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Original Article

Transcutaneous auricular vagus nerve stimulation to treat narcolepsy type 1 (TARGET-NT1): A two-arm, randomised, sham-controlled trial

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ABSTRACT

To assess exploratorily the safety and efficacy of transcutaneous auricular vagus nerve stimulation (tVNS) as an adjunctive therapy in improving symptoms in patients with narcolepsy type 1 (NT1). The TARGET-NT1 trial, a two-arm, double-blinded, sham-controlled trial was conducted from April 2022, to June 2024 at Xijing Hospital in Xi'an, China. Participants were randomised to receive tVNS treatment or sham tVNS (stVNS) treatment. Both interventions were performed for two 30-min periods per day with the same stimulation parameters but different stimulation points, for 12 weeks. The primary outcome was the change in mean sleep onset latency of maintenance of wakefulness test (MWT) from baseline to week 12. Secondary outcomes included changes in Narcolepsy Severity Scale (NSS), Epworth Sleepiness Scale (ESS), 14-item Hamilton Anxiety Rating Scale (HAMA-14), 17-item Hamilton Depression Rating Scale (HAMD-17). Among 60 randomised participants (32 men [53.3 %] and 28 [46.7 %]; mean [SD] age, 29.9 [9.9] years), 56 were included in the modified intention-to-treat (mITT) analysis. From baseline to week 12, the difference in mean change in mean sleep onset latency of MWT was 3.09 (95 % CI, 1.00, 5.88; $P = 0.0041$) as compared with stVNS group. Significant improvements in NSS-EDS (−2.61 [95%CI, −4.07, −1.15; $P = 0.0006$]), NSS-SP (−1.11 [95%CI, −1.83, −0.38; $P = 0.0030$]), NSS-HH (−2.71 [95% CI, −3.36, −2.05; $P < 0.0001$]), NSS- DNS (−0.52 [95%CI, −0.87, −0.17; $P = 0.0036$]), ESS (−3.03 [95%CI, −4.30, −1.75; $P < 0.0001$]) and HAMD-17 (−2.50 [95%CI, −4.30, −0.70; $P = 0.0069$]) were observed in the tVNS group as compared with stVNS group. This exploratory study supported the efficacy and safety of tVNS in patients with NT1 and provided insights into the mechanisms underlying tVNS treatment for NT1. The findings highlight tVNS as a potential non-pharmacological adjunctive therapy for patients with NT1. This trial was registered with the Chinese Clinical Trial Registry, ChiCTR2400094550.

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Introduction

Narcolepsy type 1 (NT1) is a chronic neurological disorder characterized by excessive daytime sleepiness (EDS) and cataplexy, with a global prevalence of approximately 25–50 cases per 100,000 individuals [1–3]. However, both non-pharmacological and pharmacological treatments have demonstrated limited efficacy within this patient cohort. Approximately 40 % of patients experience refractory EDS despite therapy [4]. Moreover, the development of drug resistance following long-term therapy may diminish medication efficacy, necessitating increased medication dosages to maintain efficacy [5]. The principal therapeutic objective for NT1 is to reduce the impact of EDS and cataplexy on quality of life, preventing impairments in academic and occupational achievements, social functioning, and reducing the heightened risk of accidents [6–10]. This underscores the need for improved treatment and an adjunctive therapy for the management of this chronic disorder [11–14].

Transcutaneous auricular vagus nerve stimulation (tVNS) is an emerging neuromodulatory therapy, distinguished by its non-invasive, cost-effectiveness without the need for battery replacements, contrasting with vagus nerve stimulation (VNS) [15]. By targeting the auricular branch of the vagus nerve—the afferent branch accessible on the body's surface—tVNS achieves effects akin to traditional VNS [16]. VNS has demonstrated potential in treating epilepsy and narcolepsy, with evidence indicating efficacy in alleviating EDS in patients [17–19]. Consequently, there is a rationale for investigating the feasibility of tVNS as an adjunctive therapeutic for NT1.

The mechanisms by which tVNS affects arousal, and alertness can be explained by various theories. The vagus nerve, via the nucleus tractus solitarius (NTS), projects to various brain regions, including the thalamus, hippocampus, hypothalamus, amygdala, posterior central gyrus, and several brainstem regions such as locus coeruleus (LC) [16,20–24]. The LC-noradrenergic (NA) pathway, as part of the ascending reticular activating system, is implicated in the regulation of wakefulness and REM sleep and shows heightened activation during tVNS [16,21–26]. This suggests that tVNS could influence alertness by affecting LC-NA pathway (Fig. 1). Despite some evidence supporting improved arousal with tVNS in patients with epilepsy, along with its feasibility for home-based treatment and mild side effects, no studies have been conducted to investigate the effect of tVNS on patients with NT1.

The aim of this exploratory study was to examine the safety and efficacy of tVNS as an adjunctive therapy for NT1. Additionally, we aimed to explore changes in brain function and functional connectivity (FC) associated with tVNS among patients with NT1. We hypothesized that patients with NT1 would have altered functional ramifications of altered patterns of neural activity after tVNS treatment, and thus relieved symptoms of NT1.

