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Research paper

Transcutaneous vagus nerve stimulation modulates amygdala functional connectivity in patients with depression

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ABSTRACT

Background: The amygdala is a key region in emotion processing, and studies have suggested that amygdala-frontal functional connectivity deficits could be modulated by antidepressants in major depressive disorder (MDD). Transcutaneous vagus nerve stimulation (tVNS), a non-invasive, peripheral neuromodulation method at the ear, has shown promising results in treating major depressive disorder (MDD) in several pilot studies. However, the neural mechanism underlying tVNS treatment of depression has not been fully investigated. In this study, we investigated how tVNS can modulate the amygdala-lateral prefrontal network resting state functional connectivity (rsFC) in mild or moderate major depressive disorder (MDD) patients.

Methods: Forty-nine MDD patients were recruited and received tVNS or sham tVNS (stVNS) treatments for four weeks. Resting state fMRI scans were applied before and after treatments.

Results: After 1 month of tVNS treatment, the 24-item Hamilton Depression Rating Scale (HAMD) scores were reduced significantly in the tVNS group as compared with the sham tVNS group. The rsFC in the tVNS group between the right amygdala and left dorsolateral prefrontal cortex was increased compared with sham tVNS. All the rsFC increases were also associated with HAMD reduction as well as reductions in the anxiety and retardation HAMD subscales.

Conclusions: tVNS can significantly modulate the amygdala-lateral prefrontal rsFC of MDD patients; our results provide insights into the brain mechanism of tVNS treatment for MDD patients.

1. Introduction

Major depressive disorder (MDD) has a high lifetime prevalence rate and is the fourth leading cause of disability worldwide (Sackeim et al., 2001). It affects a large proportion of the population by significantly impairing their occupational, social, and academic functioning (Johnson et al., 1992; Lehtinen and Joukamaa, 1994). Nevertheless, the current treatments for this disorder are far from satisfactory (Rush et al., 2003). Vagus nerve stimulation (VNS) is a Food and Drug Administration (FDA) approved method for treatment-resistant MDD in the U.S. However, the application of the method is limited by the involvement of surgery and potential side effects.

Transcutaneous vagus nerve stimulation (tVNS), a variant of traditional VNS, has on the other hand drawn the attention of researchers in recent years. As a non-invasive and low cost neural modulation method (Daban et al., 2008; Fang et al., 2014; Nemeroff et al., 2006), it has been widely applied to treat disorders such as MDD (Fang et al., 2016; Hein et al., 2013; Rong et al., 2016), epilepsy (Rong et al., 2014; Stefan et al., 2012), and prediabetes (Huang et al., 2014). The rationale of tVNS is based on an anatomical study that found that there is vagus nerve innervation (Henry, 2002; Peuker and Filler, 2002) on the surface of the ear; thus, similar effects as VNS may be achieved by superficially stimulating this area.

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Recent studies also found that both classic VNS and tVNS can affect similar brain networks (Conway et al., 2006; Dietrich et al., 2008; Frangos et al., 2015; Hein et al., 2013; Kosel et al., 2011; Kraus et al., 2007; Rush et al., 2005), including activation and deactivation across the orbitofrontal cortex, superior and medial frontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, temporal cortex, parietal area, amygdala and nucleus accumbens. These regions have been shown to be involved in emotion regulation, self-representation, reward, and external stimulus (stress, distress) interactions (Davidson et al., 2002; Grimm et al., 2008; Hasler and Northoff, 2011; Jessica S. Damoiseaux and Greicius, 2009; Mwangi et al., 2012; Pizzagalli, 2011; Rong et al., 2012; Silbersweig, 2013).

Among them, the amygdala is one of the most well-studied regions in MDD (Cullen et al., 2014; Tahmasian et al., 2013). As part of the limbic system, it has been shown to play an important role in emotional processing, fear and motivation (Mears and Pollard, 2016). Imaging studies found that compared with healthy controls, MDD patients showed abnormal activation patterns during negative stimuli (Sheline et al., 2001; Siegle, Thompson et al., 2007). For example, studies found that relative to healthy controls, MDD patients showed elevated activity in the amygdala and diminished activity in the prefrontal cortex when presented with negative stimuli (Phillips et al., 2015; Sheline et al., 2001; Siegle et al., 2002; Siegle et al., 2007). In a more recent meta-analysis, Ma (2015) found that antidepressant medication in treating patients with depression and other mood disorders affects the activity of the core emotional processing circuitry. Specifically, antidepressants increased activity in the dorsolateral prefrontal cortex (DLPFC) during both negative and positive emotional activity in patients.

