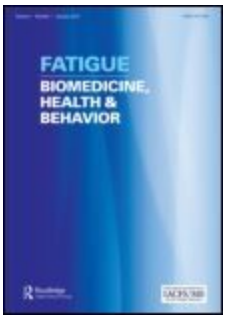

An international survey of experiences and attitudes towards Transcutaneous auricular Vagus Nerve Stimulation for people with Myalgic Encephalomyelitis / Chronic Fatigue Syndrome

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Title page

An international survey of experiences and attitudes towards transcutaneous auricular vagus nerve stimulation for people with Myalgic Encephalomyelitis / Chronic Fatigue Syndrome.

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Abstract

Background and objectives

Myalgic encephalomyelitis (ME) is a complex, multi-system neurological condition. Dysfunction of the autonomic nervous system is a primary feature in diagnostic criteria, and management may include attempts to stimulate the parasympathetic nervous system. Transcutaneous auricular vagus nerve stimulation is an intervention that has been researched in neurological disorders, e.g., epilepsy, depression. While little evidence exists for its use in ME, this survey aims to explore the experiences and attitudes of people with ME to this intervention.

Methods

A 31-question online survey was devised and released on ME websites, Twitter and Facebook pages. People with ME read the information sheet and followed an online link to the survey. The survey was open for four weeks and all answers were anonymous.

Results

116 responses were received. 56% of respondents reported favourable effects. Benefits of transcutaneous auricular vagus nerve stimulation were identified in relation to post exertional malaise, pain, gut problems, urinary problems, mental health, and the ability to leave the house. 67.2% of respondents would recommend the intervention to other people with ME. However, 4.3% would not recommend it and 6% reported it made them worse. 8.6% received support in setting up the device from healthcare workers.

Conclusion

The survey highlights that many people with ME experience significant benefits from using transcutaneous auricular vagus nerve stimulation; however due to potential negative effects there is the need for formal intervention studies to clearly identify safe parameters.

Trial registration number: This survey was not registered

Keywords: Myalgic Encephalomyelitis; Chronic Fatigue Syndrome; Transcutaneous auricular Vagus Nerve Stimulation;

Introduction

Myalgic Encephalomyelitis (ME) is a complex, acquired multi-systemic disease that may involve dysfunction of the neurological control system resulting in faulty communication and interaction between the central nervous system and major body systems[1]. Diagnostic criteria list a range of symptoms including cognitive impairments, pain, fatigue, and difficulty sleeping.[1,2] A unique feature of the illness is post-exertional malaise (PEM), which is an exacerbation of symptoms after seemingly trivial physical, cognitive, emotional and/or social activity[3].

The autonomic nervous system is an unconscious, automatic control system in the peripheral nervous system 'that regulates involuntary physiologic processes including heart rate, blood pressure, respiration and digestion' and two major systems are the parasympathetic and sympathetic[5]. Autonomic dysfunction involves an imbalance between the sympathetic and parasympathetic nervous system, and is not unique to ME[4]; however autonomic manifestations are included in diagnostic criteria for ME[1,2] , with identified symptoms of orthostatic intolerance, palpitations with or without cardiac arrhythmias, light-headedness, extreme pallor, nausea, breathlessness, temperature intolerance and bladder and bowel dysfunction. . People with ME have been shown to have increased sympathetic modulation of cardiac function[6], a low heart rate variability in comparison to healthy controls[7], and potential deficits in the brainstem and midbrain that have key roles in the autonomic nervous system[8].

Management of autonomic dysfunction includes attempts to stimulate the parasympathetic nervous system, often via the vagus nerve, which is the tenth cranial nerve and thought to be the main neural component of the parasympathetic system[9]. Direct vagus nerve stimulation is an FDA-approved therapy for depression and epilepsy, but it involves an invasive procedure and is limited to management of severe cases[10]. Transcutaneous auricular vagus nerve

stimulation (taVNS) involves stimulation of the vagus nerve via electrodes applied to part of the ear as a non-invasive technique[10]. Portable transcutaneous electrical nerve stimulators (TENS) have been manufactured specifically for the purposes of taVNS, but typical TENS devices that are conventionally used for pain management are also capable of taVNS with the addition of an ear-clip to apply the electrodes[10].

