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ORIGINAL ARTICLE

Mapping the modulating effect of transcutaneous auricular vagus nerve stimulation on voxel-based analyses in patients with first-episode major depressive disorder: a resting-state functional magnetic resonance imaging study

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Introduction: Seed-based analysis has shown that transcutaneous auricular vagus nerve stimulation (taVNS) can modulate the dysfunctional brain network in patients with major depressive disorder (MDD). However, the voxel-based neuropsychological mechanism of taVNS on patients with first-episode MDD is poorly understood. The objective of this study was to assess the effects of an 8-week course of taVNS on patients with first-episode MDD.
Methods: Twenty-two patients with first-episode MDD accepted an 8-week course of taVNS treatment. Resting-state functional magnetic resonance imaging (rs-fMRI) scans were performed before and after treatment. Voxel-based analyses were performed to characterize spontaneous brain activity. Healthy controls (n=23) were recruited to minimize test-retest effects. Analysis of covariance (ANCOVA) was performed to ascertain treatment-related changes. Then, correlations between changes in brain activity and the Hamilton Depression Rating Scale (HAM-D)/Hamilton Anxiety Scale (HAM-A) remission rate were estimated.
Results: Significant group-by-time interactions on voxel-based analyses were observed in the inferior ventral striatum (VSi) and precuneus. Post-hoc analyses showed that taVNS inhibited higher brain activity in the VSi, while upregulating it in the precuneus. Functional connectivity (FC) between the VSi and precuneus decreased. Positive correlations were found between the HAM-D remission rate and changes in brain activity in the VSi.
Conclusion: taVNS reduced the FC between VSi and precuneus by normalizing the abnormal spontaneous brain activity of VSi in first-episode MDD patients.

Keywords: Non-invasive neuromodulation; taVNS; reward processing; major depressive disorder; resting-state fMRI; ventral striatum

Introduction

Major depressive disorder (MDD) severely limits psychosocial functioning and diminishes quality of life. Transcutaneous auricular vagus nerve stimulation (taVNS) is a very promising noninvasive method for treating psychological disorders. As with invasive vagus nerve stimulation, peripheral stimulating information aroused by taVNS is conveyed into the central nervous system through the solitary tract nucleus and then affects the extensive neural circuits influenced by norepinephrinergic, serotonergic, and dopaminergic neurons.[1-3] Studies have shown that taVNS significantly improves depressive symptoms as compared with a sham procedure.[4,5] An electroencephalogram (EEG) study found that both invasive vagus nerve stimulation and taVNS caused evoked changes in activity across a set of highly distributed cortical networks that are relevant to a diverse array of clinical, rehabilitative, and enhancement applications.[6] Functional magnetic resonance imaging (fMRI) studies have revealed that, in

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healthy subjects, instant taVNS induces increased blood-oxygen-level-dependent (BOLD) signals in the right caudate, bilateral anterior cingulate, cerebellum, left prefrontal cortex, insula, precentral gyrus, and thalamus, while decreasing BOLD signals in the amygdala, hippocampus, parahippocampal gyrus, and temporal gyrus.[7] Mapping the modulating effect of taVNS on MDD patients at the level of neural disturbances would benefit translation of taVNS into clinical use.

The neural disturbances of MDD converge in many limbic-cortical circuits.[8] Namely, cognitive biases in depression are facilitated by aberrant influence from subcortical emotion processing, combined with attenuated top-down regulation.[9] In support of this, a meta-analysis of positron emission tomography (PET) studies found altered metabolism in the insula, limbic system, basal ganglia, thalamus, and cerebellum in MDD patients.[10] An earlier meta-analysis also confirmed a convergent change in the limbic-cortical brain circuit both in PET and fMRI datasets of MDD patients.[11] According to the limbic-cortical dysregulation model, seed-to-voxel functional connectivity (FC) analysis has found that taVNS can modulate some pathological regions in MDD patients.[12-17] However, a recent study revealed that antidepressants can induce permanent changes on intrinsic FC.[18] Existing studies have included patients both with first-episode and with recurrent MDD. In addition to heterogeneity in patient enrollment, FC analysis requires a preset region of interest (ROI) according to prior knowledge. In contrast, voxel-based analysis screens a certain brain region, commonly the whole brain, to find the most significant changes through rigorous statistical analysis. The most popular voxel-based analyses are amplitude of low-frequency fluctuation (ALFF),[19] used for estimating local neural activity by time-frequency transformation; regional homogeneity (ReHo),[20] which evaluates the homogeneity of a given voxel with its nearest neighbors; and functional centrality degree (FCD), a theoretical graphic approach to show a voxel's FC degree centrality.[21] Standard data preprocessing and strict statistical correction are critical to validate whether the results are robust.

Recently, an increasing number of studies have revealed similar neural disturbances to those found on PET imaging in MDD patients, but using voxel-based analyses. For example, one study found that MDD patients with non-suicidal self-injury showed higher ALFF in the right lingual gyrus and right middle occipital gyrus, and lower ALFF in the right superior frontal gyrus.[22] Another study found that MDD patients exhibited increased ReHo in the left hippocampus and decreased ReHo in the left orbitofrontal cortex.[23] Moreover, using voxel-based analyses, changes in brain activity in some regions implicated in the pathology of neurological and psychiatric disorders have been correlated with therapeutic effects.[24,25] However, few studies have employed voxel-based analysis to map the modulating effect of taVNS.

