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Functional Imaging and Physiological Modulation with Acupuncture in Parkinson's Disease and Nonhuman Primate Models of Dopamine Dysfunction

Yi-Ning Yin, Jorge E. Quintero and Zhiming M. Zhang

Abstract

Here we review functional imaging and neurophysiological evidence for the pre-clinical and clinical use of electroacupuncture, a non-pharmaceutical-based therapeutic strategy, to relieve parkinsonian symptoms. Outcomes from those studies provide evidence that the effect of electroacupuncture can be objectively measured in nonhuman primate models of Parkinson's disease and in patients with Parkinson's disease. In addition, the evidence continues to support that electroacupuncture can be used in preclinical and clinical studies simply, safely, and effectively as an alternative and complementary treatment for disorders in Parkinson's disease.

Keywords: acupuncture, pharmacological MRI, glutamate, cortex, electrochemistry

1. Introduction

Acupuncture has been gaining popularity for treatment of various disorders as an alternative therapy and has been used for years as treatment for a wide range of ailments from lower back pain to stroke to osteoarthritis to Parkinson's disease (PD) [1–5]. Classical acupuncture is based on 14 mapped main channels on the body with about 365 acupoints distributed on the channels (meridian system); the flow of Qi (the vital life force or “energy”) maintains the balance and harmony of Yin and Yang. Any blockage of these channels or abnormal movement of Qi will result in illness, and acupuncture, by stimulating these acupoints along the meridian channels with needles, helps to restore movement of the Qi and Qi homeostasis (De Qi), thus modulating the autonomic nervous system and relieving the symptoms of various illnesses [6, 7]. The underlying mechanism of acupuncture has been under intense investigation and many theories have been discussed in the scientific community. For example, connective tissues or perivascular space with decreased electrical impedance and increased electrical conductivity have been suggested to constitute the meridian channels with acupoints along the pathway [7, 8]. Nevertheless, the efficacy of acupuncture remains largely unclear because of a skeptical attitude of how acupuncture works (especially within the framework of Western Medicine),

methodological flaws, and an absence of rigorous studies using objective outcome measures [1]. To date, the clinical outcomes of acupuncture are assessed by empirical observations rather than by objective, quality analysis [1, 3, 5].

Recent, rapid advances in technology, especially the use of functional magnetic resonance imaging (fMRI) to map global and/or target-specific brain regions, have shown great promise and could be extremely helpful for acupuncture studies in human subjects when combined with subjective measurements [8]. Pharmacological MRI (phMRI), a new application of fMRI, is using fMRI methods to map drug-induced activations inside the brain [9]. In this chapter, we discuss how phMRI can be used to map dopaminergic drug-induced changes in the brain before and after acupuncture treatment in parkinsonian monkeys. Similarly, fMRI methods have been used in the PD clinic. As an example, with acute acupuncture stimulations at GB34, analysis of fMRI signals showed activations in the putamen and the primary motor cortex, and these activations induced by acupuncture were correlated with patient self-reported improvements of finger-tapping [10]. Furthermore, phMRI has been used to monitor other treatments associated with PD in a preclinical, translational study [11]. The utility of fMRI/phMRI has even been extended to differentiate dysfunction in the basal ganglia between parkinsonian and aged monkeys [12]. Based on those clinical and preclinical studies, these imaging modalities have the possibility to help untangle the underlying neural mechanisms of acupuncture.

To date, few studies have been conducted *in vivo* to directly investigate the relationship between acute acupuncture stimulation and its effects on modulating neurotransmitters especially in large animals such as the rhesus macaque. In this chapter, to our knowledge, we would be the first to begin exploring whether acupuncture stimulation could suppress, or activate, cortical glutamate in normal and PD monkeys. In addition, we will also review fMRI and phMRI studies to provide some direct evidence demonstrating the relationship between acupuncture and neuronal activity and changes in neurotransmitter signaling in the CNS.

2. Evidence from neuroimaging studies

2.1 Functional/pharmacological MRI study in nonhuman primates

Over the past two decades, our group has been working to objectively and safely monitor anti-parkinsonian effects and brain activity modulated by electroacupuncture (EA) in nonhuman primates modeling human PD. We maintained a group of late middle aged rhesus monkeys with long-term (>5 years) mild to moderate parkinsonism rendered by our standard procedures, unilateral administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [13]. This group of parkinsonian rhesus macaques was extensively evaluated by a computerized behavioral testing battery and by phMRI scans [14, 15]. First, stable parkinsonian features were observed in all animals before entering the EA study and all animals showed positive responses to a levodopa (L-dopa) challenge [14]. phMRI activation was then analyzed by our standard procedure. Briefly, while undergoing fMRI scans, animals received a subcutaneous injection of the dopamine agonist, apomorphine (APO). This pharmacological challenge then serves as the basis for assessing the changes in fMRI responses. Second, the phMRI results revealed that compared with the normal, pre-MPTP, status, APO-induced activations were found in all measured ROIs (**Figure 1A and B, Table 1**, described in [14]). The differences between normal and post-MPTP stages in response to the apomorphine challenge were significant ($P < 0.001$), especially in the caudate nucleus, putamen, primary motor cortex