Material and Methods

Study design

This was a prospective, randomised, double-blinded, sham-controlled Transcutaneous Auricular Vagus Nerve Stimulation in Patients with Narcolepsy Type 1 (TARGET-NT1) study with a 12-week treatment period. Participants were randomly assigned 1:1 to tVNS or sham tVNS (stVNS) groups in Xijing Hospital, Xi'an, China. The entire study was designed, implemented and reported in accordance with the ethical principles of the Declaration of Helsinki. Clinical protocol was previously approved by the Medical Ethical Committee of Xijing Hospital (KY20222053-C-1) and overseen by an independent Data and Safety Monitoring Board. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. Before enrolling in the project, participants and their guardians provided written informed consent. Patient enrollment spanned from April 2022, to March 2024, with the final follow-up conducted in June 2024.

Participants

Inclusion criteria for eligible patients in TARGET-NT1 was: (1) Age ≥12 years old with the ability to understand and complete the self-reported questionnaires; (2) They met the international classification of sleep disorders third edition (ICSD-3) for NT1; (3) Local residence for more than 3 months; (4) Willingness to follow the trial plan as scheduled. Patients with one of the following criteria were excluded from the study: (1) History of neurological disorders or other sleep disorders that may cause daytime sleepiness; (2) Severe psychiatric disorder involving a history of psychosis; (3) Any chronic condition affecting the ability to read or comprehend written instructions; (4) Any ear trauma; (5) Any substances abuse within the past 12 months; (6) Pregnant or nursing; (7) MRI contraindications; (8) Metallic implants or devices contraindicating tVNS.

Randomisation and masking

The statistician utilized SAS 9.4 software to generate 1:1 ratio random numbers using the permuted block randomisation method with a block size of 4 for the experimental and sham-controlled groups. The statistician assigned intervention codes (tVNS and stVNS) based on these numbers. After the baseline assessment, eligible patients were given identification numbers and doctors assigned interventions sequentially.

For tVNS, a conductive silicone electrode spring clip was affixed to the left ear, with electrodes on the cymba concha and the retroauricular area. stVNS employed an electrode clip on the earlobe. Assessments were performed by investigators blinded to the randomisation process, with

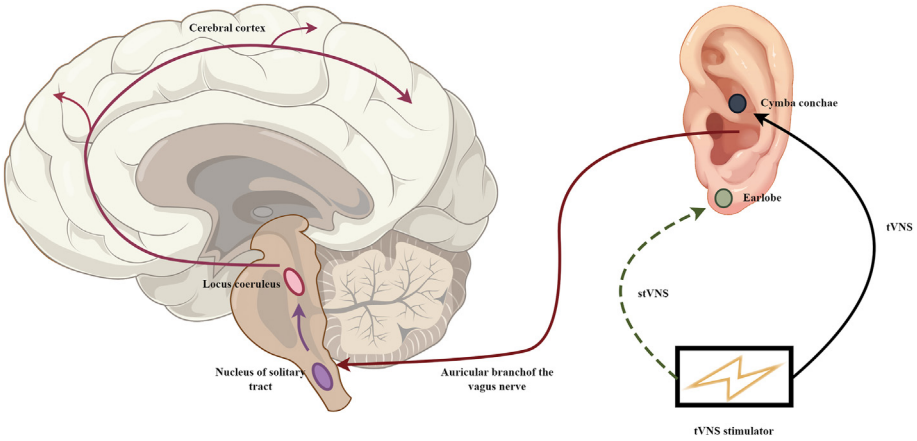

Fig. 1. The two different stimulation points of the ear electrode and possible mechanisms by which vagus nerve stimulation promotes wakefulness and alertness.

patients instructed to withhold stimulation details to preserve study blinding. Neither the patient nor the evaluator was informed of the group to which the patient was assigned.

Emergency unblinding, warranted only under circumstances where knowledge of the specific type of interventions is essential for the treatment, required documentation of date, time, and reason by the investigator. An unblinding request form was reviewed by the principal investigator before this action.

Procedures

We employed the t-VNS device tVNS501 (Ruishenan, Changzhou, China), certified by the Chinese National Institutes for Food and Drug Control. The trial included a 12-week intervention phase involving treatment with either tVNS or stVNS. Participants were instructed to abstain from unauthorized medications that could influence the efficacy of tVNS, particularly avoiding such medications for four weeks prior to randomisation. They were permitted to continue their existing medication regimen for NT1, with the stipulation that medications and dosages remained unchanged throughout the intervention period.

Both tVNS and stVNS were performed over 12 consecutive weeks. The tVNS protocol entailed a 500-μs pulse width and a 25-Hz frequency in a 30-s on/off cycle, administered for a daily total of 1 h, segmented into two 30-min periods, with at least one period occurring within 2 h before sleep. The intensity of the stimulation was personalized by patients with respect to their tolerable threshold under the guidance of doctors. Patients were advised to adjust the stimulation current (SC) in response to any reduction in subjective stimulation intensity or discomfort.

The tVNS application was confined to the left auricular concha to avoid the risk of bradycardia from efferent stimulation of the right vagus nerve innervating the sinoatrial node. This site was selected for its rich superficial vagus nerve. stVNS used the same parameters but was applied to the left earlobe, a region devoid of vagus nerve distribution (Fig. 1).

Baseline demographic and clinical characteristics of the participants were documented during the initial screening phase. Throughout the trial, detailed records of interventions and pertinent disease-related data were maintained. A comprehensive list of items for measurement is illustrated in sTable 1. The time points for the assessment of outcomes are illustrated in sTable 2. The complete list of scales used for measurement is provided in Supplement 1.