In the present study, patients with first-episode MDD were offered an 8-week course of taVNS and underwent two fMRI scans, before and after treatment. Different voxel-based analyses were employed to map the modulating effect of taVNS on these patients. Age- and gender-matched healthy controls (HCs) were recruited at the same time to minimize test-retest effects.

Methods

Participants

As shown in Figure 1, 28 patients were recruited in the taVNS group. Two experienced psychiatrists conducted a clinical interview to collect clinical information. Patients were diagnosed as having first-episode MDD according to the Structured Clinical Interview of the DSM-V.[26] Patients with comorbid Axis I disorders (except for anxiety disorders) were excluded, as were those with Axis II personality disorders or intellectual disability. The inclusion criteria were: 1) a diagnosis consistent with DSM-V diagnostic criteria for mild-to-moderate depression; 2) age 18 to 65 years; 3) right-handedness; and 4) a Hamilton Depression Rating Scale (HAM-D) score between 8 and 24. The exclusion criteria were: 1) meeting diagnostic criteria for any psychiatric disease other than depression; 2) history of any neurological diseases or serious systemic diseases; 3) history of serious suicidal ideation or suicidal behavior; and 4) any contraindications to fMRI scanning. By week 8, 22 patients had completed two sessions of fMRI scans (at 0 and 8 weeks). The 17-item HAM-D and 14-item Hamilton Anxiety Scale (HAM-A14) were assessed at the same time. Twenty-three age, gender, and education-matched HCs were recruited from the local community. All of the HCs had a HAM-D or HAM-A score less than 7. They declared no recent experience of depression (within 6 months before or during the study), had no history of a psychiatric disorder in their first-degree relatives, and had no history of use of psychotropic medications. HCs with any substance dependence or abuse and acutely suicidal were also excluded. The HC group completed the same fMRI scans but did not receive taVNS during the 8 weeks.

Transcutaneous auricular vagus nerve stimulation (taVNS) treatment

The stimulation areas of the taVNS were located on both sides of the cymba conchae (Figure 2). The stimulation parameters were consistent with our previous studies.[4,12,14-16] In brief, the dilatational wave was adjusted to 4/20 Hz with a wave width of less than 1 ms, and the intensity was adjusted based on the tolerance of the patient (tingling but no pain sensation caused by the slight electric current). Each treatment lasted 30 minutes and was carried out twice a day (i.e., once in the morning and once again in the evening), at least 5 days per week, for the duration of the treatment period (8 weeks). The patients were also instructed to record any side effects of treatment in a diary.

Magnetic resonance imaging (MRI) data acquisition

rs-fMRI scans were performed with a Siemens 3.0T Skyra MRI scanner (Siemens; Munich, Germany). A standard birdcage with a 32-channel head coil, along with

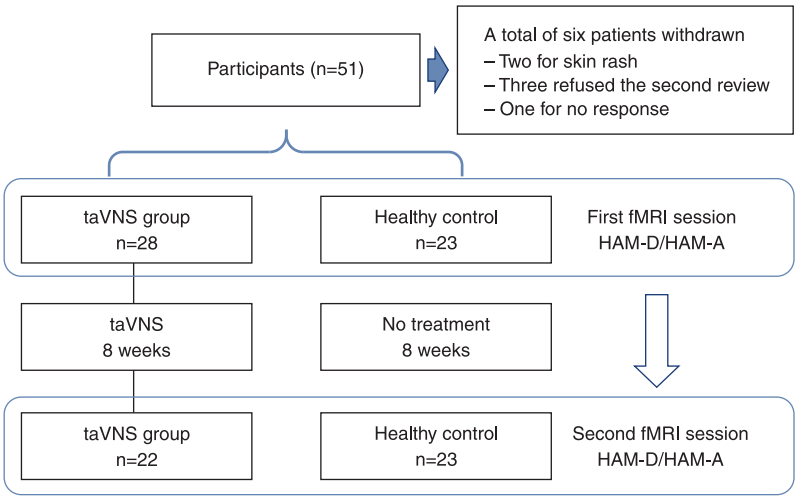

Figure 1 Overall study protocol. Fifty-one subjects were enrolled in this study. Two-way repeat-measured analysis of covariance (ANCOVA) was performed on each metric of voxel-based analysis to characterize the interactions between the transcutaneous auricular vagus nerve stimulation (taVNS) group and the healthy control group. fMRI = functional magnetic resonance imaging; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Rating Scale.

Figure 2 The electroacupuncture stimulator was attached to the bilateral cymba conchae through electrodes on the skin surface. The red dots show the target area of transcutaneous auricular vagus nerve stimulation (taVNS).

restraining foam pads, was used to minimize head motion and scanner noise. The participants were told to move as little as possible and keep their eyes closed without falling asleep. After the scan, none of them reported falling asleep during the scanning process. Resting-state functional images were acquired using a gradient echo planar imaging sequence with the following parameters: repeat time = 2,000 ms; echo time = 30 ms; flip angle = 90°, field of view = 224 × 224 mm; number of slices = 32; slice thickness = 3.0 mm; and volumes = 200. Then, high-resolution T1-weighted structural images were acquired using the MPRAGE sequence (repeat time = 2,530 ms; echo time = 2.98 ms; voxel size = 1 × 1 × 1 mm^3; field of view = 256 × 256 mm^2; slices = 43; slice thickness = 1 mm).