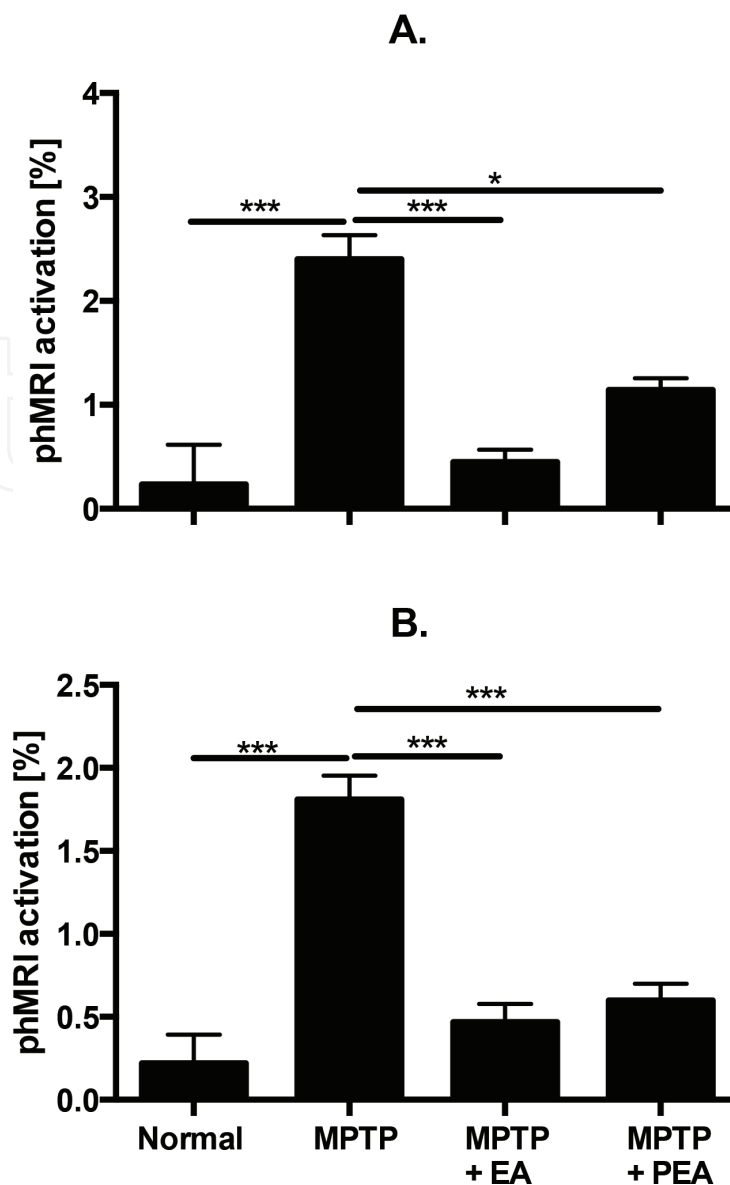
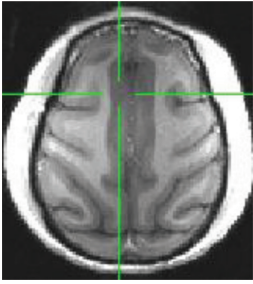
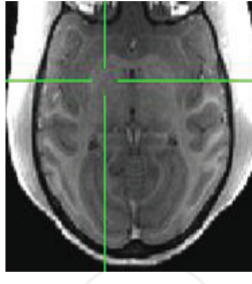
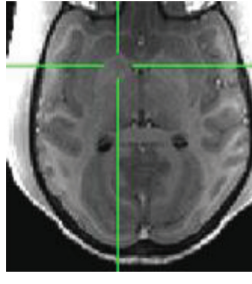


Figure 1. *phMRI activation changes of animals following different treatments. phMRI activation changes of caudate nucleus (A) and putamen (B) following MPTP administration, chronic EA treatment or post EA treatment (from [14]).*

(M1), cingulate gyrus and globus pallidus externa (GPe). In contrast, blood oxygen level dependent (BOLD) responses in the pre-motor areas and the globus pallidus interna (GPi) were not significantly different (**Table 1**). These findings were in line with previous results [16] that APO-induced activations were seen in the striatum after animals became parkinsonian. In addition to those responses described above, APO-induced activations were also observed in the MPTP-lesioned primary motor cortex and cingulate gyrus (**Figure 2** and **Table 1**).

