3), a key member of the neurotrophic growth factor family, is primarily distributed in tissues such as the spinal cord, brainstem, cerebellum, and hippocampus. It participates in neurotrophic activities and promotes

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proliferation and differentiation through the Akt/MAPK signaling pathway and is closely related to cerebral ischemia reperfusion injury, aiding in the recovery of neural functions after ischemia [16].

Insulin-like growth factor-1 (IGF-1) is an active protein polypeptide that plays a key role in neuronal growth and differentiation. Structurally similar to insulin, IGF-1 provides essential nutritional support and neuroprotective effects for maintaining neural regeneration and functional repair after injury [17]. Vascular endothelial growth factor (VEGF) is a specific mitogen produced by vascular endothelial cells and has dual roles in vascular and neural regeneration. Studies have found that VEGF not only promotes neuronal proliferation, synaptic growth, and specific activation of signaling pathways for neuroprotection but also inhibits neuronal apoptosis after cerebral ischemia and promotes angiogenesis by regulating ion channels [17-18].

3.3. Inhibitory factors for rain functional remodeling

Cysteine-dependent aspartate-specific proteases (Caspases) are a series of proteases with similar structures that exist in the cytoplasm, primarily involved in the regulation of cell growth, differentiation, and apoptosis. Among them, Caspase-3 directly mediates the cleavage of functional proteins, causing apoptosis after cerebral ischemia. Therefore, the expression of the Caspase family of proteins is detrimental to neuroprotection and functional remodeling after brain injury [17]. No go-A is mainly distributed in the central nervous system and is a neurogrowth inhibitory factor that has been proven to inhibit axonal regeneration both in vitro and in vivo. Studies have found that in the later stages of cerebral ischemia or brain injury, the upregulation of the expression levels of No go-A and its receptors makes the inhibitory effect on nerve fibers more pronounced, suggesting that they may be involved in the pathological progression of cerebral ischemia [17,19].

4. fMRI in Post Stroke brain remodeling

In recent years, the development of neuroimaging technology has provided more intuitive methods and means for the study of brain functional remodeling after stroke, especially functional magnetic resonance imaging (fMRI). It can not only study the changes in brain functional networks under resting conditions but also be combined with brain tissue structural images to more comprehensively observe the dynamic changes in brain function and tissue remodeling after stroke, providing a new perspective for the study of post-stroke brain functional remodeling. Brain functional remodeling is the foundation of stroke recovery. The recovery of neurological function after stroke is the result of the participation of multiple factors, involving both the functional compensation of the healthy side of the brain and the functional remodeling of the residual nervous system around the lesion area [20]. Applying fMRI to observe the changes in brain functional areas during the process of stroke recovery, as well as the effects of drug intervention or rehabilitation training, is conducive to more intuitively exploring the mechanisms of post-stroke brain functional remodeling, providing important basis for formulating more effective stroke recovery programs.

5. TCM and brain remodeling post stroke

5.1. Chinese herbal medicine

Traditional Chinese Medicine (TCM) holds the view that the core pathophysiology of stroke is due to the imbalance of Yin and Yang, and the disorder of Qi and blood that encroaches upon the brain. Therefore, the key to treatment is to regulate the flow of Qi and blood. In recent years, it has been discovered that TCM can promote brain functional remodeling after stroke through various mechanisms, thereby exerting neuroprotective effects.

5.1.1. Single-Ingredient medicinals

The Chinese medicinal herb San qi has the characteristics of promoting blood circulation to remove blood stasis without harming the body's vital energy, and its therapeutic effects in the treatment of cerebrovascular diseases are well-established. Modern research indicates that its main component, Panax notoginseng saponins (PTS), plays a significant role in brain functional remodeling after cerebral ischemia. Yan Yongxing et al. [21] observed the changes in neurological function scores and levels of related proteins

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at different recovery periods in a rat model of focal cerebral ischemia-reperfusion treated with PTS. The results showed that the infarct volume and neurological deficit scores in the PTS treatment group were reduced at various treatment times, accompanied by a decrease in No go-A expression. Therefore, it is believed that PTS may promote the recovery of neurological function and brain functional remodeling after stroke by inhibiting the expression of No go-A after cerebral ischemia-reperfusion. Cui Fang yuan et al. [22] also found that PTS can enhance the expression of SYN and PSD-95 at different times, promoting synaptic remodeling and functional reorganization. In addition, PTS can also promote the recovery of neural function by regulating the expression of VEGF and IGF-1[23-24]. Traditional medicine believes that the Chinese herb Ephedra has the effect of activating blood circulation and unblocking collaterals, and it is commonly used to treat conditions such as yin carbuncles, lumps, and phlegm nodules that are associated with phlegm and blood stasis. Current reports [25] show that the use of Ephedra in combination with other Chinese herbs can improve neurological deficit symptoms caused by cerebral ischemia, especially the recovery of limb function after stroke sequelae. Zhao Xiao Ke et al. [26] observed the influence of the main component of Ephedra, ephedrine, on the recovery of motor function in a rat model of cerebral ischemia. The results showed that the recovery effect of the treatment group was significantly better than that of the control group, accompanied by increased expression levels of GAP-43 and SYP. Therefore, it is believed that ephedrine improves motor function by promoting neural remodeling and regulating the expression of structural reconstruction molecules.