Functional magnetic resonance imaging (fMRI) data preprocessing

rs-fMRI images were preprocessed with DPABI.[27] The first 10 time points for the spin saturation effects and subjects' adaptation were removed. Slices were adjusted for timing and spatial realignment. The structural images were coregistered to the functional images and then segmented using diffeomorphic anatomical registration through exponentiated Lie algebra (DARTEL) to

compute transformations from the individual native space to the Montreal Neurological Institute (MNI) space. Several nuisance signals, including head motion parameters estimated by Friston's 24-parameter model,[28,29] linear trends, and mean signals of the white matter and cerebrospinal fluid, were regressed from the normalized image.

Following previous recommendations which contribute to improving the reproducibility of fMRI studies,[29-31] we used different strategies to minimize the impact of micro head motion. First, each subject's framewise displacement (FD) value was estimated using Jenkinson's formula; those who had an FD value greater than 0.2 were eliminated.[30] Second, we cut the volumes with micro head motion $>$ 0.5 mm in ReHo analysis for scrubbing of ''bad'' time points. However, to ensure the continuity of the time series, we did not perform such scrubbing in the ALFF and FCD analyses.[29] Furthermore, although no participant was excluded after analysis of micro head motion and no significant differences were found between the two groups, we conservatively evaluated the effects of head motion on our results by adding FD values as a covariate in the statistics.

Despite the sample size, the limited signal-to-noise ratio, and disputes in sampling and preprocessing strategies
for fMRI data, existing voxel-based analysis studies are sometimes contradictory.[32-36] In the present study, standard data preprocessing and strict statistical correction were performed to reveal the most significant brain effect elicited by taVNS. The results were also cross-validated by three different voxel-based analyses. The ALFF values were calculated as the average square root of the power spectrum range of 0.01-0.1 Hz and were converted to a frequency domain through the fast Fourier transform process.[19] They were calculated in the normalized images after smoothing into the MNI space with a 6-mm full width at half maximum (FWHM) Gaussian kernel. ReHo was calculated by voxels based on Kendall concordance coefficient theory for the time series of a given voxel with its 27 nearest neighbors.[20] FC strength (FCS) maps were first computed as the sum of the *r* value of the Pearson correlations of time series between a given voxel and all of the other voxels. FCD maps were binarily defined in FCS maps using a summed *r* threshold of 0.25; this threshold has been used in previous studies and is sensitive at detecting topological alterations of brain disorders using voxel-wise degree centrality approach.[18,21,25,37] They were calculated in the normalized images after band pass filtering (0.01-0.01 Hz), which reduced the effects of low-frequency drift and high-frequency noise. The ReHo and FCD maps were smoothed into MNI space (with a 6-mm FWHM Gaussian kernel). All of the calculated maps were transformed to *z* values to make the data more in line with a normal distribution, which also contributes to global signal denoising. FC represents the Pearson correlations between the time series of ROIs, which were characterized on ALFF and defined as active or deactive regions. The FC metrics were transformed according to Fisher's *r*-to-*z* transformation.

Statistical analyses

Baseline clinical data were analyzed using *t* tests or Mann-Whitney *U* tests as appropriate for data and chi-square tests for categorical variables. Pre- and post-treatment HAM-D and HAM-A scores were compared using paired *t* tests in the taVNS group. All tests were two-sided, with $p < 0.05$ denoting statistical significance; R software and R studio for Windows were used for all analyses.

Statistical analyses of fMRI metrics were performed with DPABI; repeat-measures two-way analysis of covariance (ANCOVA) and post-hoc analyses were performed to compare the group (i.e., taVNS group, HC group)-by-time (i.e., weeks 0 and 8) interactions (Figure 1). To exclude the voxels showing significant changes over time, the calculated metric of each voxel-based analysis result was restricted within its corresponding mask (i.e., ALFF, ReHo, FCD). We generated these masks by performing paired *t* tests on each voxel-based analysis metric of the HC group. The changes over time were defined with a threshold of uncorrected $p < 0.05$.[38,39] With this setup, the interactions would display the neural changes that were due to treatment vs. test-retest effects. Multiple comparisons of the statistical maps were thresholded according to Gaussian random field (GRF) theory, combining cluster $p < 0.05$ with voxel $p < 0.001$ (two-tailed). Post-hoc analyses were performed by two-sample *t* tests for baseline between-group comparisons and paired *t* tests for within-group comparisons in each group. The above statistics were controlled for age, gender, education, and FD values.

Ethics statement

The study was registered on the International Clinical Trials Registry Platform (https://trialsearch.who.int/, no. NCT03607331). All clinical investigative procedures were conducted according to the principles expressed in the Declaration of Helsinki. All patients were recruited using advertisements and by sending flyers to the hospitals involved in the study.

Results

Clinical outcomes

At baseline, there were no significant differences in age ($t = 0.569$, $p = 0.574$), gender ($\chi^2 = 2.097$, $p = 0.350$), or education ($Z = -0.824$, $p = 0.461$) between the taVNS group and the HC group. Significant reductions in HAM-D and HAM-A score were observed after 8 weeks in the taVNS group (Table 1).