The chronic EA treatment appeared to alter neuronal activities in some examined areas such as the caudate nucleus, putamen, primary motor cortex, cingulate gyrus and GPe in which strong APO-evoked activations were initially observed after MPTP lesions but then were significantly reduced after the EA treatment. In some cases, the BOLD activations nearly returned to the levels seen in the normal (pre-lesion) stage (**Figure 1A** and **B** and **Table 1**). However, the phMRI responses were relatively mild in the pre-motor cortex and GPi (**Table 1**). As shown in **Figures 1** and **2**, the most affected regions were the caudate nucleus and primary motor cortex. For example, the APO-induced activations were reduced more than 5-fold in the caudate nucleus and 4-fold in the primary motor cortex. Interestingly,

	Cingulate	GPe	GPi
ROIs			
Normal	0.74 ± 0.25	-0.27 ± 0.3	-0.16 ± 0.26
MPTP	2.16 ± 0.09 ^a	1.92 ± 0.13 ^a	0.84 ± 0.41
MPTP + EA	0.58 ± 0.23 ^b	0.54 ± 0.19 ^{d,e}	0.44 ± 0.31
MPTP + PEA	0.85 ± 0.11 ^c	0.69 ± 0.09 ^f	1.11 ± 0.14 ^d

GPe, globus pallidus externa; GPi, globus pallidus interna; ROIs, region of interest; EA, electroacupuncture; PEA, post electroacupuncture (from [14]).

^a*P* < 0.001 vs. normal.
^b*P* < 0.001 vs. MPTP.
^c*P* < 0.001 vs. MPTP + EA.
^d*P* < 0.05 vs. normal.
^e*P* < 0.01 vs. MPTP.
^f*P* < 0.05 vs. MPTP + EA.

Table 1.
BOLD-responses in some cortical and subcortical areas.

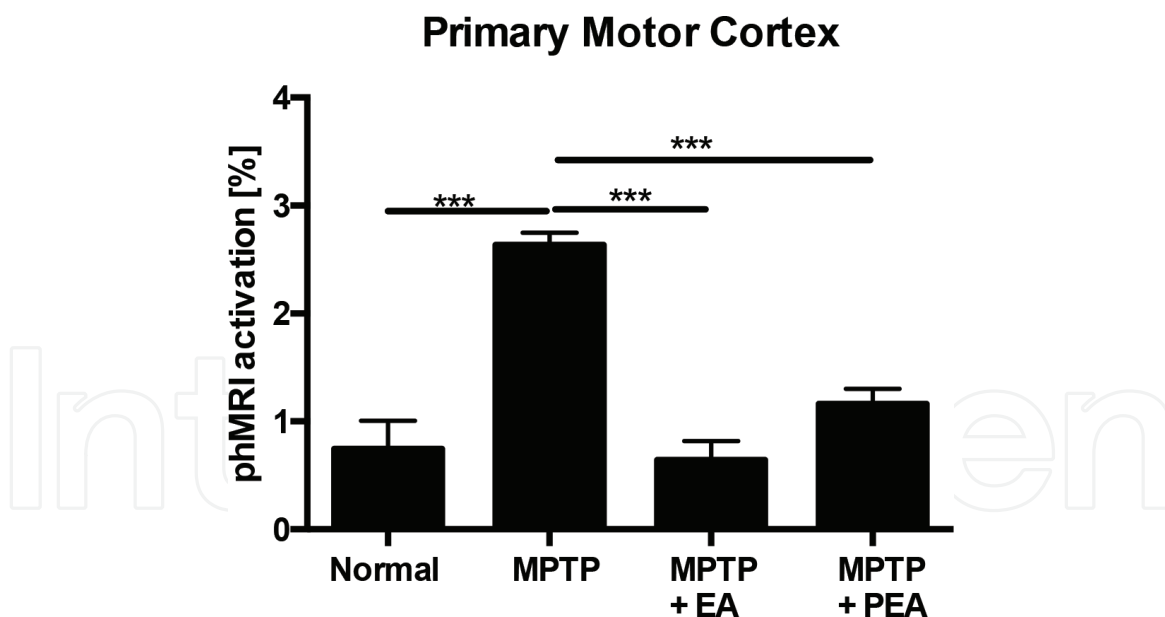


Figure 2.
phMRI activation changes of primary motor cortex following MPTP administration, chronic EA treatment or post EA treatment (adapted from [14]).

residual effects were observed 3 months after the last EA treatment in the caudate nucleus, putamen, primary motor cortex, and cingulate gyrus regions judged by comparing the values of BOLD-activations between MPTP + EA and MPTP + PEA (3 months post EA treatment). A significant difference ($P < 0.05$) between MPTP + EA and MPTP + PEA was also seen in the GPe (**Table 1**). The results strongly suggest that anti-parkinsonian effects of EA can be objectively assessed, and fMRI/phMRI could be readily translated into the clinic with minor modifications.