The acquisition of fMRI brain images was scheduled at two time points: after randomisation and allocation, and at the end of the 12-week intervention. fMRI acquisition and data processing were provided in Supplement 1.

Outcomes

The primary efficacy outcome was the change in the mean sleep onset latency of maintenance of wakefulness test (MWT) from baseline to week 12, a clinical tool designed to objectively assess patients with NT1 in maintaining wakefulness and alertness [27].

The secondary outcomes included the change in the mean sleep onset latency of maintenance of MWT at other timepoints, as well as the change in Narcolepsy Severity Scale (NSS) from baseline to week 12, to assess the severity of narcolepsy symptoms. The NSS comprises five subscales: NSS-EDS, NSS-CTP, NSS-SP, NSS-HH and NSS-DNS. The score range for the NSS was 0–57, with higher scores indicating more severe narcolepsy symptoms [28,29]. Additional secondary outcomes included the changes in Epworth Sleepiness Scale (ESS) [30], 14-item Hamilton Anxiety Rating Scale (HAMA-14) [31], 17-item Hamilton Depression Rating Scale (HAMD-17) [32], EuroQol Life Quality-5 Dimensions (EQ-5D) and EuroQol Life Quality-5 Dimensions Visual Analogue Scale (EQ-5D VAS), from baseline to week 12.

Statistical analysis

This is an exploratory study, and no formal sample size calculation was made. It was believed that 60 subjects (30 per arm) would satisfy the study objectives. The modified Intention-to-treat (mITT) analysis included all participants from the Full Analysis Set (FAS) who were randomised into the study; however, participants with incomplete baseline data or those who failed to provide efficacy and safety data post-intervention were excluded from the FAS. The Safety Set (SS) consisted of all participants who had received at least one intervention session following randomisation and had post-intervention safety evaluation data available.

For the primary efficacy analysis, a linear mixed-effects model was utilized. This model incorporated intervention, follow-up time, and their interaction as fixed effects, with the baseline MWT measurement included as a covariate. The random effect was based on participant ID. The mean difference between the two groups at each follow-up assessment, along with its 95 % confidence interval (CI), was estimated from the model. Additionally, a covariate-adjusted mixed model for the primary efficacy outcome was performed by including three baseline covariates: age, gender, and BMI. Missing data were assumed to be missing at random within the mixed model analysis, and no imputation was conducted for the primary efficacy outcome. To assess the sensitivity of the result to this assumption, we used the last observation carried forward (LOCF) method to handle missing efficacy outcomes.

Other secondary efficacy outcomes were conducted in a similar way as the primary efficacy outcome analysis. The proportions of participants with adverse events (AEs) between two groups were compared using the Chi square test or Fisher exact test.

ALFF, Reho and FC maps were compared between stVNS and tVNS groups using two-sample T tests. Voxels were considered to be remained met stringent criteria: a p-value below 0.05 following family-wise error correction. During the preprocessing step, the mean frame-wise displacement was calculated and accounted for by including this term as a covariate. Changes in mean ALFF and Reho were extracted from regions with significant difference before and after intervention, and Pearson correlation was calculated to assess the relationship between these changes and changes in mean sleep onset latency of MWT.

Results

Patients and characteristics

Initially, 85 participants eligible for inclusion criteria were screened. Sixty participants (32 men [53.3 %]; mean [SD] age, 29.9 [9.9] years) were enrolled and randomised, and 56 participants (31 men [55.4 %]; mean [SD] age, 29.3 [9.9] years) were included in modified ITT analysis (Fig. 1). Finally, 51 participants completed the 12-week intervention and assessment, and 9 participants (15 %) dropped out (tVNS group, 4 [13.3 %]; stVNS, 5 [16.7 %]). Among these, 6 withdrew due to personal problems or scheduling conflicted with reexaminations. Two were considered lost to follow-up for not being reached by phone. One had difficulty in using the device because the electrodes did not fit tightly to the skin of the ear (Fig. 2). There was no significant difference in compliance between the two groups.

Table 1 lists the demographics and baseline characteristics of randomised participants, which were well balanced except for the sleep paralysis (SP), disturbed nocturnal sleep (DNS) scores of NSS and mean MSLT sleep latency. Thirty-one (51.7 %) patients had received treatment for narcolepsy: 18 (30.0 %) with stimulants (eg, modafinil, methylphenidate), 13 (21.7 %) with anti-cataplectic drugs (eg, SSRIs, SNRIs). The medication regimen was maintained throughout the trial.