In recent decades, resting-state functional connectivity (rsFC) analysis has been widely used in MDD research. rsFC measures the temporal dependency of neuronal activation patterns between anatomically separated brain regions during rest (Biswal et al., 1995), which allows us to probe the functional correlation of one brain region with other brain regions in terms of networks and explore how brain regions subserve common neural procedures (Jessica S. Damoiseaux and Greicius, 2009). Previous studies have revealed abnormal rsFC in patients with depression between the amygdala and parts of the frontal cortex, such as the ventral prefrontal cortex (Tang et al., 2013) and orbitofrontal cortex (Cullen et al., 2014). Additionally, studies also showed that antidepressant treatments can normalize rsFC between the amygdala and the anterior cingulate cortex (Anand et al., 2007) as well as task-based functional connectivity between the amygdala and prefrontal cortex (Chen et al., 2008).

In this study, we investigated the modulation effects of tVNS on rsFC in MDD patients. Previous studies (Cullen et al., 2014; Pannekoek et al., 2014; Tang et al., 2013) showed that the amygdala-frontal rsFC was aberrant in depression and was related to overall depression severity. We thus hypothesized that tVNS would significantly modulate the rsFC of the amygdala-frontal network in adults with MDD.

2. Materials and methods

Here we provide a brief description of the methods and focus on the procedures and analysis details relevant for this study. The full details of the study are reported elsewhere (Fang et al., 2016; Rong et al., 2016). In our previous study, we reported how tVNS modulates the resting state functional connectivity of the default network using independent component analysis (Fang et al., 2016). In this manuscript, we focus on how tVNS modulates the resting state functional connectivity of the extended amygdala network using a seed-to-whole-brain method, the results of which have never been reported.

2.1. Participants

The Institutional Ethics Committee of the China Academy of Chinese Medical Sciences approved this study. All patients were recruited using advertisements and by sending flyers to the four hospitals involved in the study. Forty-nine patients with mild or moderate MDD were recruited for the trial. ICD-10 classification of mental and behavioral disorders was used for diagnosis of MDD. Patients who voluntarily provided informed consent and met inclusion/exclusion criteria were enrolled in this study.

Inclusion criteria: 1) Meets ICD-10 diagnosis standard of a depressive episode: mild (2 typical +2 other core symptoms), moderate (2 typical +3 other core symptoms); 2) 18–70 years of age; 3) Ceased taking anti-depressive or other psychiatric medications 2 weeks before beginning the intervention; 4) Junior high or higher level education (in order to understand the scales); 5) Exhibited symptoms for 2 weeks to 2 years.

Exclusion criteria: 1) Ongoing addiction to drugs and alcohol; 2) Bipolar disorder; 3) Organic mental disorder; 4) Drug-induced depression; 5) Seasonal affective disorder; 6) Severe medical disorders; 7) Pregnant women; 8) Postpartum depression; 9) Dementia or other cognitive disorders; 10) Patients who did not agree to sign the consent form.

2.2. Procedures

Due to safety and ethical concerns and to increase the homogeneity of the study, we decided to include only patients with mild or moderate depressive symptoms. We used a single-blinded clinical trial to investigate the antidepressant effects of solo tVNS treatment. Since the patients had tVNS as their only treatment, the first cohort all received tVNS for 12 weeks. After demonstrating the effect of tVNS, we recruited a second cohort of patients who received four weeks of sham tVNS before shifting to real tVNS for 8 weeks. The fMRI scans were applied at the beginning and after 4 weeks of treatment. In this manuscript, we compared clinical outcomes and resting state functional connectivity changes between the real tVNS and sham tVNS groups during baseline and the initial four weeks of each treatment, in which the real tVNS cohort received tVNS and the sham tVNS cohort received sham tVNS. Please see Fang et al. (2016) and Rong et al. (2016) for more details of the overall experimental design.

2.3. Intervention

After screening, all patients were trained to apply tVNS or sham tVNS. All subsequent treatments were self-administered by the patients at home. Patients were also instructed to complete a patient diary booklet each day to describe any side effects corresponding with or temporally related to treatment. The investigators checked all booklets at the end of the 4-week treatment. All procedures performed in the sham tVNS treatment group were identical to the procedures for the real tVNS group.

2.4. tVNS

Location: The points for tVNS are located in the auricular concha area where there is rich vagus nerve distribution (Fig. 1). tVNS was applied on the concha area of both ears simultaneously during the treatment.

Intervention procedure: Patients took a seated position or lay on their side. After the stimulation points were disinfected according to standard practice, ear clips were attached to the ear area (auricular concha) at the stimulation site. Stimulation