Between- and within-group patterns

As in previous, large-sample studies, the taVNS group showed abnormalities in cortical-subcortical regions. Specifically, compared to HCs, the taVNS group showed lower ALFF values in cortical regions (including the dorsolateral prefrontal cortex and orbitofrontal gyrus) and higher ALFF values in some subcortical structures

Table 1 Sample characteristics of the participants

Items	taVNS (n=22)	HC (n=23)	χ^2/ t/z	p-value
Age (years)	43.05±14.90	44.04±0.437	-0.569[†]	0.574
Gender (M/F)	4/18	5/18	0.914[‡]	0.339
Education (years)	14.16±3.01	14.57±3.13	-0.824[§]	0.461
HAM-D, pre	16.68±4.57	2.04±0.43	0.0[§]	< 0.001
HAM-D, post	6.14±3.71	3.65±2.04	76.5[§]	< 0.001
HAM-D score Δ	10.55±5.30	-	4.48[‖]	< 0.001
HAM-A, pre	18.09±6.80	3.43±1.27	0.0[§]	< 0.001
HAM-A, post	6.55±4.59	3.04±1.77	66.5[§]	< 0.001
HAM-A score Δ	11.55±7.39	-	4.43[‖]	< 0.001

F = female; HAMA = 14-items of Hamilton Anxiety Scale score; HAM-D = 17-item Hamilton Depression Rating Scale score; HC = healthy control; M = male; post = week 8; pre = baseline; taVNS = transcutaneous auricular vagus nerve stimulation.
[†] Independent *t* tests.
[‡] Fisher's exact tests.
[§] Mann-Whitney *U* tests.
[‖] Paired *t* test.

(including the anterior cingulate cortex, dorsomedial prefrontal cortex, ventral striatum, anterior thalamus, hippocampus, and amygdala; $p_{cluster} < 0.05$ and $p_{voxel} < 0.001$, *GRF* corrected, two-tailed) (Figure S1, available as online-only supplementary material). In the taVNS group, within-group comparison showed decreased ALFF values in the anterior cingulate cortex, dorsomedial prefrontal cortex, and thalamus after 8 weeks of taVNS treatment (Figure S2). No within-group difference was found in the HC group.

Group × time interactions

As shown in Figure 3 and Table 2, group-by-time interactions ($p_{cluster} < 0.05$ and $p_{voxel} < 0.001$, *GRF* corrected, two-tailed) indicate that, in MDD patients, taVNS modulated a cluster mainly involving the inferior ventral striatum (VSi) and anterior thalamus, and a cluster mainly involving the precuneus, posterior cingulate cortex (PCC), and paracentral lobe (precuneus cluster). Post-hoc analyses revealed that the mean ALFF values in VSi were significantly higher in the taVNS group compared to the HC group at baseline, and reduced significantly after treatment. The taVNS group showed increased ALFF values in the precuneus cluster after 8 weeks of treatment (Figure 3) ($p_{cluster} < 0.05$ and $p_{voxel} < 0.001$, *GRF* corrected, two-tailed). ReHo and FCD analyses showed similar findings (Figure S3, available as online-only supplementary material).

The FCs between the VSi and precuneus cluster defined by ALFF analysis were estimated before and after taVNS treatment. As VSi was mainly primarily associated with medial orbitofrontal cortex (mOFC), involved in affective division,[40] we also generated a mOFC mask according to the Brainnetome Atlas (http://atlas.brainnetome.org/download.html) as a control condition. We found the FC between VSi and the precuneus cluster decreased after taVNS treatment ($t = 2.095$, $p = 0.048$), while no significant FC change was observed between the VSi and mOFC ($t = -0.05739$, $p = 0.934$).

Further relationships were explored between the changes in spontaneous brain activity and HAM-D/HAM-A remission rate. We observed positive correlations between the changes of mean ALFF values in the VSi cluster and HAM-D remission rate ($r = -0.763$, $p < 0.001$) (Figure 3). ReHo analysis showed similar findings (Figure S3). In addition, we found a positive correlation between the reduced VSi-precuneus FC values and the HAM-D remission rate ($r = -0.869$, $p < 0.001$) (Figure S4, available as online-only supplementary material).

Discussion

Our study showed that taVNS reduced HAM-D scores by downregulating the spontaneous brain activity of the VSi while upregulating activity in the precuneus and by reducing the FCs between the VSi and the precuneus.