2.2 Functional MRI studies in humans

In human studies, acupuncture stimulations that directly modulate brain activity can also be observed [17, 18]. An example of this was carried out by Li and colleagues [17] who used fMRI to investigate the potential neuromechanism of acupuncture on tremor in patients with Parkinson's disease. Li and colleagues compared fMRI signals in patients with Parkinson's disease who were either in the true acupuncture group (TAG) or the sham acupuncture group (SAG). Participants received levodopa for 12 weeks and received the study intervention twice weekly. Participants in TAG were acupunctured on DU20, GB20, and the Chorea-Tremor Controlled Zone. Participants in SAG were given sham acupuncture. fMRI scans of the participant's brains were obtained before and after the 12-week period. As shown in **Figure 3**, acupuncture had specific effects on the activity of the cerebrocerebellar pathways as shown by a decrease in regional homogeneity (ReHo)—an indication of a decrease in local/regional activity. Other measures of brain activity, degree centrality (DC), and amplitude low-frequency fluctuation (ALFF) values, also showed decreases after acupuncture compared to sham. Meanwhile, increased ReHo values were observed within the thalamus and motor cortex [17]. The results of this clinical study demonstrate that functional imaging can directly detect and measure acupuncture-induced brain activities even at the level of the neural network.

In a separate clinic study to examine the underlying mechanisms of acupuncture in patients with major depressive disorders, Wang et al. [19] investigated the resting state functional connectivity (rsFC) in the left and right amygdala before and after verum acupuncture plus the antidepressant fluoxetine versus sham acupuncture plus fluoxetine. Resting-state fMRI data was collected before the first and last treatments. Participants received the study intervention for 8 weeks. Verum acupuncture treatment participants showed (1) greater clinical improvement than sham participants based on the depression rating scales; (2) increased rsFC between the left amygdala and subgenual anterior

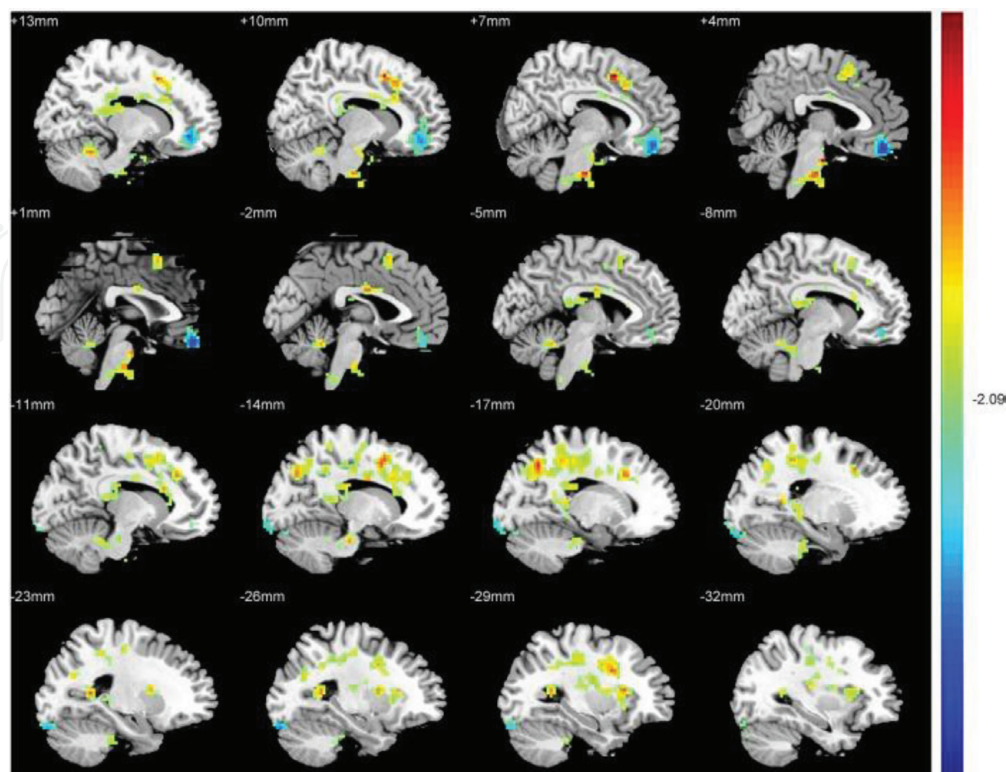


Figure 3. Differences in ReHo values between the TAG and SAG. ($P < 0.05$, AlphaSim corrected). Warm colors represent positive ReHo values; blue (cold) colors represent negative ReHo values (from [17]).