5.1.2. Prepared Chinese medicines

Prepared Chinese medicine Shu Luo Pian, which contains Radix Paeoniae Rubra, Gardenia, and Earthworm, has the effects of cooling blood, resolving stasis, extinguishing wind, and unblocking collaterals, and has shown good clinical efficacy for the heat and blood stasis syndrome in the recovery period of stroke patients. Shen Ya Ning[27] found through experimental research that Shu Luo Pian can significantly reduce the cerebral infarction rate, brain index, and brain water content in rats with middle cerebral artery occlusion and ischemia-reperfusion, improve the hemorheology of "blood stasis syndrome" rats, and promote the proliferation of vascular endothelial growth factor (VEGF) in the infarction area, which promotes the regeneration of the central nervous system and achieves functional reorganization and remodeling. Xue Sai Tong injection, whose main component is Panax no to ginseng total saponins, is commonly used for the blood stasis obstruction syndrome in hemiplegia due to stroke. It not only improves cerebral edema and promotes glial cell response in rats with multiple cerebral infarctions but also promotes axonal regeneration and recovery of neural function by upregulating the expression of NGF [28]. Other scholars have found that Shen Mai injection can regulate the expression of GAP-43 and SYP proteins after cerebral ischemia, upregulate BDNF, and downregulate No go-A, promoting the growth of axons and synaptic reconstruction of neurons in the cerebral cortex around the ischemic focus [29-30]. Ma Dai chao et al. [31] found that Shen Xiong Di Wan (extracts of Astragalus, Salvia miltiorrhiza, and Ligusticum chuanxiong) can upregulate the expression of neuron growth-related proteins such as GAP-3 and SYN and the proliferation and differentiation of endogenous neural stem cells during the brain injury repair process, thereby promoting neural plasticity after ischemic injury.

5.1.3. Traditional Chinese medicine compounds

Fu Jian Pian is a traditional Chinese medicine compound developed based on the clinical experience of Professor Wang Xin Lu, mainly composed of Polygonum multiflorum, Taxillus chinensis, Cassia tora, Epimedium, and others, and has the effect of nourishing the liver and kidneys. Clinical studies have shown that Fu Jian Pian has a good promoting effect on the recovery of neurological function after cerebral infarction [32]. Hu Huai Qiang et al. [33] found that Fu Jian Pian can significantly inhibit the expression of Nogo-A around the cerebral infarction area in rats, relieve the inhibition of central nerve regeneration, and thus promote nerve regeneration. Zhou Yong Hong et al. [34] further explored the mechanism of action of Fu Jian Pian in terms of neuronal differentiation, axonal growth, and synapse formation. The study showed that Fu Jian Pian can regulate the expression of factors such as MAP-2, GAP-43, and SYN, improve the activity of astrocytes, promote the regeneration of ischemic stroke nerve axons, induce neural function remodeling, and thus promote the recovery of neurological function after cerebral infarction. The self-formulated prescription Kai Qiao Tong Fu Tang, mainly composed of Borneol, Rhubarb, Hirudo,

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Ligusticum chuanxiong, Achyranthes bidentata, Imperata cylindrica, and Atractylodes, has the effects of activating blood circulation, opening orifices, and protecting neurons in the acute phase of cerebral infarction. Liu Shu quan et al. [35] believe that Kai Qiao Tong Fu Tang can increase the positive expression of VEGF protein in the ischemic penumbra area of brain tissue in rats with cerebral infarction, promote the proliferation of vascular endothelial cells and the formation of new blood vessels, which is beneficial to neural function remodeling. Liu Hui xian et al. [36] explored the mechanism of action of the classic prescription for stroke, Bu Yang Huan Wu Tang, and the study showed that Bu Yang Huan Wu Tang can increase the expression of NGF and GDNF in ischemic brain tissue, thereby increasing the expression of GAP-43 and PSD-95, and can significantly promote synaptic remodeling of neurons after ischemia. Some scholars have also found that alkaloids and glycosides in Bu Yang Huan Wu Tang may inhibit the expression of Caspase-3, inhibit neuronal apoptosis after ischemia, and promote functional recovery [37].

