The development of visual neuroimaging research of acupuncture in the treatment of Parkinson’s disease

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ABSTRACT
Parkinson’s disease (PD) is a progressive neurodegenerative disorder commonly observed in middle-aged and elderly. Currently, its etiology and pathogenesis are still not completely understood. It is associated with many symptoms that severely affect patients’ health and quality of life. At present, the PD clinical treatment mainly aimed to alleviate symptoms, and both medicinal and surgical treatments have side effects and treatment blind spots. The use of acupuncture for the treatment of PD is relatively widespread, and its safety and efficacy have been gradually accepted by the public and medical professions. However, the efficacy of acupuncture in experimental studies remains controversial. Therefore, this paper reviews imaging studies on the use of acupuncture for the treatment of PD. From the study, it shows that acupuncture can improve the neuronal activity, activate the neuronal activity in damaged brain regions, affect relevant neural networks and brain circulation, improve cerebral metabolism, and cause structural changes in related brain regions. Intuitive and visible imaging studies provide objective bases on the use of acupuncture for the treatment of PD.

1 Introduction

Parkinson’s disease (PD) is a progressive neurodegenerative disease of the central nervous system commonly observed in middle-aged and elderly. Epidemiological studies showed that the PD prevalence in people aged ≥ 65 years in China until 1999 was 1.7% [1], and the total number of patients with PD is 1.7 million. As China’s aging population increases, this number will increase at a rate of 100,000 people per year. By 2030, the number of patients with PD is estimated to be 5 million in China, accounting for about half the number of patients with PD worldwide [2]. Currently, individual and family financial burdens of patients with PD in China are still quite heavy. With the large number of patients, there is an immense financial burden on the society [3].

PD is also a disease that affects many systems with complex and variable symptoms. In addition to tremors, myotonia, bradykinesia, and other motor disorders, sleep disorders (insomnia,
abnormal sleep behavior during rapid eye movement, and excessive diurnal somnolence), autonomic dysfunction (constipation, urinary disorders, and orthostatic hypotension), sensory disorders (anosmia, pain, restless legs syndrome), psychiatric symptoms (anxiety, depression, hallucinations, cognitive impairment, and dementia), and other non-motor symptoms are also observed [4–5]. At present, oral drugs and surgery have demonstrated good efficacy for motor symptoms such as tremors, rigidity, bradykinesia, and dyskinesia. However, these treatments are associated with their corresponding disadvantages. All 6 major anti-Parkinsonian medications [anticholinergic drugs, amantadine, levodopa, DR agonists, monoamine oxidase B (MAO-B) inhibitors, and catechol-O-methyltransferase (COMT) inhibitors] require long-term and concomitant administration, with each of them has its own side effects. The side effects include dry mouth, orthostatic hypotension, edema, abnormal mental state (hallucinations, impulse control disorder), and insomnia. These side effects will aggravate the non-motor symptoms of the patient [6]. Currently, no medication has been reported effective for the treatment of postural and balance disorders, and long-term efficacy is not observed in adjusting the medications. This is the main reason for falls and fractures in patients with PD. Surgeries cost much, and show limited efficacy against midline symptoms, postural and balance disorders.

With the changes in medical model and further understanding of the disease, the focus of the medical world has been gradually shifted to the non-motor symptoms of PD. Studies showed that the improvement of motor symptom in PD does not occur in parallel to the non-motor symptoms, and anti-Parkinsonian medications and surgery are almost ineffective in improving non-motor symptoms. The non-motor symptoms have a greater impact than the motor symptoms on the patients in terms of the quality of life, morbidity, and mortality as the disease progresses and with factors such as medications, age, psychological factors [7]. Currently, medication is the primary treatment method, with surgery as an ancillary treatment that mainly targets motor symptoms. There are still blind spots in the treatment of non-motor symptoms and side effects in usage of drugs. With these treatment difficulties, new treatment methods and surgical procedures are urgently needed to provide a safe and effective treatment against the non-motor symptoms and drug side effects.