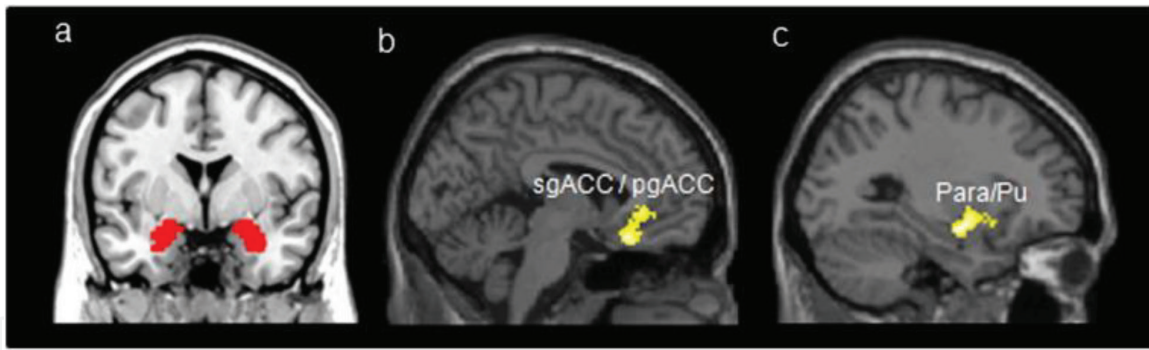


Figure 4. Amygdala seed locations and brain regions with significant changes (post minus pre) of rsFC with the amygdala (a) modulated by the verum acupuncture plus fluoxetine compared with sham acupuncture plus fluoxetine treatment in the left sgACC/pgACC (b) and left Para/Pu (c). Abbreviations: sgACC, subgenual anterior cingulate cortex; pgACC, pregenual anterior cingulate cortex; Para, parahippocampus; Pu, putamen (from [19]).

cingulate cortex (sgACC)/pregenual anterior cingulate cortex (pgACC); (3) increased rsFC between the right amygdala and left parahippocampus/putamen. And finally, the strength of the amygdala-sgACC/pgACC rsFC was positively associated with a corresponding clinical improvement (**Figure 4**). Their findings show the additive effect of acupuncture to antidepressant treatment and suggest that this effect may be achieved through the limbic system, especially the amygdala and the ACC [19].

3. Evidence from electrochemical studies

In the brain, glutamatergic transmission plays a key role in the normal physiology of those systems that modulate motor activity (especially in the basal ganglia). In Parkinson's disease, glutamatergic transmission is considerably affected particularly in the direct and indirect nigrostriatal pathways, which are known to involve glutamatergic hyperactivity. The glutamatergic hyperactive pattern, through a dual role, may exacerbate PD by first promoting excitotoxic events that contribute to the neurodegenerative process and, secondly, by contributing to the pathophysiology of dyskinesias and motor fluctuations that are associated with the chronic use of levodopa [20]. Since excitotoxicity is a glutamate-receptor-mediated phenomenon, growing interest and work have been dedicated to the research for modulators of glutamate neurotransmission that might enable new therapeutic interventions to slow the neurodegenerative process and ameliorate PD symptoms.

To explore the role of glutamate excitotoxicity in both acupuncture and pathogenesis of PD, we designed a study to address the question of whether changes in cortical glutamate levels were one of the underlying mechanisms of EA (previously unpublished results). Based on human acupuncture studies in patients with PD, we trained two rhesus monkeys with mild but stable parkinsonian features (MPTP-induced) including bradykinesia, rigidity on the affected upper and lower limbs. In addition, stooped posture and mild postural instability were also evident [13]. Then, these animals were treated with chronic (intermittent) EA treatments (3 session/week/4 months) at acupoints ST 36, GB34, or LI 4 (**Figure 5**). Subsequently, they were also studied for behavioral changes by a non-biased, computerized testing battery. Results demonstrated that EA significantly improved motor functions measured by increased movement speed after a 4-month EA treatment (data now shown). Following the last EA treatment and behavioral tests, animals were anesthetized and resting levels of L-glutamate were measured in the primary motor areas (upper body) by enzyme-based biosensors [21] with acute EA stimulation at GV14 + EX-B9 or GV14 + ST 36 or LI 4 on both sides, or GV14 + non-acupoints (**Figure 5**). EA-induced