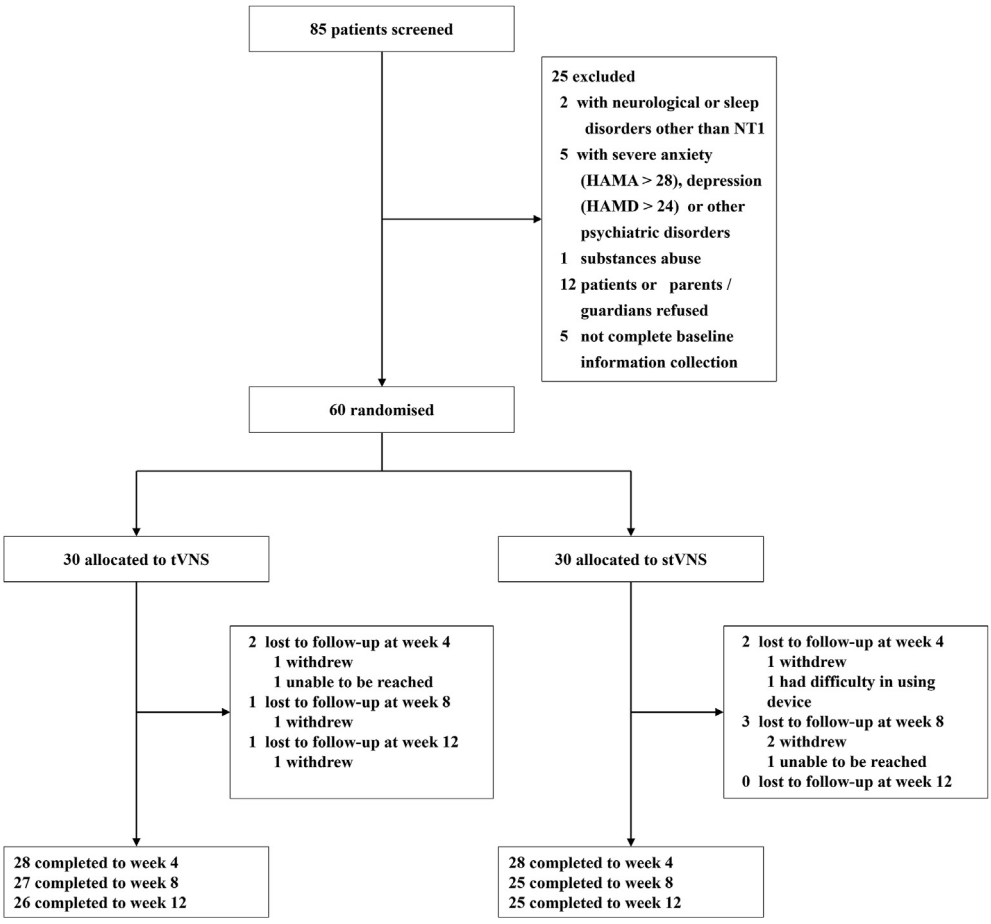

Fig. 2. Flow diagram.

Stimulation parameters were reported in the FAS: The mean daily stimulation duration was 2.2 h (SD = 0.5; range 0.0–3.1 h). The mean daily SC was 1.5 mA (SD = 0.8; range 0.5–3.4 mA).

Blinding evaluation

Following the trial, the questionnaire survey was conducted among the participants. The results indicated that, in the tVNS group (n = 26), 15 participants believed they had received tVNS, while 11 thought they had received stVNS. In the stVNS group (n = 25), 12 participants believed they had received tVNS, and 13 thought they had received stVNS. There was no statistically significant difference in the distribution between the two groups and 96.1 % of participants (49/51) had a mean daily stimulation duration above the predefined threshold of 2.0 h.

Primary outcome

Compared with the stVNS group, the tVNS group showed a significantly greater increase in mean sleep onset latency of MWT (difference 3.09, 95 % CI 1.00, 5.18, p = 0.0041) (Table 2). Although the difference was not significant at week 8, the tVNS group still had a higher mean sleep onset latency of MWT than the stVNS group. In further covariate adjusted analysis, the difference in mean sleep onset latency of MWT was maintained (sTable 3). The results remained similar when we used the LOCF strategy to impute missing mean sleep onset latency of MWT at follow-up visits (sTable 4).

Secondary outcomes

In the analysis of the NSS subscales at week 12, the tVNS group exhibited lower scores as compared to the stVNS group, with significant differences in all components except for NSS-CTP (NSS-EDS [difference −2.61, 95 % CI -4.07, −1.15, p = 0.0006], NSS-SP [difference −1.11, 95 % CI -1.83, −1.15, p = 0.0030], NSS-HH [difference −2.71, 95 % CI -3.36, −2.05, p < 0.0001], NSS-DNS [difference −0.52, 95 % −0.87, −0.17, p = 0.0036] (Table 2). Similar results were found in ESS at week 12, the tVNS group exhibited lower scores as compared to the stVNS group (difference −3.03, 95 % CI, −4.30, −1.75, p < **0.0001**), and this difference increased with intervention time (Table 2).

Compared with the stVNS group, the tVNS group showed a significantly greater reduction in HAMD-17 scores (difference −2.50, 95 % CI -4.30, −0.70, p = 0.0069) and a significantly greater increase in EQ-5D scores (difference 0.05, 95 % CI 0.02, 0.09, p = 0.0035) at week 12. The tVNS group had a greater reduction in HAMA-14 (difference −1.19, 95%CI -2.78, 0.39, p = 0.1375) and a greater increase in EQ-5D VAS (difference 4.04, 95%CI -1.14, 9.22, p = 0.1251), though no significant difference was found at week 12 (Table 2). The results remained similar when we used covariate adjusted analysis and the LOCF imputation (sTables 3 and 4).

Safety

During the treatment period, 3 patients in the tVNS group experienced a total of 4 AEs, while 5 patients in the stVNS group experienced 5

Table 1
Demographics and baseline characteristics of patients with NT1.

