

## Transcutaneous Auricular Vagus Nerve Stimulation: A Novel Non-Invasive Non-Pharmacologic Treatment for Major Depressive Disorder

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### Abstract

USFDA formally approved Vagus Nerve Stimulation (VNS) as an adjunct therapy for treatment-resistant depression in 2005. High expense and possible post-op infection is the obstacle of VNS promotion. Previously, our studies revealed that the concha region is the only superficial region of vagus nerve in mammals. Whether concha region stimulation (Transcutaneous auricular vagus nerve stimulation, taVNS) can reach similar effect in reducing depression as classic VNS? We have been carrying out animal experiments and clinical trials to verify it. These studies have been revealing that taVNS is a novel safe and low-cost non-invasive non-pharmacologic efficacy-guaranteed treatment for major depressive disorder.

**Keywords:** Transcutaneous auricular vagus nerve stimulation (taVNS); Major depressive disorder (MDD); Auricular concha; Acupuncture

### Introduction

Major depressive disorder (MDD) is a devastating and unremitting problem, which causes high rates of disability and becomes a heavy burden to both patients and society, and is projected to become the second leading cause of disability worldwide by the year 2020 [1]. Despite the urgent need, current pharmacologic treatment for this disorder is far from satisfaction due to high nonresponse rates to treatments, high relapse rates, and frequent intolerable side effects [2]. What's more, women during pregnancy and lactation should avoid some antidepressants for potential hazard for fetus or infants [3,4]. And professional athletes with anxiety attack would fail in analeptic inspection if taking antidepressants [5]. Non-pharmacologic treatments for these problems are urgently needed.

Vagus nerve stimulation (VNS) has been approved by FDA as a somatic treatment for treatment-resistant depression in 2005 [6,7]. However, some factors limited the treatment to patients, including high cost, the involvement of surgery, perioperative risks, and potentially significant side effects [8].

Auricular acupuncture inspired us to develop transcutaneous auricular vagus nerve stimulation (taVNS) years ago. Auricular



Figure 2: Ear pins for that cured Princess Diana's stress.

acupuncture (Figure 1) is a very important part of Traditional Chinese Medicine (TCM) [9]. Since the ancient time, Chinese doctors have been using auricular acupuncture to treat a wide range of diseases, including insomnia, depression and anxiety etc. [10]. Princess Diana used to take ear pins in order to relieve her stress (Figure 2).

Also, based on anatomical studies which suggest that the ear is the only place on the surface of human bodies where there is afferent vagus nerve distribution [11,12], especially in the auricular concha (Figure 3) [13], a direct stimulation of these afferent nerve fibers on ear supposes to have similar effect to classic VNS in reducing depressive symptoms without surgical intervention (Figure 4) [14].

In order to verify the hypothesis and find out the mechanism of taVNS for the treatment of MDD, our team took out the following animal experiments and clinical studies. We invented electrical stimulator with ear clips for both rodent and human to stimulate the ear concha safely non-invasively.

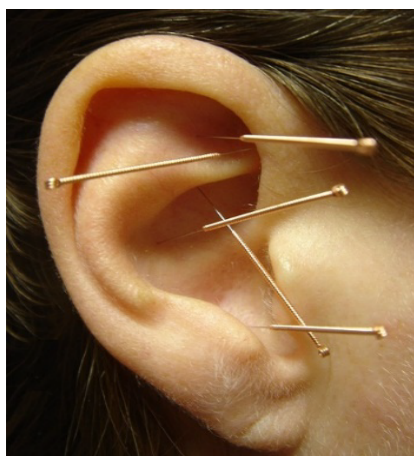


Figure 1: Auricular acupuncture.

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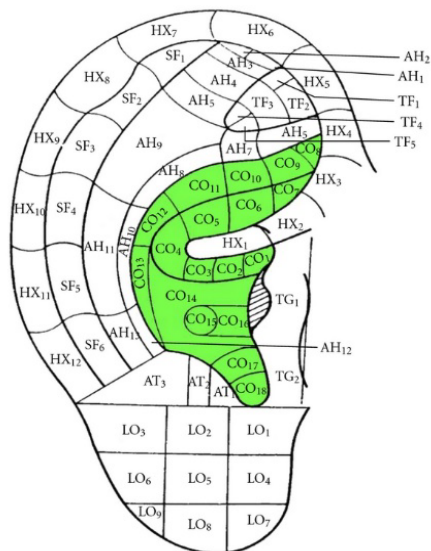
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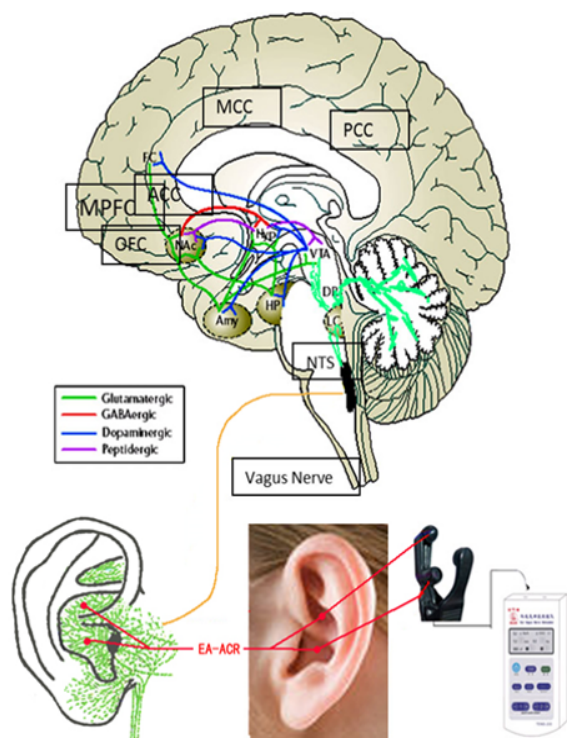
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## Animal Experiments