The striatum is the primary input nucleus of the basal ganglia. Striatal subregions are involved in different cortico-striatal-thalamic-cortical (CSTC) circuits for managing memory, learning, task execution, and reward progression, some of which were demonstrated to be associated with treatment mechanisms and responses in MDD.[41-44] CSTC abnormalities in patients with MDD are closely related to reward deficiency. For example, low motivation is associated with a blunted striatal response to reward-related stimuli.[45] Greater pretreatment reward sensitivity and higher resting-state FC between bilateral VSi are associated with a positive response to bupropion.[46] During loss vs. reward stimuli, higher coupling was also found between the striatum and posterior default mode network (DMN), which could also predict the severity of depressive symptoms in MDD patients.[47] As in our study, MDD patients have shown striatum hyperactivity in many rs-fMRI studies,[18,48,49] and a combination of mean ALFF and fractional ALFF in the right striatum was selected as a feature of SVM to discriminate MDD patients and HC. Above all, the hypofunctions in the frontal-parietal cortex and hyperactivities in limbic structures found by our study are indicative of cortical-striatal dysregulation in MDD patients. taVNS affects the neural circuits influenced by norepinephrinergic, serotonergic, and dopaminergic neurons.[1-3] Our study found that an 8-week course of taVNS treatment was able to downregulate the VSi, and the clinical response to taVNS treatment was associated with the reversal of abnormally

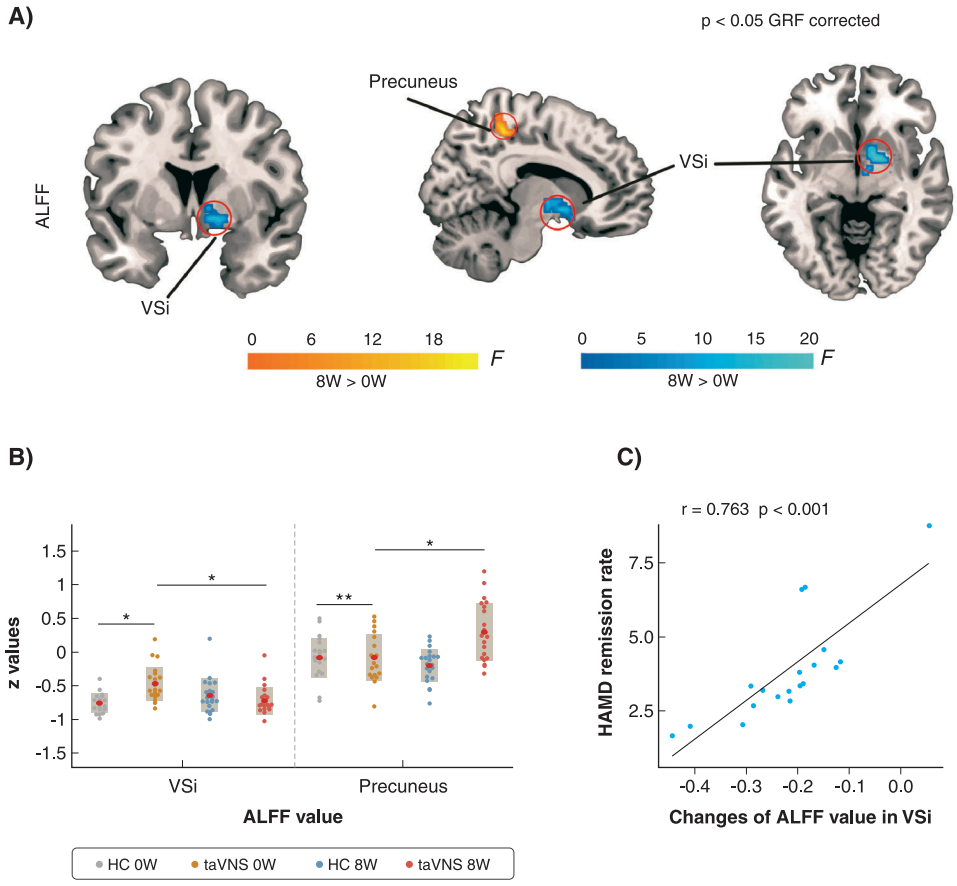

Figure 3 Changes in amplitude of low-frequency fluctuation (ALFF) values between baseline and week 8 (8W). A) The warm color shows the interaction in a cluster mainly involving the posterior cingulate cortex and precuneus; the cold color shows the interaction located in the inferior ventral striatum (VSi), including the ventral caudate, nucleus accumbens, and anterior thalamus. B) Post-hoc analysis of mean ALFF values of each cluster, as defined by the group-by-time interactions. C) Relationship between the 17-item Hamilton Depression Rating Scale (HAM-D-17) remission rate and the changes in mean ALFF values in the VSi cluster. 0W = week 0; GRF = Gaussian random field; HC = healthy control; taVNS = transcutaneous auricular vagus nerve stimulation. * Post-hoc analysis $p < 0.05$; ** post-hoc analysis $p > 0.05$.

increased brain activity in the right VSi; the treatment-related changes may be explained by the vagus-forebrain projections.

The present study also found that taVNS upregulated a cluster involving the precuneus and PCC, and that FC reductions between VSi and the precuneus cluster correlated positively with clinical response. The precuneus and PCC are involved in the posterior DMN, and abnormal FCs within the DMN are frequently reported in MDD. The PCC and VSi are anatomically linked brain regions; a higher coupling was found between the striatum and posterior DMN during loss vs. reward stimuli in MDD patients, which also predicted the severity of depressive symptoms.[47] The increased FCs between the two regions explain the biased reward processing of MDD patients. Consistent with our study, modulating effects of taVNS on the resting-state FCs between the reward network and the affective network were found in previous studies. For example, increased FCs between the left VSi and rostral cingulate cortex (rACC) were seen during the first taVNS session in MDD patients.[17] Another study found that FC value changes between the posterior DMN and anterior insula, parahippocampus, and orbitofrontal cortex were associated with HAMD remission.[14] Overall, we speculate that taVNS would relieve MDD symptoms by reducing the abnormal coupling between the striatum and posterior DMN, thus alleviating the biased reward processing observed in MDD patients.