Characteristics	stVNS (n = 30)	tVNS (n = 30)	P [d]
Demographic features			
Age (years)[a]	28.50 ± 9.20	31.23 ± 10.28	0.290
Sex[b]			0.605
Male	15 (50 %)	17 (57 %)	
BMI (kg/m^2)[a]	26.31 ± 3.09	27.08 ± 2.90	0.323
Symptomatic features			
CTP[b]	29 (97 %)	29 (97 %)	>0.999
SP[b]	16 (53 %)	23 (77 %)	0.058
HH[b]	23 (77 %)	22 (73 %)	0.766
DNS[b]	26 (87 %)	25 (83 %)	0.718
Clinical features			
Age of onset (years)[a]	14.40 ± 5.92	16.77 ± 7.37	0.183
Disease duration (years)[c]	12.00 (9.00, 20.00)	13.00 (9.00, 18.00)	0.745
Medication status[b]			0.846
No medication intake	14 (47 %)	15 (50 %)	
Stimulant	10 (33 %)	8 (27 %)	
Anti-cataplectic drug	6 (20 %)	7 (23 %)	
Self-reported scales			
NSS-EDS[a]	17.70 ± 3.44	18.87 ± 4.10	0.245
NSS-CTP[c]	6.00 (5.00, 8.00)	7.00 (5.00, 7.00)	0.994
NSS-SP[c]	3.00 (0.00, 5.00)	5.00 (3.25, 6.00)	**0.029**
NSS-HH[c]	4.00 (3.00, 5.75)	6.50 (5.00, 7.75)	**0.003**
NSS-DNS[c]	1.00 (1.00, 2.00)	2.00 (0.00, 2.00)	0.826
ESS[a]	18.27 ± 3.02	19.00 ± 3.02	0.350
HAMA-14[c]	8.5 (6.3, 11.0)	8.5 (7.0, 13.0)	0.795
HAMD-17[a]	12.7 ± 5.4	12.1 ± 4.4	0.637
MSLT			
Mean sleep onset latency (min)[a]	4.85 ± 1.91	3.68 ± 1.89	**0.020**
SOREMPs[c]	4.00 (3.00, 5.00)	4.00 (4.00, 5.00)	0.217
MWT			
Mean sleep onset latency (min)[c]	7.6 (5.0, 10.0)	5.0 (2.5, 7.5)	0.206

[a] Mean (SD).
[b] n (%).
[c] Median (IQR).
[d] Welch Two Sample *t*-test; Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test; NT1, Narcolepsy Type 1; BMI, Body Mass Index; CTP, Cataplexy; SP, Sleep Paralysis; HH, Hypnagogic Hallucinations; DNS, Disturbed Nocturnal Sleep; NSS-EDS, Narcolepsy Severity Scale-Excessive Daytime Sleepiness (subscale score range 0–25; higher scores indicate increased drowsiness); NSS-CTP, Narcolepsy Severity Scale-Cataplexy (subscale score range 0–13; higher scores indicate increased drowsiness); NSS-SP, Narcolepsy Severity Scale-Sleep Paralysis (subscale score range 0–8; higher scores indicate aggravated sleep paralysis); NSS-HH, Narcolepsy Severity Scale-Hypnagogic Hallucinations (subscale score range 0–8; higher scores indicate aggravated hallucinations); NSS-DNS, Narcolepsy Severity Scale-Disturbed Nocturnal Sleep (subscale score range 0–3; higher scores indicate more disturbed sleep); ESS, Epworth Sleepiness Scale (total score range 0–24; higher scores indicate increased drowsiness); HAMA-14, 14-item Hamilton Anxiety Rating Scale (total score range 0–56; higher scores indicate elevated anxiety); HAMD-17, 17-item Hamilton Depression Rating Scale (total score range 0–51; higher scores indicate elevated depression); MSLT, Multiple Sleep Latency Test; SOREMPs, Sleep Onset REM Periods; MWT, Maintenance of Wakefulness Test.
Footnote: bold font indicates significant results.

AEs. No significant difference observed in the between-group comparison of AEs. The reported AEs included headache, dizziness, insomnia, and fatigue. Additionally, 1 patient in the tVNS group experienced 1 device-related AE, while 2 patients in the stVNS group experienced 2 device-related AEs. These events were characterized by erythema at the site where the electrodes were placed, which improved when the stimulation intensity was reduced. No significant differences were found in differences of physiological indicators (such as systolic blood pressure, diastolic blood pressure and heart rate) between the two groups from baseline to the end of treatment. No abnormal findings related to vital signs were reported as AEs.

fMRI results

After stVNS or tVNS, the tVNS group exhibited significantly larger changes in mean ALFF and Reho values compared to the stVNS group in certain areas of the brain especially the brainstem (sFigure 1). Additionally, there was a significant positive correlation between changes in mean ALFF and Reho values in the brainstem region and changes in mean sleep onset latency of MWT in the tVNS group (sFigure 2).

The results of the seed-based whole brain FC analysis demonstrated that, after stVNS or tVNS, the tVNS group exhibited significantly greater changes in FC between the brainstem region and the anterior cingulate cortex, left putamen, thalamus, precuneus, bilateral parahippocampus, hippocampus, and amygdala compared to the stVNS group. Moreover, FC change between the brainstem region and the right thalamus was significantly lower in the tVNS group compared to the stVNS group (sFigure 3).