Individuals with ME are reporting the use of taVNS through support groups on social media and personal stories shared online, but there are no qualitative studies or surveys exploring experiences and attitudes to this intervention. The present survey, therefore, aimed to explore the experiences of and attitudes towards taVNS in people with ME.

Method

Ethical approval was obtained from the University of Liverpool. An online survey was developed by ME researchers and two knowledgeable patients who use taVNS. Thirty-one open and closed questions were devised using the Jisc online survey system. The survey used tick boxes to reduce the energy requirement needed to answer survey items that were linked to open space to allow typed-in expansion of the answers. Questions aimed to gather: demographics, the type of taVNS used, parameters of stimulation, and the effects of taVNS (see Table 1). The survey was piloted by a number of people with ME via a special interest Facebook group, to determine the ease of filling out the questionnaire.

The survey, as advertised on the Physios for ME website (www.physiosforme.com) and promoted via social media, began with an initial participant information sheet to be read before the participants clicked on a link for the survey. Consent was assumed if they clicked on the link. The inclusion criteria were self-identified people with ME who reported use of taVNS, past or present. The survey was open for four weeks and all data collected was

anonymous. Data analysis, as performed by the research team, used descriptive and inferential statistics for the quantitative data generated by the closed questions and content analysis of the qualitative data from the open questions. Participants were asked if they would also take part in follow-up semi-structured interviews. This data will be reported in a subsequent publication. Quantitative data were coded and entered into IBM SPSS (version 25.0). Descriptive and inferential statistics were performed, including Spearman's rho, Kruskal-Wallis H Test, and logistic regression. Data were examined for the assumptions of the relevant test. When significant ($p =< 0.05$), the Kruskal-Wallis H Test was followed by post hoc analysis.

For logistic regression, data were converted into dummy variables. Participants were categorised into a binary dependent variable where group (1) rated taVNS as beneficial and group (2) rated it as non-beneficial. A second binary variable categorized any experience of short or longer-term harmful effects from taVNS where group (1) experienced harmful effects and group (2) did not experience harmful effects. To develop a binary logistic regression model, independent variables that had a p-value of less than 0.25 were considered into the model. A forward selection stepwise (Wald) procedure was conducted[8]. Responses to open ended questions were analysed using content analysis and provide additional insight into the experiences. More detailed thematic analysis will combine the open question responses with data from the follow-up semi-structured interviews and reported in detail in a separate paper.

Table 1 here

Results

Demographics

116 responses were received (see Table 2). Most participants were aged between 35-70 (84%), residents of the United Kingdom (60.3%) and female (85.3%). The most commonly reported co-morbidity was Postural Orthostatic Tachycardia Syndrome (57.8%). The most often reported trigger for their ME was post-viral (78%).

Table 2.

Parameters of taVNS

The majority of respondents had been using taVNS for less than a year (89.6%). Most respondents used a transcutaneous electrical nerve stimulation (TENS) device (75.9%), followed by Parasym (17.2%), and Nemos (2.6%). The median pulse rate was 30Hz, and pulse width was 200uS. The left side of the body was the most common to apply the device (81.9%) and the most common location on the ear was the tragus (84.5%). The average number of usage days per week was 6.16 (95% CI: 5.85-6.48). The average length of each session was 29 minutes (95% CI: 25.73-33.04). The average number of sessions per day was 1.73 (95% CI: 1.51-1.94). Since starting taVNS, some respondents changed the settings of the device (45.7%); the location of application (23.3%); and the type of electrodes (22.4%). Table 3 provides more detail about the use of taVNS.

Table 3 here

Effects of taVNS

65 respondents (56%) reported their experience of taVNS as beneficial; 19 (16%) as very beneficial, 22 (18%) as moderately beneficial, and 24 (20%) as mildly beneficial. 16 (13%) respondents said taVNS had no effect, and 7 (6%) said it made them worse.