5.2. Acupuncture

Both domestic and international studies have shown that acupuncture intervention has good clinical efficacy in stroke recovery, and the exploration of its mechanism of action has always been a focus of researchers. Currently, experimental research mainly focuses on the regulation of neurotransmitters in brain tissue by acupuncture, as well as the impact on related enzymology and structures such as synapses. In recent years, fMRI technology has been increasingly applied to the study of the mechanisms of acupuncture because of its high temporal and spatial dimensions, non-invasiveness, dynamics, non-radioactivity, and the combination of function and structure, which conforms to the holistic and functional characteristics of acupuncture meridians, and can better reflect the dynamic changes in brain functional activity during acupuncture.

5.2.1. Body acupuncture

Yang ling Quan is one of the most frequently used and effective acupoints in the clinical treatment of hemiplegia caused by stroke, and has become the entry point for many scholars to study the mechanism by which acupuncture promotes the remodeling of brain function after stroke. Liu Hongwei et al.[38] found that the brain areas activated by needling the left Yang ling Quan in healthy individuals (right precentral gyrus, left precentral gyrus, left superior temporal gyrus, etc.) highly overlap with the brain areas activated during passive finger movement of the left hand (right precentral gyrus, right postcentral gyrus, etc.), mainly focusing on the motor function area, providing a possible theoretical basis for the treatment of motor dysfunction by needling Yang ling Quan. Other studies [39] have found that in the brain network of hemiplegic patients' passive movement, there is a reduction in effective connections between the cerebellum, basal ganglia, limbic system, and cortex, leading to functional integration disorders within the motor system. Needling Yang ling Quan can increase attention to the affected side, reduce compensatory movement of the healthy side limbs, and greatly help to shorten the time for motor function recovery. It can also enhance bidirectional information transmission between the cerebellum and the cortex, which is beneficial for the integration of sensory and motor functions and promotes motor function remodeling. Si Wei Jun et al. [40] further proposed that needling Yang ling Quan may promote the recovery of hemiplegia by regulating the motor-related network (left anterior insula, inferior frontal gyrus, precentral gyrus, fusiform gyrus, cerebellum, etc.). Zhang Yong et al. [41] discussed the central effect mechanism of needling Yang ling Quan from the perspective of the default mode network (DMN), and the results showed that needling Yang ling Quan can enhance the functional connectivity between the anterior cingulate and posterior cingulate in the default mode network of stroke hemiplegic patients, thereby promoting the recovery of motor function, cognitive function, and memory function in stroke hemiplegic patients.

5.2.2. Scalp acupuncture

The pathogenesis of stroke is located in the brain, characterized by obstruction of cerebral vessels or bleeding into the cerebral vessels. Scalp acupuncture, due to its horizontal meridian connections and integration with modern Western medical anatomy, can directly stimulate scalp acupoints to enhance the coordination and compensatory effects between cortical functional areas, promoting the improvement of corresponding neural functions. Cui Fang yuan et al. [42] studied the immediate effect of needling scalp acupoints on the limb activity of patients with stroke hemiplegia, and the results showed that the recovery of

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motor function after stroke is closely related to the role of the cerebellum. Shen Zai yin [43] found that the main brain areas constituting the motor function network of hemiplegic patients include important brain functional areas such as the cerebellum, brainstem, precuneus, lingual gyrus, cingulate gyrus, inferior parietal lobule, insula, and caudate nucleus. After scalp acupuncture treatment, the brain areas in this network exhibit dynamic fluctuations, especially with enhanced functional connectivity in the right anterior cingulate, right precentral gyrus, body of the right caudate nucleus, and left precuneus, which is speculated to be one of the mechanisms of action of scalp acupuncture. The cluster needling therapy of head points [44-45] can effectively improve the functional state of nerve cells in the ischemic penumbra of cerebral infarction by inhibiting the expression of the pro-apoptotic gene Caspase-3, or increasing the positive expression of MAP-2 in the ischemic cortex, and promote the proliferation of glial cells, thereby playing a role in brain protection.

5.2.3. Electroacupuncture

Electroacupuncture is an organic combination of traditional Chinese acupuncture therapy and modern technology. By regulating the intensity and frequency of acupoint stimulation, it can further enhance the therapeutic effect of acupuncture and has a good promoting effect on the recovery of neurological function after stroke. Zhou Yuan Cheng et al. [46] found that electroacupuncture stimulation of the "Zu San Li" and "Nei Guan" acupoints can upregulate the expression of GAP-3 positive cells in the infarction area of cerebral infarction rats, promoting the repair of nerve tissue and functional remodeling. Han Yong sheng et al.[47] found that electroacupuncture at the bilateral Nei Guan, Shui Gou, San yin jiao, and Bai hui acupoints can significantly enhance the expression levels of GAP-43 and SYN in the cortex around the ischemic area of the brain, effectively regulate neuronal function, promote the recovery of motor function in rats with focal cerebral infarction, and induce axonal regeneration and synaptic reconstruction in a focal ischemia-reperfusion rat model, thereby promoting the recovery of neural function. Han Xiaohua et al. [48] found that the combination of electroacupuncture at Bai hui and Da Zhui acupoints with repetitive transcranial magnetic stimulation can significantly upregulate the expression of SYN in the hippocampus of rats with cerebral ischemia, promote the growth of axons of nerve cells at the damaged site, and promote the recovery of neural function.