Retention rate

Among the 26 participants with NT1 who completed the treatment intervention in the tVNS group, 17 participants expressed their willingness to continue tVNS therapy, while 9 participants declined further tVNS intervention. The primary reasons for refusal were as follows: 1. Time-consuming and significant impact on daily life (7 patients, 26.9 %); 2. Unsatisfactory improvement of symptoms (6 patients, 23.1 %); 3. High cost of the device (2 patients, 7.7 %).

In the exit interviews, participants described various ways in which they perceived tVNS had relieved their narcolepsy symptoms. A summary of these qualitative insights is presented in sTable 5.

Discussion

This study is the first to evaluate the safety and efficacy of tVNS in patients with NT1. We investigated the changes in mean sleep onset

Table 2
Summary statistics and results from mixed model analysis of primary and secondary outcomes.

	Descriptive statistics				Mixed model analysis	
	tVNS		stVNS		Difference (95 % CI)	p value
	N	Mean (SD)	N	Mean (SD)		
MWT						
Baseline	30	6.44 (5.06)	30	7.48 (4.63)		
4 weeks	28	8.94 (5.48)	28	7.01 (4.74)	2.41 (0.40–4.43)	**0.0192**
8 weeks	27	8.86 (4.34)	25	7.27 (4.30)	2.00 (−0.07 to 4.08)	0.0585
12 weeks	26	9.43 (4.24)	25	6.67 (4.05)	3.09 (1.00–5.18)	**0.0041**
NSS-EDS						
Baseline	30	18.87 (4.17)	30	17.70 (3.50)		
4 weeks	28	17.96 (3.70)	28	17.89 (3.70)	−0.48 (−1.89 to 0.92)	0.4957
8 weeks	27	16.74 (2.70)	25	17.84 (2.95)	−1.54 (−2.99 to −0.09)	**0.0370**
12 weeks	26	15.69 (2.87)	25	17.92 (3.17)	−2.61 (−4.07 to −1.15)	**0.0006**
NSS-CTP						
Baseline	30	6.40 (2.11)	30	6.67 (2.87)		
4 weeks	28	6.57 (2.70)	28	6.32 (2.92)	0.31 (−0.61 to −0.61)	0.5077
8 weeks	27	6.11 (2.45)	25	6.52 (3.06)	−0.32 (−1.27 to 0.64)	0.5144
12 weeks	26	6.12 (2.25)	25	6.28 (2.94)	−0.12 (−1.08 to 0.85)	0.8138
NSS-SP						
Baseline	30	4.43 (2.80)	30	2.77 (2.80)		
4 weeks	28	3.96 (2.71)	28	2.68 (2.97)	−0.13 (−0.82 to 0.57)	0.7226
8 weeks	27	3.30 (1.98)	25	3.04 (3.10)	−1.13 (−1.85 to −0.41)	**0.0023**
12 weeks	26	3.15 (2.05)	25	2.92 (2.78)	−1.11 (−1.83 to −0.38)	**0.0030**
NSS-HH						
Baseline	30	5.53 (2.78)	30	3.83 (2.51)		
4 weeks	28	3.93 (2.39)	28	3.89 (2.69)	−1.06 (−1.69 to −0.43)	**0.0012**
8 weeks	27	2.67 (1.57)	25	4.04 (2.42)	−2.33 (−2.98 to −1.68)	**<0.0001**
12 weeks	26	2.50 (1.66)	25	4.28 (2.78)	−2.71 (−3.36 to −2.05)	**<0.0001**
NSS-DNS						
Baseline	30	1.23 (0.97)	30	1.33 (0.84)		
4 weeks	28	0.61 (0.63)	28	1.18 (0.82)	−0.52 (−0.86 to −0.19)	**0.0022**
8 weeks	27	0.63 (0.63)	25	1.08 (0.86)	−0.47 (−0.82 to −0.13)	**0.0072**
12 weeks	26	0.54 (0.65)	25	1.04 (0.84)	−0.52 (−0.87 to −0.17)	**0.0036**
ESS						
Baseline	30	19.00 (3.02)	30	18.27 (3.02)		
4 weeks	28	17.86 (3.02)	28	18.57 (2.75)	−0.92 (−2.14 to 0.30)	0.1369
8 weeks	27	16.82 (1.64)	25	18.24 (2.39)	−1.63 (−2.89 to −0.37)	**0.0119**
12 weeks	26	15.65 (2.84)	25	18.52 (2.49)	−3.03 (−4.30 to −1.75)	**<0.0001**
HAMA-14						
Baseline	30	9.43 (4.31)	30	9.30 (4.60)		
4 weeks	28	9.00 (3.81)	28	9.43 (5.08)	−0.61 (−2.13 to 0.91)	0.4291
8 weeks	27	9.00 (4.51)	25	9.40 (3.91)	−0.38 (−1.95 to 1.19)	0.6340
12 weeks	26	8.54 (4.23)	25	9.64 (4.78)	−1.19 (−2.78 to 0.39)	0.1375
HAMD-17						
Baseline	30	12.07 (4.35)	30	12.67 (5.40)		
4 weeks	28	10.43 (4.93)	28	11.79 (5.35)	−0.85 (−2.58 to 0.87)	0.3289
8 weeks	27	9.78 (3.89)	25	13.40 (6.57)	−2.86 (−4.64 to −1.08)	**0.0019**
12 weeks	26	9.42 (3.60)	25	12.80 (5.87)	−2.50 (−4.30 to −0.70)	**0.0069**
EQ-5D						
Baseline	30	0.67 (0.10)	30	0.66 (0.08)		
4 weeks	28	0.71 (0.08)	28	0.68 (0.09)	0.02 (−0.01 to 0.05)	0.1847
8 weeks	27	0.71 (0.09)	25	0.65 (0.08)	0.05 (0.01–0.08)	**0.0092**
12 weeks	26	0.73 (0.07)	25	0.67 (0.08)	0.05 (0.02–0.09)	**0.0035**
EQ-5D VAS						
Baseline	30	62.20 (12.54)	30	65.10 (11.82)		
4 weeks	28	67.64 (13.57)	28	67.54 (13.69)	2.58 (−2.39 to 7.54)	0.3065
8 weeks	27	64.67 (15.46)	25	63.24 (13.40)	3.37 (−1.76 to 8.50)	0.1960
12 weeks	26	68.08 (11.97)	25	66.40 (11.56)	4.04 (−1.14 to 9.22)	0.1251
HR						
Baseline	30	71.93 (7.57)	30	73.80 (6.39)		
4 weeks	28	74.00 (8.99)	28	71.14 (9.25)	3.11 (−1.52 to 7.74)	0.1861
8 weeks	27	71.67 (7.73)	25	75.04 (6.86)	−2.65 (−7.45 to 2.15)	0.2773
12 weeks	26	72.41 (7.61)	25	75.04 (11.42)	−1.91 (−6.71 to 2.89)	0.4335
SBP						
Baseline	30	115.13 (9.64)	30	115.80 (7.59)		
4 weeks	28	115.54 (9.47)	28	114.89 (10.41)	0.86 (−3.82 to 5.53)	0.7177
8 weeks	27	114.89 (7.35)	25	115.20 (8.23)	0.26 (−4.62 to 5.13)	0.9169
12 weeks	26	114.15 (8.21)	25	114.92 (9.38)	−0.30 (−5.22 to 4.61)	0.9033

