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Review Article

Potential role of acupuncture in the treatment of Parkinson's disease: A narrative review

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ABSTRACT

Background: The prevalence of Parkinson's disease (PD) has grown rapidly compared to that of other neurological disorders. Acupuncture has been used to address the complex symptoms of PD. Recently, similarities in the mechanisms of action between acupuncture and neuromodulation have received considerable attention. This review aims to summarize the evidence regarding these similarities to suggest potential role of acupuncture in the treatment of PD.

Methods: The literature from two electronic databases, PubMed and Google Scholar, was searched using the search terms 'Acupuncture', 'Parkinson's disease', 'Vagus nerve stimulation', and 'Brain functional connectivity'. We then explored the evidence for the effectiveness of acupuncture in PD and evaluated the evidence for similarities in the mechanisms of action between acupuncture and neuromodulation.

Results: Data suggests that acupuncture treatment is effective for PD symptoms by modulating inflammation and brain functional connectivity (BFC). These acupuncture effects have been shown to be similar to neuromodulation in controlling inflammation and BFC. Based on the shared mechanisms of action, potential acupuncture mechanisms that may ameliorate a wide range of PD symptoms include but are not limited to (1) vagal activation of the anti-inflammatory pathway and (2) BFC enhancement.

Conclusion: The development of acupuncture strategies based on shared mechanisms with neuromodulation will provide new treatment options for patients with PD as personalized neuromodulating therapies. Further studies are needed to gather scientific evidence for optimizing parameters in PD patients.

1. Introduction

Parkinson's disease (PD) is a fast-growing neurodegenerative disorder characterized by the presence of movement disorders such as resting tremors, rigidity, bradykinesia, and postural instability.[1] Its prevalence increases with age until it peaks between the ages of 85 and 89 years, and affects 2–3% of the population aged 65 years or older.[2,3] Patients with PD also experience a range of non-motor symptoms at different disease stages that become more common as the disease progresses.[4] Although dopaminergic medication is effective in most PD patients with initial motor symptoms, they may experience worsened symptoms when the medication dose wears off.[1] To overcome this limitation, non-pharmaceutical strategies such as neuromodulation to stimulate the brain and neural activity have been attempted.[5] Deep brain stimulation (DBS) has been approved for patients with PD, and vagus nerve stimulation (VNS) is undergoing a clinical trial in patients with PD.[5,6] Acupuncture has also been used to treat motor and non-motor symptoms, and its mechanism of action on neural circuits has been studied.[7]

Recently, the similarities in the mechanisms of acupuncture and neuromodulation have received considerable attention.[8] Advancements in neuromodulating devices and strategies have been made based on their shared anatomical targets and stimulating techniques in the field of pain and nausea control.[9,10] To date, however, progress in connecting acupuncture and neuromodulating therapy in PD has been limited, despite their wide use. A study of this connection will provide insights into new acupuncture strategies and more clinical options for patients and clinicians. Acupuncture can be a less expensive and less invasive option, and can easily alter the stimulation parameters according to the patient's condition and symptoms.

As recent neuromodulation research has revealed many potential targets in PD pathology, new strategies for applying acupuncture as a neuromodulating therapy for PD are possible. Thus, in

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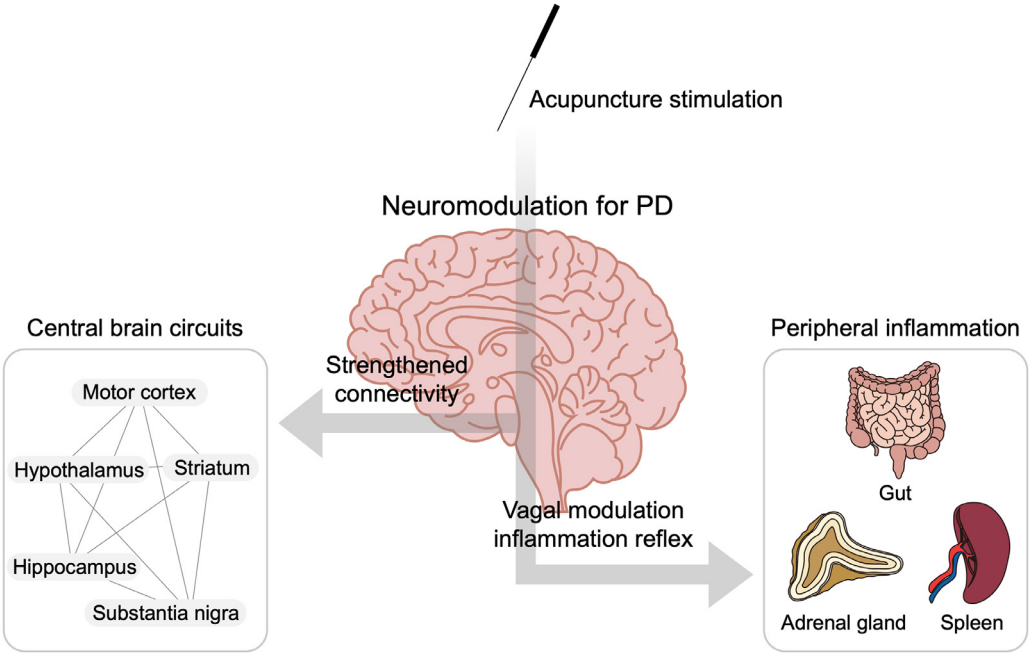