Several studies have showed that Chinese medicine can effectively relieve the symptoms of Parkinson’s disease. In particular, acupuncture is widely used in PD treatment. Acupuncture can significantly improve myotonia, tremors, and other motor symptoms. When combined with Madopar treatment, it can reduce the dose of Madopar and its side effects, and delay disease progression [8–14]. At the same time, acupuncture shows good treatment results for non-motor symptoms of PD, such as sleep disorder, psychiatric disorders, and autonomic dysfunction [9, 15, 16]. However, due to the uniqueness of acupuncture treatment, related studies have methodological limitations and no sufficient objective evidence, so it results in low credibility and poor influence of the study results. Hence, the treatment characteristics and advantages of acupuncture in PD are not fully recognized, limiting its application and promotion in patients with PD. Therefore, this paper reviews and summarizes visual imaging studies of acupuncture treatment in PD to direct the objective research on acupuncture and provide intuitive evidence for the popularization of acupuncture in PD treatment.
2 Visual neuroimaging research of acupuncture in Parkinson’s disease

In recent years, with the progression of medical imaging, functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT), positron emission tomography (PET) and susceptibility weighted imaging (SWI) have demonstrated superiority in brain studies due to their good imaging on changes in cerebral metabolism, neurotransmitters, transporters, and receptors. This has resulted in the increasing application of imaging techniques in neurological diseases, and these techniques are widely used in the early diagnosis, monitoring, efficacy assessment, and scientific research of PD. Simultaneously, due to the uniqueness of acupuncture research, relevant studies are usually affected by subjective factors and questions on the placebo effect tend to be posed for relevant study results. However, as imaging techniques are objective, intuitive, and can compensate the shortcomings in normal acupuncture studies, imaging techniques have become important ancillary methods in acupuncture research.

2.1 fMRI research of acupuncture in PD

Yeo et al. [17] compared and investigated the fMRI responses of 12 patients with PD and 12 healthy volunteers to Yanglingquan (GB34) acupuncture. Compared with healthy volunteers, patients with PD showed significant enhancement of brain activity at the prefrontal cortex and precentral gyrus, which is particularly significant in the left hemisphere. GB34 acupuncture can activate the above damaged regions and putamen in patients with PD and activate the cortical neural networks in these brain regions. Another fMRI study by Yeo et al. [18] showed that reduction in neural responses in the brains of patients with PD were more widespread, including the putamen, thalamus, and supplementary motor areas, as compared with those in healthy subjects. GB34 acupuncture can activate the above damaged regions and increase neuronal activity in the regions related to PD, including the substantia nigra, caudate nucleus, thalamus, and putamen.

Wang et al. [19] employed fMRI to observe differences in regional homogeneity (ReHo) of the brain activity before and after acupuncture in patients with PD. They found that the Unified Parkinson’s Disease Rating Scale (UPDRS) scores of patients with PD were significantly decreased and improved tremors, rigidity, and bradykinesia may be related to neuronal activity changes from 6 sessions of acupuncture treatment. Brain neuronal activity changes were observed before and after acupuncture treatment. An increase of ReHo was observed in the dorsolateral prefrontal cortex, left posterior lobe of cerebellum, right inferior parietal lobule, and left precuneus and a decrease of ReHo was observed in right inferior temporal gyrus, right supplementary motor area, left and right lentiform nucleus, left and right thalamus, and left caudate nucleus.

2.2 SPECT research of acupuncture in PD

In the SPECT study by Huang et al. [20], 10 patients were randomized to the oral levodopa group and levodopa with complementary scalp electro-acupuncture group to observe brain responses of patients with PD. The results of their study showed that the difference in hemispheric regional cerebral blood flow (rCBF) was not significant in patients with PD, and striatal dopamine transporter (DAT) activity was significantly reduced in the most affected hemisphere. Compared with the status prior to treatment, increase of the rCBF in the frontal lobe, occipital lobe, basal ganglion, and cerebellum in the most affected hemisphere was observed in the levodopa with complementary scalp electro-acupuncture groups, but DAT levels in the basal ganglion...
remained unchanged. In contrast, no changes of rCBF were observed in the oral levodopa group, and DAT activity in the most affected hemisphere was significantly increased. Researchers hypothesized that the efficacy of acupuncture treatment for PD is associated with its effects on the cerebral blood flow and not the DAT activity of the basal ganglion. Huang et al. [21] employed SPECT to observe the effects of scalp acupuncture on rCBF in patients with PD. After 5 weeks of scalp acupuncture combined with Madopar treatment, patients in the combined treatment group showed significant improvements in tremors, rigidity, and movement disorders. After acupuncture and drug treatment, rCBF in the frontal lobe, occipital lobe, basal ganglion, and cerebellum of the severely affected hemisphere showed significant improvement; however, no significant changes of rCBF were observed in various brain regions in the mildly affected hemisphere. This shows that scalp acupuncture combined with Madopar can improve tremors, rigidity, and movement disorders in patients with PD, and these symptoms are associated with improved local cerebral blood flow.