(*continued on next page*)

Table 2 (*continued*)

	Descriptive statistics				Mixed model analysis	
	tVNS		stVNS		Difference (95 % CI)	p value
	N	Mean (SD)	N	Mean (SD)		
DBP						
Baseline	30	71.83 (8.05)	30	68.43 (7.22)		
4 weeks	28	71.61 (7.66)	28	70.61 (8.68)	−0.28 (−4.59 to 4.02)	0.8974
8 weeks	27	72.26 (6.95)	25	71.68 (10.11)	−0.35 (−4.80 to 4.09)	0.8748
12 weeks	26	71.96 (8.47)	25	68.56 (8.50)	2.49 (−2.00 to 6.97)	0.2748

MWT, Maintenance of Wakefulness Test; NSS-EDS, Narcolepsy Severity Scale-Excessive Daytime Sleepiness (subscale score range 0–25; higher scores indicate increased drowsiness); NSS-CTP, Narcolepsy Severity Scale-Cataplexy (subscale score range 0–13; higher scores indicate increased drowsiness); NSS-SP, Narcolepsy Severity Scale-Sleep Paralysis (subscale score range 0–8; higher scores indicate aggravated sleep paralysis); NSS-HH, Narcolepsy Severity Scale-Hypnagogic Hallucinations (subscale score range 0–8; higher scores indicate aggravated hallucinations); NSS-DNS, Narcolepsy Severity Scale-Disturbed Nocturnal Sleep (subscale score range 0–3; higher scores indicate more disturbed sleep); ESS, Epworth Sleepiness Scale (total score range 0–24; higher scores indicate increased drowsiness); HAMA-14, 14-item Hamilton Anxiety Rating Scale (total score range 0–56; higher scores indicate elevated anxiety); HAMD-17, 17-item Hamilton Depression Rating Scale (total score range 0–51; higher scores indicate elevated depression); HR, Heart Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.
Footnote: bold font indicates significant results.

latency of MWT after a 12-week intervention period of tVNS treatment compared with stVNS. The findings indicated that tVNS treatment enhanced the capacity to sustain wakefulness and significantly alleviated symptoms, especially SP, HH, and DNS, while also modulating mood. Additionally, our analysis revealed that, relative to baseline and stVNS, tVNS elicited significant activations in the brainstem region.

In this study, the change in the mean sleep onset latency of MWT from baseline to week 12 was chosen as the primary outcome, as it objectively reflects the severity and improvement of EDS. A mean sleep latency of less than 8 min is considered abnormal, while 8–40 min (including 40 min) indicates that sleepiness is not significant [33]. Before the intervention, the mean sleep onset latency of MWT at baseline for both groups was below the clinical threshold. However, after 12 weeks of intervention, only the tVNS group had a mean sleep onset latency of MWT above the clinical threshold. The between-group difference in MWT of 3.09 min achieved statistical significance.

Our analysis from three treatment visits showed that the efficacy of tVNS improved with longer treatment, whereas the stVNS group did not demonstrate a comparable trend. These findings align with previous studies for narcolepsy, indicating that prolonged tVNS treatment duration might enhance wakefulness maintenance [19]. However, further investigation is necessary to determine whether long-term tVNS is associated with more AEs and whether patients can tolerate this treatment.