Fig. 1. The potential mechanism of acupuncture neuromodulation in patients with PD.
In the central nervous system, acupuncture strengthens brain functional connectivity. In the peripheral nervous system, acupuncture modulates inflammation via the cholinergic anti-inflammatory pathway. PD, Parkinson's disease.

this article, we suggest acupuncture strategies based on these mechanisms: (1) vagal activation of the anti-inflammatory pathway and (2) enhancement of the brain functional connectivity (BFC) to improve a wide range of PD symptoms (Fig. 1).

2. Acupuncture and neuromodulation: insights from intersections

2.1. Neuromodulating effect of acupuncture

Acupuncture stimulation induces alterations in neural activity and brain response. Stimulation begins when the needle is inserted into specific body points called acupoints.[11] This, in turn, directly or indirectly stimulates the peripheral nerves of the corresponding acupoints, such as the median nerve for PC6 and the vagus nerve for auricular acupoints.[12,13] Acupuncture stimulation also activates or deactivates brain regions that is closely related to the pain matrix and affects a wide range of neural circuits that contribute to the sensory, cognitive, and affective states.[11]

Optimal acupuncture stimulation depends on many factors, such as the location of the acupoint, stimulation techniques, intensity, and frequency, needle placement and depth, and the number of needles.[14,15] Acupuncture stimulation can easily be adjusted by controlling these factors. For instance, after a needle is inserted, additional stimulation can be added by manual manipulation or by sending electrical impulses to the needles using electroacupuncture (EA).[11] In a study that compared the magnetic resonance imaging (fMRI) signal induced after different types of acupuncture stimulations, the fMRI signal increase was more widespread after the EA stimulation than after the manual acupuncture. Additionally, even within the same EA stimulation, the signal increase was affected by the stimulation frequency.[16]

2.2. The intersections of acupuncture and neuromodulation

Acupuncture and neuromodulation overlap in terms of their concepts and clinical practice.[10] A well-known overlap is the relationship between acupuncture and VNS. Torres-Rosas *et al.* applied EA at ST36 in an animal model of sepsis to determine whether this could be an alternative way of stimulating the vagus nerve to control systemic inflammation.[17] This stimulation induced sciatic nerve activation and an anti-inflammatory effect mediated by dopamine. In other words, this discovery identified the shared therapeutic targets of acupuncture and neuromodulation. Some acupuncture-related knowledge is also applied to neuromodulation devices. For instance, transcutaneous electrical nerve stimulation used for pain control was inspired by acupuncture needles stimulated with electrical energy. Wrist bands stimulating PC6 are widely used to control nausea.[9]

3. Prospective use of acupuncture to control inflammation in patients with PD

3.1. Inflammation in PD

Extensive evidence has suggested that inflammatory responses are one of the factors in neurodegeneration in PD. Inflammation irritates α-synuclein propagation, and α-synuclein toxins may aggravate the inflammatory response.[18] Moreover, research on the brain-gut axis further supports possible role of intestinal inflammation in driving systemic and neuronal inflammation in patients with PD.[19]

3.2. Anti-inflammatory effects of VNS and acupuncture for PD

Research has demonstrated the potential benefits of VNS in cellular and animal models of PD and speculated that this may be related to its anti-inflammatory effect. In an animal experiment, VNS intervention improved locomotion, and decreased inflammation in substantia nigra and locus coeruleus.[6,20,21] The effects of VNS on non-motor symptoms of PD remain unknown. However, previous clinical studies in other diseases suggest that VNS is promising for treating depression, anxiety, and autonomic functions.[22]