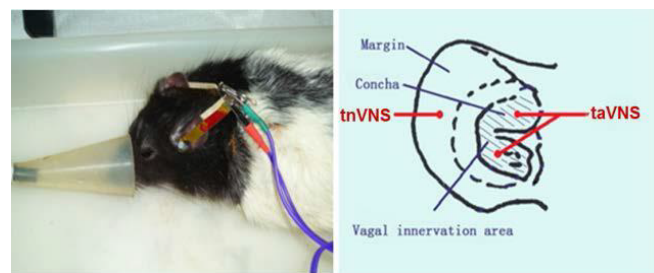
Depression rat models were established by chronic unpredictable mild stress (CUMS). We compared behavior changes of depressive rats by auricular concha region (transcutaneous auricular VNS, taVNS) or ear tip (no distribution of vagus nerve, as transcutaneous none VNS, tnVNS) under electro-stimulation. We found out that electro-stimulated auricular concha can slow down the development of



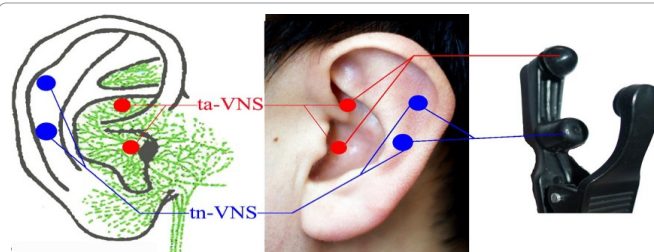
**Figure 3:** Auricular concha is the main area where the auricular vagus nerve distributed.



**Figure 4:** taVNS has the same pathways with classic VNS on the neural circuitry of mood.



**Figure 5:** taVNS and tnVNS in rats.



**Figure 6:** taVNS and tnVNS in humans.

depression behavioral status in depressive rats better than stimulated ear-tip, the none vagus nerve distribution area [15] (Figure 5). Electro-stimulated auricular conchae can also down regulated levels of plasma cortisol and ACTH elevated by CUMS. TaVNS helps relieved depression is possibly mediated via regulation of hypothalamic-pituitary-adrenal (HPA) axis hyperactivity [16].

To observe TaVNS for innate depression. We choose Zucker diabetic fatty (ZDF, fa/fa) rats, which develop depression-like behaviors. TaVNS helped relieved depression in ZDF rats, possibly through IR expression upregulation [17] and triggering melatonin secretion [18].

## Clinical Studies

160 cases of volunteers with mild to moderate depression were enrolled in a nonrandomized, controlled clinical trial. The first cohort of patients (n = 91) only received transcutaneous auricular VNS (taVNS) for 12 weeks. In the second cohort (n = 69), patients first received 4 weeks of transcutaneous none VNS (tnVNS) followed by 8 weeks of taVNS (Figure 6). The results suggest that taVNS is a promising, safe, and cost-effective therapeutic method for mild to moderate MDD [19].

49 MDD patients were recruited with 34 patients completed in another nonrandomized, controlled clinical trial. After 1 month of taVNS treatment, compared with the tnVNS group, the 24-item Hamilton Depression Rating Scale score reduced significantly in the taVNS group. The functional connectivity (FC) between the default mode network (DMN) and anterior insula and parahippocampus decreased; the FC between the DMN and precuneus and orbital prefrontal cortex increased compared with tnVNS. All these FC increases are also associated with 24-item Hamilton Depression Rating Scale reduction. Overall, taVNS can significantly modulate the DMN FC of MDD patients [20].

More studies are in process. For instance, we are exploring the mechanism of taVNS in the fields of metabolism in chronic stressed adult male rats (Chinese Postdoctoral Science Foundation: 2016M590185). Previously, we also proposed that P2 receptors (in particular the P2Y<sub>1</sub> receptor subtype), which recognize extracellular ATP and ADP, are

involved in the pathophysiology of major depression, thus they may play a critical role in the mediation of the antidepressive effects of acupuncture (Joint Sino-German Research Project: GZ1236). We are focusing studying the role of P2Y<sub>1</sub> receptors in depression syndrome, and in the antidepressive effects of transcutaneous auricular vagus nerve stimulation (taVNS) in different animal models. In clinical studies, we are looking for neural biomarkers of transcutaneous auricular vagus nerve stimulation (taVNS) treatment success in depression (Natural Science Foundation of Beijing: No. 7111007) etc.

In order to overcome the disadvantages of both antidepressants and classic vagus nerve stimulation (VNS) for major depressive disorder (MDD), we developed transcutaneous auricular vagus nerve stimulation (taVNS). Both animal experiments and clinical trials have been taking out to test its efficacy. Briefly speaking, taVNS, a novel non-invasive non-pharmacologic treatment for MDD, is a safe and low-cost method to relieve depression significantly. These studies also show a bright prospect of taVNS in other mental disorders. Further studies should be carried out to confirm it.

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