2.4 SWI research of acupuncture in PD

Wang et al. [24] employed SWI to evaluate the efficacy of acupuncture treatment for PD and its effects on substantia nigra pars compacta (SNc). After 3 acupuncture sessions, no significant changes were observed in the H-Y grading of SNc width in patients with stages I–II PD, whereas significant increased in the SNc width was observed after treatment in those with stages III–IV PD, and the patients with stage IV PD showed the most significant increase. The results of the study showed that the efficacy of acupuncture treatment for PD is related to an increase in SNc width.

2.5 Neuroimaging research of acupuncture on animal models of PD

Lee et al. [25] used fMRI to observe different responses to acupuncture of MPTP-HCl-induced PD brains and normal brains in dogs to determine acupuncture effects on the cerebral activity. Results of their study showed that acupuncture at the Zhusanli (ST 36) acupoint can decrease the blood oxygenation level-dependent signal intensity in the basal ganglia, limbic system, and cerebellum, thereby significantly affecting the activation status of the brain. Moreover, they have observed that acupuncture at the same acupoint in different individuals may produce different brain regulation effects, and the specific effect is determined based on the pathological status of the brain. Zhang et al. [26] employed phMRI to assess the brains of 6 middle-aged Rhesus monkeys to objectively and safely study the anti-parkinsonian effects of electro-acupuncture. Results showed that long-term electro-acupuncture treatment can significantly improve the movement speed and...
fine motor performance of PD monkeys and the effectiveness of this treatment remained 3 months after the acupuncture. The phMRI results showed that long-term electro-acupuncture can improve the neuronal activity in the striatum, primary motor cortex (M1), cingulate gyrus, and global pallidus externa (GPe) in the ipsilateral hemisphere, thereby changing MPTP-induced PD brain lesions.

These studies showed that acupuncture treatment can affect the local cerebral blood flow, improve cerebral metabolism, improve dopamine transporter activity and neuronal activity at the striatum, and activate neuronal activity in damaged brain regions to affect relevant neural networks and cause structural changes in related brain regions to achieve the effects of acupuncture in both patients with PD or even animal researches. Molecular mechanistic studies [27] showed that acupuncture can reduce the loss of dopaminergic neurons, promote the synthesis, reuptake of dopamine and increases dopamine levels as it contributes to the normalization of basal ganglia activity and enhances the neurotransmission of postsynaptic dopamine [28–30]. Acupuncture can also increase superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX) activity in the serum, decrease malondialdehyde (MDA) levels, improve the antioxidant activity [31–33] and the mitochondrial function. Furthermore, acupuncture can reduce the expression levels of IL-β and TNF-α, restore DNA damage, reduce the overexpression of caspase-3 and Bax genes, and normalize neuroinflammatory responses and cell apoptosis [33]. Electroacupuncture plays a neuroprotective role by activating the expression and secretion of brain-derived neurotrophic factor (BDNF) and PI3K/Akt pathways [34]. Also, acupuncture can increase the α-synuclein autophagic clearance through m-TOR-independent pathway [35]. Hence, acupuncture imaging and efficacy mechanistic studies can provide objective bases for the efficacy, safety, and feasibility of acupuncture treatment for PD.

The use of imaging techniques to evaluate the effector mechanisms and assess the efficacy of acupuncture in PD treatment has good application prospects. However, there are still problems to be addressed: (1) Imaging studies on acupuncture treatment in PD are still at the exploratory stage and require further research, such as increase in sample size, expansion of research directions, and in-depth studies. (2) There is diversity in acupuncture prescriptions. Even though acupoints with definite efficacy are gradually discovered to date, more studies are required to screen for optimal acupoint combinations and prescriptions should be adjusted according to the individual’s status. (3) There are diverse acupuncture methods commonly used to date, including scalp acupuncture, body acupuncture, abdominal acupuncture, and acupuncture combined with medications. Further research is required to determine the strengths of different methods and their mechanisms, as well as their suitability based on symptoms and optimal intervention nodes. (4) A large number of studies are still required on the imaging of effector mechanisms in the acupuncture treatment for PD to determine treatment mechanism of acupuncture.

3 Conclusion

Currently, the etiology of PD remains unclear and PD has a complex pathogenesis, with many clinical symptoms and treatment gaps. In clinical applications, acupuncture has some advantages and can potentially treat PD. Although neuroimaging can objectively demonstrate the efficacy of acupuncture treatment, further imaging studies are required to explore the mechanisms of efficacy so that acupuncture treatment for PD can be promoted and popularized to benefit more patients.
Conflict of interests

All contributing authors have no conflict of interests.

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