According to a systemic review of 14 clinical reports of PD patients, acupuncture treatment was effective for both motor symptoms and non-motor symptoms of PD including psychiatric disorders, sleep problems, and gastrointestinal diseases.[7] Ani-

mal experiments have revealed the anti-inflammatory effects of acupuncture related to symptom improvements in a PD model.[23] Microglial activation and inflammatory events were reduced after acupuncture stimulation at GB34 and LR3 in a mouse model of PD.[24] Another study on a mouse model of PD also demonstrated a reduced neuroinflammatory response along with the improvement of motor symptoms and comorbid anxiety after acupuncture treatment at GB34 and ST36. The authors further suggested that the effect of acupuncture on the suppression of neuroinflammation might be related to the control of gut microbial dysbiosis.[25] Commonly used anti-inflammatory drugs currently available are known to have non-specific side effects, as they suppress the immune system to treat systemic inflammation. On the other hand, EA stimulation of acupoints offers several clinical benefits, especially in the case of PD, by exhibiting a targeted anti-inflammatory effect in specific body parts. This is achieved by selectively activating a specific signal pathway, thus avoiding the non-specific side effects that are commonly associated with drug treatments. This might be helpful in treating distinct pathological characteristics of PD.[26]

3.3. Cholinergic anti-inflammatory pathway of VNS and acupuncture

The vagus nerve innervates internal organs and regulates functional homeostasis, including inflammatory response.[22] Its regulation of inflammation involves three pathways: the anti-inflammatory hypothalamic-pituitary-adrenal axis, cholinergic anti-inflammatory pathway, and splenic sympathetic anti-inflammatory pathway.[27] These pathways have been suggested to be therapeutic targets for acupuncture and VNS. VNS targets involve the cholinergic anti-inflammatory pathway mediated by acetylcholine and $\alpha-7$-nicotinic acetylcholine receptors of macrophages which inhibits inflammatory cytokines, such as tumor necrosis factor-α.[27]

Anti-inflammatory pathways were also activated by EA stimulation in experimental animal models. When somatosensory stimulation at LI4 reaches the brain, muscarinic acetylcholine receptor (mAChR)-mediated signaling starts. The efferent vagus nerve is activated in association with mAChR-mediated signaling in the brain. The vagus nerve induces catecholaminergic signaling in the spleen and suppresses inflammatory cytokines.[28] Another study demonstrated the suppression of systemic inflammation induced by EA at ST36, mediated by the production of catecholamines in the adrenal gland and modulated by the activation of the sciatic and vagus nerves.[17]

3.4. Optimizing conditions for anti-inflammation

Selecting the appropriate stimulation conditions is one of the main challenges in any neuro-stimulating therapies because it is directly related to the therapeutic effects and the occurrence of side effects.[29] Acupuncture mechanisms for the vagal modulation of inflammation have been revealed under specific conditions. For example, when EA stimulated ST36, prokineticin receptor 2-positive neurons selectively drove the vagal-adrenal reflex in a mouse model of systemic inflammation.[26]

Different stimulating intensities, locations, or acupoints, have been reported to drive different neural pathways in their anti-inflammatory effect. Low-intensity EA at ST36 activates the vagal-adrenal axis and operates in non-splenic tissues, whereas high-intensity EA at ST25 activates the spinal-sympathetic axis and can suppress splenic inflammation, resulting in anti-inflammatory effects. Furthermore, in another study, acupuncture treatment at ST36 showed the opposite effect in the modulation of inflammation according to disease states, as demonstrated in mouse models with or without lipopolysaccharide exposure.[30] These conditions have clinical implications for optimized stimulation parameter selection in acupuncture strategies tailored to the symptoms of each patient with PD.

4. Prospective use of acupuncture to alter BFC in patients with PD

4.1. Alteration of BFC in PD

The importance of understanding alternation in BFC in PD patients has been emphasized in understanding the mechanism of DBS. Although this neuromodulation has been traditionally used on the premise that it modulates pathological activity within brain networks by targeting a highly focal anatomical area, current studies show that its impact goes beyond the stimulation site itself.[31–33]

Patients with PD show alterations in BFC that are widely distributed throughout the brain. Brain circuit dysfunction can spread to other brain networks and affect multiple brain areas or the functional connectivity between them.[31,32] Network imaging biomarkers have begun to reveal characteristic alterations in BFC that explain complex clinical manifestations and progression in patients with PD.[34] The PD mouse model also showed impairments in brain networks and functional connectivity.[35] These impairments in BFC showed improvement after acupuncture treatment in the mice model, along with the improvement in motor function and the afeted areas in the brain involving the motor cortex, substantia nigra, and striatum which are closely related to PD pathology. BFC enhancement was also shown in the hippocampus and hypothalamus implying that acupuncture may improve non-motor symptoms of PD such as memory, cognition, anxiety, and sleep disorders.