Some studies have reported results opposite to our findings.[50-53] For example, one fMRI study found that ALFF in the ventral striatum (low at baseline) had increased after 2 weeks of repeated transcranial magnetic stimulation. Several reasons may contribute to these differences: first, the limited sample size, different sample characteristics, and the site effect of fMRI. Second, MDD is a complex disease, and a large-sample study and meta-analysis also showed contradictory subtypes among MDD patients.[54] Third, drug therapies have sustained effects on patients with MDD.[18,36] We speculate that the inversion of regional activities may reflect the status of trends from compensation to decompensation. Since we employed different algorithms to validate our findings, we believe they are robust.

Table 2 Changes in spontaneous brain activity after treatment

Hemisphere/Item	BA	Brain regions (AAL)	Cluster size (mm^3)	MNI coordinates			Peak intensity
				X	Y	Z	
R							
ALFF	25/48	VSi Anterior thalamus	1,080	18	0	-6	21.0849
L							
ReHo	25/48	VSi Anterior thalamus	324	-18	9	-9	18.8081
R							
FCD	25	VSi	999	6	6	-12	22.3406
L/R							
ALFF	5	Precuneus PCC Paracentral lobe	486	12	-39	54	23.4968
L/R							
ReHo	4	Precuneus PCC Paracentral lobe	567	-6	-21	51	19.1346

AAL = Anatomical Automatic Labeling; ALFF = amplitude of low-frequency fluctuation; BA = Brodmann area; FCD = functional centrality degree; L = left side; MNI = Montreal Neurological Institute; PCC = posterior cingulate cortex; R = right side; ReHo = regional homogeneity; VSi = inferior ventral striatum.

Nevertheless, we should interpret our data cautiously, as voxel-based analyses are a more exploratory method less based on actual neuroanatomy and can only reveal the top 5% significant changes throughout the entire brain. A recent study argued that small p-values may conceal some important findings.[55]

Another limitation of this study is that, although abnormalities in the temporal lobe and visual cortex have been observed in MDD patients,[46,56-59] our findings did not show modulating effects on these regions. One explanation was that the dysregulation in some subcortical regions that appeared insensitive to treatment may act as trait vulnerability markers, and the relatively strict multiple-comparison correction makes our voxel-based analyses only reveal the most significant brain regions within potentially changed networks.

Striatal subregions were also involved in different CSTC circuits, such as managing memory, learning, and task execution. Cognitive impairment is common in patients with MDD, even in those who are assessed as being in remission. Our study did not assess any cognitive-related scores. The potential therapeutic effect of taVNS on cognitive function in MDD patients should be explored in further studies.

In conclusion, our findings suggest that abnormalities in the brain areas involved in reward processing and emotion regulation could be normalized by taVNS in patients with first-episode MDD outside of a task situation. Standard strategies in fMRI preprocessing contribute to consistent and robust results.

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Disclosure

The authors report no conflicts of interest.

References

1 Butt MF, Albusoda A, Farmer AD, Aziz Q. The anatomical basis for transcutaneous auricular vagus nerve stimulation. J Anat. 2020; 236:588-611.
2 Frangos E, Ellrich J, Komisaruk BR. Non-invasive access to the vagus nerve central projections via electrical stimulation of the external ear: FMRI evidence in humans. Brain Stimul. 2015;8:624-36.
3 Mu Q, Bohning DE, Nahas Z, Walker J, Anderson B, Johnson KA, et al. Acute vagus nerve stimulation using different pulse widths produces varying brain effects. Biol Psychiatry. 2004;55:816-25.
4 Rong P, Liu J, Wang L, Liu R, Fang J, Zhao J, et al. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: a nonrandomized controlled pilot study. J Affect Disord. 2016;195:172-9.
5 Hein E, Nowak M, Kiess O, Biermann T, Bayerlein K, Kornhuber J, et al. Auricular transcutaneous electrical nerve stimulation in depressed patients: a randomized controlled pilot study. J Neural Transm (Vienna). 2013;120:821-7.
6 Schuerman WL, Nourski KV, Rhone AE, Howard MA, Chang EF, Leonard MK. Human intracranial recordings reveal distinct cortical activity patterns during invasive and non-invasive vagus nerve stimulation. Sci Rep. 2021;11:22780.
7 Kraus T, Hösl K, Kiess O, Schanze A, Kornhuber J, Forster C. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation J Neural Transm (Vienna). 2007;114:1485-93.