5.3. Other therapies

Massage therapy is one of the characteristic treatment techniques of Traditional Chinese Medicine (TCM). It stimulates local areas of the limbs by following the meridians and acupoints, which can activate the corresponding brain functions to varying degrees and promote the recovery of paralyzed limbs. Jin He [49] used fMRI technology to explore the mechanism by which massage techniques improve muscle tone disorders in stroke-affected limbs. The results showed that after point pressure on the Hegu acupoint, there was varying degrees of activation in the right cerebral cortex and cerebellum/limbic system of stroke patients, with a small amount of activation on the left side. It is preliminarily considered that the compensation and reorganization ability of brain function should be achieved by promoting the improvement of muscle tone in the affected upper limb.

Acupoint injection therapy involves the use of appropriate small doses of medication at selected acupoints, which can produce a therapeutic effect as strong as or stronger than that of a large dose of intravenous injection in a short period of time. Wang Chun et al. [50] supplemented the rehabilitation treatment of stroke patients in the recovery period with acupoint injection of thrombolytic agents, which significantly improved the patients' clinical symptoms and quality of life scores. However, further research and discussion are needed on the mechanism by which this therapy promotes the recovery of brain function.

6. Issues and prospects

Brain functional remodeling after stroke is a comprehensive result influenced by multiple factors. Although neural function can be restored through various pathways after cerebral ischemic injury, due to the complexity of the central nervous system and the presence of many unknown factors, not all injuries to the central system are recoverable. Therefore, the mechanisms of brain plasticity still need to be explored and

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studied. The foundation of stroke recovery lies in the internal connections of newly generated neurons in the brain, the reconstruction of new functions, and the compensation for structural damage.

Currently, the therapeutic effects of motor therapies such as Brunnstrom and Bo bath in rehabilitation medicine have been confirmed and are widely used in the rehabilitation treatment of stroke patients.

7. Conclusion

Traditional Chinese medicine therapies, guided by the holistic concept and syndrome differentiation and treatment of TCM, have certain regulatory and promoting effects on the recovery of neural functions after stroke through comprehensive, multi-target, and multi-pathway approaches. At present, preliminary progress has been made in the biological mechanisms of how traditional Chinese medicine promotes brain function remodeling, as well as in neuroimaging mechanisms, accumulating some convincing experimental data that provide a basis for using traditional Chinese medicine to improve neural functions after stroke. However, overall research is still in its early stages, and there are still many issues. Due to the different onset times of stroke, the left and right sides of the injury, the degree of motor impairment, and the differences in rehabilitation techniques, the neural activation effects of Chinese medicine rehabilitation methods vary, leading to different results. Therefore, issues such as the optimal time window for traditional Chinese medicine intervention, the intensity and duration of intervention methods still need further research. In addition, the research methods are relatively singular, making it difficult to highlight and reflect the dynamic, multi-dimensional, and timely characteristics of traditional Chinese medicine in promoting brain function remodeling.

8. Conclusion

In summary, the recovery of neurological function after stroke is a comprehensive treatment process. While focusing on modern movement and physical rehabilitation therapies, the unique features and advantages of traditional Chinese medicine treatment should be fully utilized. The combination of various therapies should be applied to enhance the neural plasticity of stroke patients and promote the comprehensive recovery of neural functions. In addition, modern electrophysiological, molecular biological, and emerging neurofunctional imaging techniques should be fully utilized. Combined with the characteristics of clinical staging treatment of stroke, the difficult issues of motor function and language and cognitive function recovery after stroke should be explored from the perspective of brain function remodeling. Research ideas on the role of traditional Chinese medicine in promoting brain function recovery should be discussed.

Scholars should actively carry out basic and clinical research on the promotion of brain function remodeling after stroke by traditional Chinese medicine. From the perspective of micro-molecular biology to the macro level of neuroimaging, a comprehensive understanding of the integration and reconstruction mechanisms of neuronal structure and functional information by traditional Chinese medicine should be achieved. This will provide a theoretical basis and data support for the development of traditional Chinese medicine rehabilitation plans for stroke patients.

9. References

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