4.2. BFC enhancement of acupuncture

A series of fMRI studies in healthy participants proved that acupuncture can alter brain connectivity. The fMRI studies showed that acupuncture intervention regulates multiple physiological systems and functional connectivity.[36] The multiple physiological systems include the limbic system, the area where signal intensities are downregulated after acupuncture stimulation induces *de-qi*.[37] Acupuncture also enhanced BFC involving default mode network (DMN). This DMN is also known to be clinically relevant to PD.[38] The loss of cognitive function shown in PD patients is related to decreased DMN connectivity.[39]

Several studies have compared fMRI data before and after acupuncture treatment in patients with PD. In patients with PD whose motor function improved after acupuncture intervention at GB34, the putamen and primary motor cortex showed increased activation. The authors suggested that the effect of acupuncture on motor function may be related to the basal ganglia-thalamocortical circuit.[40] In another fMRI study, the change in BFC after acupuncture treatment was studied in PD patients with comorbid pain conditions. After acupuncture stimulation at GV20, Shen Guan, and GB34, patients showed BFC alterations that were significantly correlated with improvement in their pain condition.[41] Further fMRI studies of different brain regions associated with non-motor symptoms are needed to clarify how acupuncture alters BFC and the related symptoms in PD patients.

5. Discussion

The connection between acupuncture and neuromodulation in modulating inflammation and BFC provides potential acupuncture strategies for patients with PD. The peripheral stimulation by acupuncture reduces peripheral and central inflammation and

the anti-inflammatory effect may be distinctively effective in improving gait and overall motor symptoms as well as non-motor symptoms, such as neuropsychiatric symptoms, autonomic symptoms, and pain. Several animal studies have revealed the anti-inflammatory effects of vagal stimulation by acupuncture under different conditions, such as stimulation sites, intensity, or animal conditions. fMRI studies have found that BFC alterations in patients with PD after acupuncture treatment are significantly correlated with improvements in clinical symptoms.

Inflammation and BFC are two important biomarkers in the pathology of PD. Acupuncture treatment has been effective in improving inflammation and normalizing BFC in PD mice models.[23,35] Current evidence on the acupuncture strategies based on the two discussed mechanisms has limitations in that their neuromodulating effects have mostly been studied in animal models of PD or in healthy human participants. Therefore, further acupuncture mechanism studies on human patients with PD are needed, especially along with evaluations of changes in clinical symptoms and related biomarkers. Moreover, additional fMRI studies on patients with PD regarding changes in the BFC and PD symptoms before and after acupuncture intervention are needed. Research on different treatment outcomes depending on acupuncture stimulation sites, intensities, treatment duration, and patient conditions is also needed to set specific stimulation parameters in clinical contexts.

Recently, new technologies such as smartwatches and mobile applications have been considered for clinical use to monitor data that may affect fluctuating symptoms in patients with PD.[42] These technical advancements have made personalized treatments for patients with PD more feasible. Further acupuncture stimulation selectivity depending on different parameters may support more optimal conditions for personalizing the general effects of anti-inflammation and BFC alternation in acupuncture treatment. Acupuncture treatment has the potential benefit of being a less expensive, less invasive, and personalized neuromodulating therapy that patients will feel more comfortable receiving. Stimulation can be easily altered according to the acupoints, stimulating techniques, and intensities to induce different therapeutic effects. Further studies on the two acupuncture mechanisms and their optimizing stimulation parameters for PD patients are needed to make less invasive, personalized neuromodulating therapy more feasible.

CRediT authorship contribution statement

Jaeyoung Park: Conceptualization, Writing – original draft, Writing – review & editing. **Ju-Young Oh:** Conceptualization, Writing – original draft, Writing – review & editing. **Hi-Joon Park:** Conceptualization, Writing – original draft, Writing – review & editing.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Ethical statement

Not applicable.

Data availability

Not applicable.

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