8 Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci. 1997;9:471-81.
9 Disner SG, Beevers CG, Haigh EAP, Beck AT. Neural mechanisms of the cognitive model of depression. Nat Rev Neurosci. 2011;12: 467-77.
10 Su L, Cai Y, Xu Y, Dutt A, Shi S, Bramon E. Cerebral metabolism in major depressive disorder: a voxel-based meta-analysis of positron emission tomography studies. BMC Psychiatry. 2014;14:321.
11 Sacher J, Neumann J, Fünfstück T, Soliman A, Villringer A, Schroeter ML. Mapping the depressed brain: a meta-analysis of structural and functional alterations in major depressive disorder. J Affect Disord. 2012;140:142-8.
12 Fang J, Egorova N, Rong P, Liu J, Hong Y, Fan Y, et al. Early cortical biomarkers of longitudinal transcutaneous vagus nerve stimulation treatment success in depression. Neuroimage Clin. 2017;14:105-11.
13 Liu J, Fang J, Wang Z, Rong P, Hong Y, Fan Y, et al. Transcutaneous vagus nerve stimulation modulates amygdala functional connectivity in patients with depression. J Affect Disord. 2016;205:319-26.
14 Fang J, Rong P, Hong Y, Fan Y, Liu J, Wang H, et al. Transcutaneous vagus nerve stimulation modulates default mode network in major depressive disorder. Biol Psychiatry. 2016;79:266-73.
15 Tu Y, Fang J, Cao J, Wang Z, Park J, Jorgenson K, et al. A distinct biomarker of continuous transcutaneous vagus nerve stimulation treatment in major depressive disorder. Brain Stimul. 2018;11:501-8.
16 Zhang Z-X, Zhang Y, Li S-Y, Zhang J-L, Liu Z-H, Chen Y-F, et al. Transcutaneous auricular vagus nerve stimulation for impaired glucose tolerance: a randomized controlled trial protocol. World J Acupunct Moxibustion. 2021;31:160-4.
17 Wang Z, Fang J, Liu J, Rong P, Jorgenson K, Park J, et al. Frequency-dependent functional connectivity of the nucleus accumbens during continuous transcutaneous vagus nerve stimulation in major depressive disorder. J Psychiatr Res. 2018;102:123-31.
18 Yan CG, Chen X, Li L, Castellanos FX, Bai TJ, Bo QJ, et al. Reduced default mode network functional connectivity in patients with recurrent major depressive disorder. Proc Natl Acad Sci U S A. 2019; 116:9078-83.
19 Zang YF, Yong H, Chao-Zhe Z, Qing-Jiu C, Man-Qiu S, Meng L, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev. 2007;29:83-91.
20 Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. Neuroimage. 2004;22:394-400.
21 Di Martino A, Zuo XN, Kelly C, Grzadzinski R, Mennes M, Schvarcz A, et al. Shared and distinct intrinsic functional network centrality in autism and attention-deficit/hyperactivity disorder. Biol Psychiatry. 2013;74:623-32.
22 Yan R, Huang Y, Shi J, Zou H, Wang X, Xia Y, et al. Alterations of regional spontaneous neuronal activity and corresponding brain circuits related to non-suicidal self-injury in young adults with major depressive disorder. J Affect Disord. 2022;305:8-18.
23 Hao H, Chen C, Mao W, Zhong J, Dai Z. Aberrant brain regional homogeneity in first-episode drug-naive patients with major depressive disorder: a voxel-wise meta-analysis. J Affect Disord. 2019;245: 63-71.
24 Guan M, Wang Z, Shi Y, Xie Y, Ma Z, Liu Z, et al. Altered brain function and causal connectivity induced by repetitive transcranial magnetic stimulation treatment for major depressive disorder. Front Neurosci. 2022;16:855483.
25 Luo B, Qiu C, Chang L, Lu Y, Dong W, Liu D, et al. Altered brain network centrality in Parkinson's disease patients after deep brain stimulation: a functional MRI study using a voxel-wise degree centrality approach. J Neurosurg. 20221-8.
26 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington: American Psychiatric Publishing; 2013.
27 Yan CG, Wang X Di, Zuo XN, Zang YF. DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. Neuroinformatics. 2016; 14:339-51.
28 Friston KJ, Williams S, Howard R, Frackowiak RSJ, Turner R. Movement-related effects in fMRI time-series. Magn Reson Med. 1996;35:346-55.
29 Yan CG, Cheung B, Kelly C, Colcombe S, Craddock RC, Di Martino A, et al. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. Neuroimage. 2013;76:183-201.
30 Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage. 2002;17:825-41.
31 Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 2012;59:2142-54.
32 Chen X, Lu B, Yan CG. Reproducibility of R-fMRI metrics on the impact of different strategies for multiple comparison correction and sample sizes. Hum Brain Mapp. 2018;39:300-18.
33 Kochunov P, Ryan MC, Yang Q, Hatch KS, Zhu A, Thomopoulos SI, et al. Comparison of regional brain deficit patterns in common psychiatric and neurological disorders as revealed by big data. Neuroimage Clin. 2021;29:102574.
34 Liu ZZ, Qu HJ, Tian ZL, Han MJ, Fan Y, Ge LZ, et al. Reproducibility of frequency-dependent low frequency fluctuations in reaction time over time and across tasks. PLoS One. 2017;12:e0184476.
35 Ji L, Zhang H, Potter GG, Zang YF, Steffens DC, Guo H, et al. Multiple neuroimaging measures for examining exercise-induced neuroplasticity in older adults: a quasi-experimental study. Front Aging Neurosci. 2017;9:102.
36 Yang Z, Telesford QK, Franco AR, Lim R, Gu S, Xu T, et al. Measurement reliability for individual differences in multilayer network dynamics: cautions and considerations. Neuroimage. 2021;225: 117489.
37 Yang H, Chen X, Chen Z-B, Li L, Li X-Y, Castellanos FX, et al. Disrupted intrinsic functional brain topology in patients with major depressive disorder. Mol Psychiatry. 2021;26:7363-71.
38 Wang L, An J, Gao HM, Zhang P, Chen C, Li K, et al. Duloxetine effects on striatal resting-state functional connectivity in patients with major depressive disorder. Hum Brain Mapp. 2019;40:3338-46.
39 Wang L, Xia M, Li K, Zeng Y, Su Y, Dai W, et al. The effects of antidepressant treatment on resting-state functional brain networks in patients with major depressive disorder. Hum Brain Mapp. 2015; 36:768-78.
40 Soares-Cunha C, Coimbra B, Sousa N, Rodrigues AJ. Reappraising striatal D1- and D2-neurons in reward and aversion. Neurosci Biobehav Rev. 2016;68:370-86.
41 Rappaport BI, Kandala S, Luby JL, Barch DM. Brain reward system dysfunction in adolescence: Current, cumulative, and developmental periods of depression. Am J Psychiatry. 2020;177:754-63.
42 Rupprechter S, Romaniuk L, Series P, Hirose Y, Hawkins E, Sandu AL, et al. Blunted medial prefrontal cortico-limbic reward-related effective connectivity and depression. Brain. 2020;143:1946-56.
43 Sequeira SL, Silk JS, Ladouceur CD, Hanson JL, Ryan ND, Morgan JK, et al. Association of neural reward circuitry function with response to psychotherapy in youths with anxiety disorders. Am J Psychiatry. 2021;178:343-51.
44 Sheline YI. Neuroimaging studies of mood disorder effects on the brain. Biol Psychiatry. 2003;54:338-52.
45 La Buissonniere-Ariza V, Fitzgerald K, Meoded A, Williams LL, Liu G, Goodman WK, et al. Neural correlates of cognitive behavioral therapy response in youth with negative valence disorders: A systematic review of the literature. J Affect Disord. 2021;282:1288-307.
46 Ang YS, Kaiser R, Deckersbach T, Almeida J, Phillips ML, Chase HW, et al. Pretreatment reward sensitivity and frontostriatal resting-state functional connectivity are associated with response to bupropion after sertraline nonresponse. Biol Psychiatry. 2020;88:657-67.
47 Quevedo K, Ng R, Scott H, Kodavaganti S, Smyda G, Diwadkar V, et al. Ventral striatum functional connectivity during rewards and losses and symptomatology in depressed patients. Biol Psychol. 2017;123:62-73.
48 Chen Q, Bi Y, Zhao X, Lai Y, Yan W, Xie L, et al. Regional amplitude abnormalities in major depressive disorder: a resting-state fMRI study and support vector machine analysis. J Affect Disord. 2022;308:1-9.
49 Huang L, Huang G, Ding Q, Liang P, Hu C, Zhang H, et al. Amplitude of low-frequency fluctuation (ALFF) alterations in adults with subthreshold depression after physical exercise: A resting-state fMRI study. J Affect Disord. 2021;295:1057-65.
50 Angelides NH, Gupta J, Vickery TJ. Associating resting-state connectivity with trait impulsivity. Soc Cogn Affect Neurosci. 2017;12: 1001-8.
51 Gong J, Wang J, Qiu S, Chen P, Luo Z, Wang J, et al. Common and distinct patterns of intrinsic brain activity alterations in major