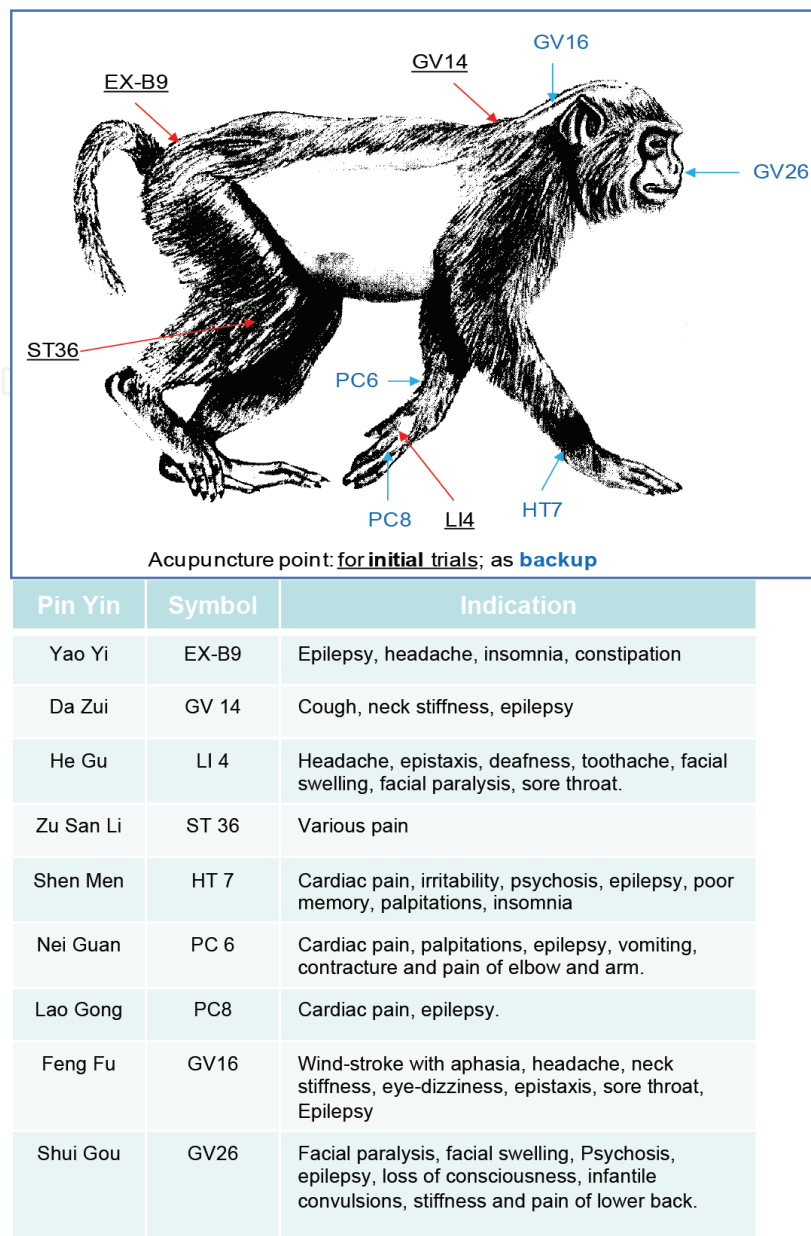


Figure 5.
 Acupuncture points used in the study.

changes in cortical glutamate could be recorded in real time (2 Hz) with glutamate-sensitive biosensors (**Figure 6A**). The EA treatments of GV14 + EX-B9, or GV14 + ST 36 significantly decreased basal levels of glutamate in the primary motor cortex on the hemisphere contralateral to the MPTP-lesion immediately after the stimulator was turned on and returned to baseline levels after it was turned off. By contrast, stimulation of GV14 and a non-acupuncture point produced no fluctuation in basal glutamate activity (**Figure 6B**). These results support the idea that EA can produce transient effects on cortical levels of glutamate that could be a means of providing a potential therapy for PD.

Acupuncture can alter extracellular glutamate as seen in our pilot nonhuman primate study and those results are supported by acupuncture studies in rodents. Lee et al. reported that acupuncture can attenuate extracellular glutamate levels in a global ischemia model in rat. In the study, the authors found that acupuncture at GB34 and GB39 significantly suppressed glutamate function compared to control animals [22]. Later, Kim et al. demonstrated that acupuncture at HT7 can inhibit methamphetamine-induced behaviors, dopamine release and hyperthermia in the nucleus accumbens through the group II metabotropic glutamate receptors [23].