Yaroslav Winter and colleagues observed that following six months of VNS treatment, patients exhibited a 39.6 % improvement in ESS scores compared to baseline, surpassing the recommended clinically significant difference for this measure (25 %) [34]. The absolute change in ESS scores was 6.3 points, exceeding the minimal important difference of 2.5 points [35]. In our study, among patients who received tVNS, there was 17.4 % improvement in ESS after 12-week compared to baseline, which was below the clinically important difference. However, the absolute difference in ESS scores was 3.3 points, which was above the minimal important difference. Based on the improvement in ESS scores among patients with narcolepsy, the efficacy of tVNS was less effective than VNS.

tVNS significantly alleviated sleep paralysis (SP), hypnagogic hallucinations (HH), and disturbed nocturnal sleep (DNS) in patients with NT1. This suggests tVNS may positively impact some symptoms via specific neural mechanisms while having limited effects on others. The improved symptoms may be linked to abnormal REM sleep intruding into wakefulness [36,37]. tVNS likely stabilizes sleep-wake transitions and reduces abnormal REM fragments, thereby easing sleep paralysis and hallucinations. Cataplexy is linked to imbalances in several neurotransmitters, especially dopamine and noradrenaline [38]. The dopamine system, crucial for movement regulation, may be not significantly modulated by tVNS. In contrast, traditional pharmacological treatments, like selective serotonin reuptake inhibitors and noradrenaline reuptake inhibitors, directly alter these neurotransmitter levels, effectively improving cataplexy symptoms [39,40]. As a neuromodulation technique, tVNS may not achieve the same degree of neurotransmitter regulation as medication.

tVNS treatment was well-tolerated in this study with AEs being comparable to those reported in previous studies [41,41,42]. No cardiac arrhythmias or blood pressure abnormalities were observed during tVNS treatment, although it is important to note that the parasympathetic innervation of the heart by vagus nerve stimulation should be carefully considered. Device-treatment-related AEs of tVNS such as erythema are much less severe compared to VNS such as pharyngitis and hoarseness associated with invasive implantation procedure [43,44]. The advantages of tVNS as a non-invasive treatment over VNS warrant further investigation. However, tVNS as a self-administered therapy requires a higher level of compliance than VNS. In the follow-up development of tVNS, the device needs to be further improved to facilitate the daily use for patients.

Recently, fMRI techniques have been utilized to examine alterations in brain imaging signals induced by tVNS [16,22,24]. In a previous study, Eleni Frangos and colleagues found that tVNS could increase activity in the brainstem regions, including NTS and LC, and achieve central projections consistent with VNS [16]. Diba Borgmann and colleagues also found that downstream targets of vagal afferents, including NTS, substantia nigra, and subthalamic nucleus, showed a significant response to acute tVNS [24]. Aligning with these brain imaging studies focusing on the brain's response to tVNS, we found that after 12-week of tVNS treatment, these brainstem regions, significantly exhibited increased ALFF and Reho activity in response to tVNS.

The brainstem contains LC, pivotal for sustaining arousal and vigilance via NA projections to subcortical regions involved in cortical activation [25,26]. Our study found a positive association between the prolonged mean sleep onset latency of MWT and increased mean ALFF and Reho values in the brainstem region. We hypothesized this might be because the increase in the patient's state of arousal is partly due to the vagus nerve projecting to the NTS through its afferent fibers and thereby activating the LC, leading to widespread cortical activation via the LC-NA pathway [45–47].

Afferent fibers projecting to the NTS are intricately linked with various brain structures both directly and indirectly, including the hypothalamus, amygdala, insula, thalamus [48,49]. Notably, some of these brain regions, involved in the onset and remission of NT1 [50], provide a foundation for therapeutic interventions targeting NT1. Our findings reveal that tVNS significantly modulates the positive and negative connectivity relationships between the brainstem region and cortical/subcortical regions involved in mood regulation, subjective well-being, memory and cognitive function. This aligns with the findings of a recent study examining the therapeutic efficacy of tVNS for

major depressive disorder [51]. These results also partially explain why tVNS improves mood, relieves the symptoms and improves quality of life among patients with NT1.

The limitations of this trial are as follows: 1) This is an exploratory study with a small sample size, and the intervention period may be insufficient for the therapeutic effects of tVNS to stabilize. Further research with a larger sample size and longer study periods is required to assess the long-term impacts of this therapeutic approach. 2) In fMRI studies, precise localization of brainstem nuclei is challenging, so we used the entire brainstem region as the seed region. 3) The treatments were self-administered by the patients with NT1, and thus patient adherence might have impacted the observed results. 4) The measurement of the load of applied stimulation was not included in the analysis, dose-response relationships require further study.

Conclusion

This trial provided some evidence of the efficacy and safety of tVNS in patients with NT1 and insights into the mechanisms underlying tVNS treatment for NT1. The findings highlight tVNS as a potential non-pharmacological adjunctive therapy for patients with NT1 to relieve symptoms.

Authors Contributions

L.Y.H: conception, design and funding acquisition; P.Y.H and Z.Y.C: writing the manuscript; X.Z.L, W.Z.H, H.G.Y, W.X.L, Y.L, Y.N, W.D.W, Z.X.B, W.X.Y, Q.S.Y, L.C·W, Z.Z, G.Y·W and S.X.D: recruiting patients, assisting with follow-up and collecting the clinical data; Z.Y.Q: supervision; P.R, W·K.J and W.D.L: statistic analysis, data interpretation and accessing and verified data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data availability

This study's data supporting the results and the trial protocol are available by contacting the corresponding author upon reasonable request.

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Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurot.2025.e00604.

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