depression and bipolar disorder: voxel-based meta-analysis. Transl Psychiatry. 2020;10:353.
52 Wei X, Shen H, Ren J, Liu W, Yang R, Liu J, et al. Alteration of spontaneous neuronal activity in young adults with non-clinical depressive symptoms. Psychiatry Res Neuroimaging. 2015;233: 36-42.
53 Yuan C, Zhu H, Ren Z, Yuan M, Gao M, Zhang Y, et al. Precuneus-related regional and network functional deficits in social anxiety disorder. Compr Psychiatry. 2018;82:22-29.
54 Chang M, Womer FY, Gong X, Chen X, Tang L, Feng R, et al. Identifying and validating subtypes within major psychiatric disorders based on frontal-posterior functional imbalance via deep learning. Mol Psychiatry. 2021;26:2991-3002.
55 Jia XZ, Zhao N, Dong HM, Sun JW, Barton M, Burciu R, et al. Small P values may not yield robust findings. Sci Bull (Beijing). 2021;66: 2148-52.
56 Rolle CE, Fonzo GA, Wu W, Toll R, Jha MK, Cooper C, et al. Cortical connectivity moderators of antidepressant vs placebo treatment response in major depressive disorder. JAMA Psychiatry. 2020;77: 397-408.
57 Di Simplicio M, Norbury R, Harmer CJ. Short-term antidepressant administration reduces negative self-referential processing in the medial prefrontal cortex in subjects at risk for depression. Mol Psychiatry. 2012;17:503-10.
58 Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele JD. Abnormal temporal difference reward-learning signals in major depression. Brain. 2008;131:2084-93.
59 Chin Fatt CR, Cooper C, Jha MK, Aslan S, Grannemann B, Kurian B, et al. Dorsolateral prefrontal cortex and subcallosal cingulate connectivity show preferential antidepressant response in major depressive disorder. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021;6:20-8.