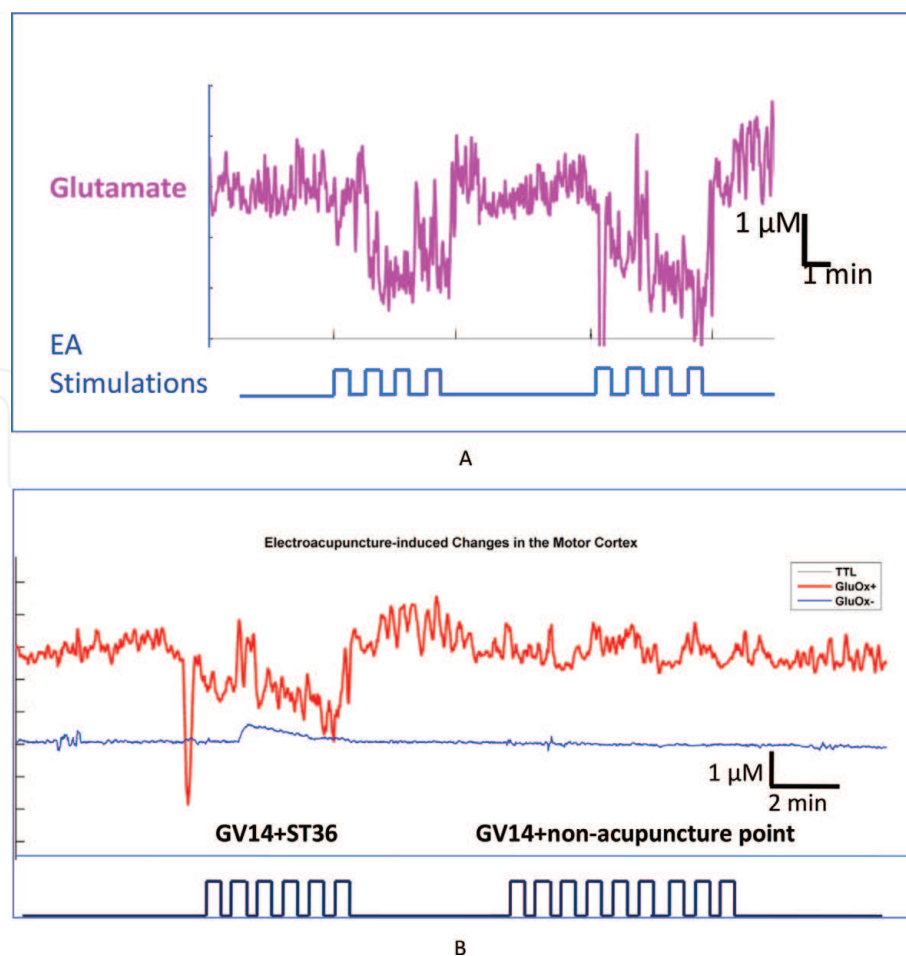


Figure 6.

(A) Real-time measurements of the basal glutamate change in the motor cortex with and without acupuncture stimulations. Glutamate changes in the unlesioned motor cortex produced by EA stimulation at GV14 + ST36 (right side). Glutamate biosensors were used to measure glutamate levels. One biosensor recording site is coated with glutamate oxidase and capable of detecting glutamate a reference biosensor recording site lacking glutamate oxidase and incapable of detecting glutamate is used to subtract interfering agents. (B) Real-time measurement of the basal glutamate changes in the motor cortex with and without acupuncture stimulations. Glutamate changes in the unlesioned motor cortex produced by EA stimulation at GV14 + ST36 (right side) and GV14 + nonacupuncture points. TTL: transistor-transistor logic (event marker). GluOx+ (biosensor recording site coated with glutamate oxidase and capable of detecting glutamate), GluOx- (biosensor recording site lacking glutamate oxidase and incapable of detecting glutamate). Note the stimulation induced artifact in the reference channel (GluOx- recording site) during the course of stimulation that subsides when EA stimulation is terminated. Zoomed inset of **Figure 6A**.

4. Evidence from objective behavioral testing

4.1 Objective behavioral testing in preclinical studies

For years, our group has been developing testing methods to objectively measure behavioral changes before and after intermittent EA treatments in parkinsonian monkeys. Recently, we reported that EA-induced improvement of parkinsonism in rhesus macaques can be effectively measured using a non-biased, non-invasive and computerized behavioral testing battery [14]. The battery primarily includes a videotracking system to measure movement speed, an Actical accelerometer to monitor home-cage activity 24 h a day, 7 days a week, and an upper limb movement analysis panel to measure a subject retrieval time [14, 24]. As shown in **Figure 7**, significantly decreased movement speed (A), and home cage activity (B), and longer performance time of the affected hand (C) were found following MPTP administration. The movement speed and fine motor performance time were markedly

improved with chronic EA treatment (**Figure 7A and C**), and movement speed and fine motor performance times virtually returned to pre-MPTP levels. The cage activity was increased but did not reach statistically significant levels because of large variance (**Figure 7B**). Meanwhile, the fine motor performance time was still

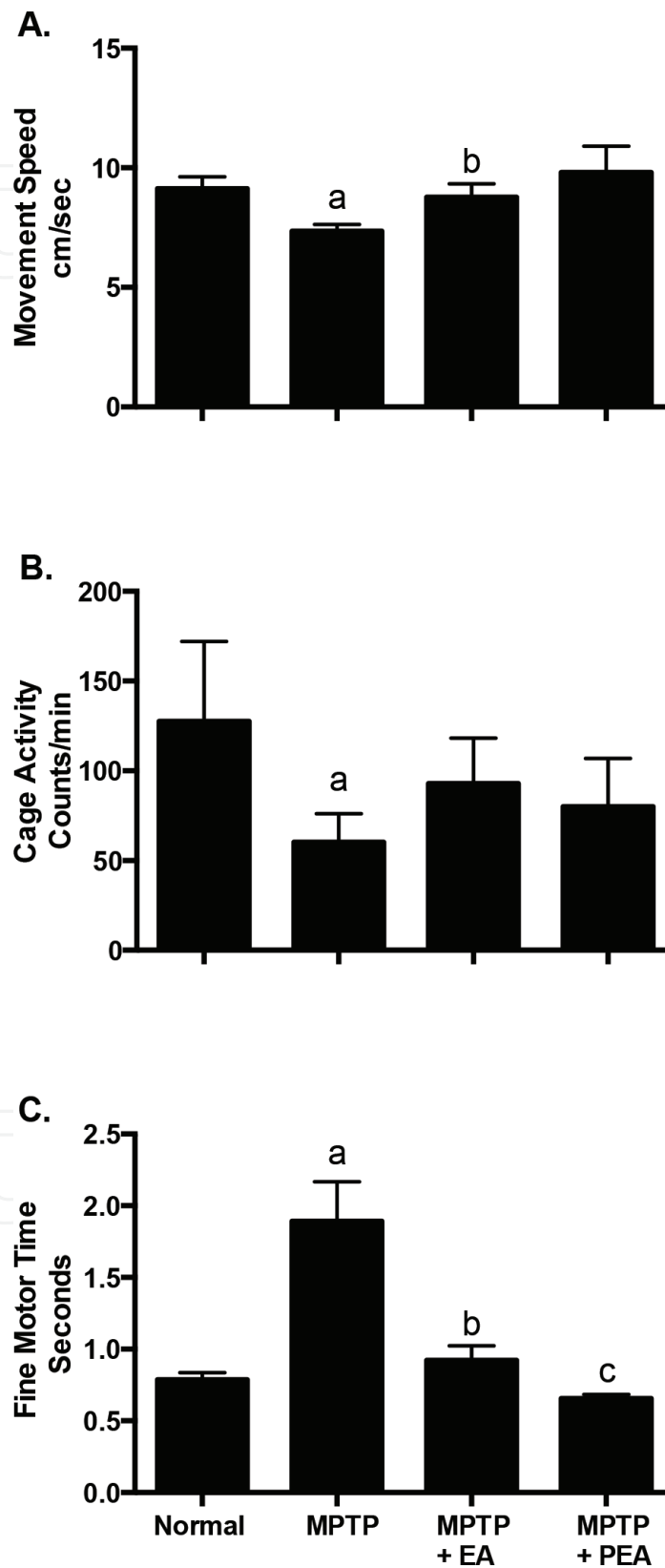


Figure 7. Behavior changes of animals following different treatments. Movement speed (A), home cage activity (B) and fine motor performance time changes (C) following MPTP administration, chronic EA treatment or post EA treatment (at least 1 months after last EA treatment). (a) $P < 0.05$ compared with normal; (b) $P < 0.05$ compared with MPTP; (c) $P < 0.05$ compared with MPTP + EA (from [14]).

improving one-month post EA treatment (**Figure 7C**). In addition, all animals responded positively to levodopa challenge evident by a 261% increase of home-cage activity measured via Actical counts.

4.2 Objective behavioral testing in clinical studies

In the acupuncture clinic, objective assessments using novel computerized technologies are drawing more attention. Lei and colleagues used body-worn sensor technology in patients with PD to measure a variety of gait parameters [3]. The authors found that EA improved gait function and achieved statistically significant improvements in gait speed under a variety of walking tasks including single-task habitual walking, single-task fast walking, and dual-task fast walking. No significant changes were observed in the control group. Meanwhile, gait improvements were correlated with the activities of daily living component of the Unified Parkinson's Disease Rating Scale (UPDRS). This study further indicates that the effectiveness of EA treatment can be objectively measured and while still used with traditional instruments such as the UPDRS.

5. Summary

Current evidence shows that EA generates measurable changes in the brain that are detectable with functional imaging, behavioral responses, and neurotransmitter signaling. The results from nonhuman primates also provides direct evidence between EA stimulations and dynamic alterations in the resting levels of glutamate in the motor cortex, which may at least partially explain a mechanism of action for EA in the nervous system. Nevertheless, we are only at beginning of a quest to better understand the mechanism of action that underlie acupuncture. The few studies with limited number of subjects will have to expand if we are to understand how acupuncture affects the central nervous system.

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