The remaining participants either did not know what effect taVNS had (N=9, 8%) or suggested that it was too soon to tell (N=19, 16%); however, 93 (80%) said they were continuing to use taVNS. 78 respondents (67%) would recommend taVNS to other people with ME, 5 (4%) would not recommend it, and 33 (28%) were unsure. The association between the duration of using taVNS and its perceived effect was statistically significant, but small (r = .25, P < .05).

The perceived changes in severity of symptoms before and after using taVNS are listed in Table 4. While some individuals did not report a change in the severity of symptoms after using taVNS, they rated the effect of taVNS favourably. There was an increase in the number of subjects experiencing mild symptoms, and a decrease in those experiencing very severe symptoms after using taVNS. However, the majority of people experiencing moderate or severe symptoms before taVNS did not significantly change after taVNS.

Table 4. About here.

From the point of initiating taVNS, a Kruskal-Wallis H Test showed statistically significant self-reported improvements in some symptoms and activities across the five time points (1: 0 - 1 month, 2: 1 - 3 months, 3: 3 - 6 months, 4: 6 - 12 months, 5: 1 year +). These improvements were in post-exertional malaise (H (4) = 9.54, P = .049); pain (H (4) = 10.04, P = .04); gut problems (H (4) = 20.71, P < .001); urinary problems (H (4) = 12.34, P = .015) and mental health issues (H (4) = 13.95, P = .007). There were also significant improvements in the ability to leave the house (H (4) = 10.01, P = .040).

Some users described very positive experiences; *"For me it is a life changing improvement", "Major change in gut motility and calming the sympathetic nervous system", "Most notably I am able to eat a wider variety of foods without side effects now"*. Others reported a benefit

for general management; "*Most of the improvements were in the first couple of months. I have plateaued somewhat but feel that ongoing use maintains my improvement. It also is helpful as a 'PRN' treatment for symptoms".* It must be acknowledged, however, that identifying taVNS as the only factor leading to a positive change is not possible, as a number of people commented*; "Difficult to determine taVNS effects from lifestyle changes and supplements", "Too many other concomitant interventions for this to have any meaning in isolation".*

40.5% of participants reported no short-term harmful effects and 85% no long-term harmful effects of taVNS. However, the most common short-term and long-term harmful effects reported were irritation at the site of stimulation (35.3% short-term, and 86% long-term effects), headache (14.7% short-term effects), fatigue (8.6% short-term effects) and insomnia (8.6% of short-term users) (Table 4). Some attributed its use to a worsening of symptoms: *"Led to a major crash which took months to recover from"* while others found application of the device too difficult, *"Doing anything that involves raising my arms is hard and triggers breathlessness and other symptoms. And the whole process of getting the clip and sticker pad on was very tiring. There's no way I could do this every day".*

Support

Only 8.6% participants reported having support from health care providers, with most support coming from other taVNS users (33.6%) and Facebook Groups (31.9%) (Table 3); *"I have had to work out how much to use it through trial and error", "I need guidance and help to understand if I'm doing it right, or different ways of using the equipment. I had to look up on YouTube how to use the ear clip, but there didn't seem to be any set way of doing it. Also, lots*

of people said it might be dangerous… The CFS clinic doctor had no idea about it, but said she was interested in finding out more. Some guidelines would help."

Logistic regression

All test assumptions were met. No outliers nor multicollinearity were detected. First, variables that could predict the lack of benefits of taVNS were not identified. Second, the variables that predict the probability of short-term or intermittent harmful effects were having difficulty controlling the intensity of stimulation and the side of applying taVNS (individuals who used taVNS on the left side were less likely to develop short-term or intermittent harmful effects). Table 6 shows details of the model. Third, variables that could predict the occurrence of longer-term harmful effects from taVNS were not identified.

Table 5: About here.

Discussion

This study aimed to explore the experiences and attitudes of people with ME towards taVNS. Survey participants were mainly female between the ages of 30 – 70[1] reflecting the larger ME population. The majority of respondents were from the UK so it is not clear if more people in the UK are using taVNS or that the survey did not reach many of the English-speaking ME populations in the rest of the world. In future surveys, the survey link would need to be shared with more global ME organisations. The results of this survey therefore reflect the experiences of people with ME mainly in the UK.

The putative benefits of taVNS were identified in the significant differences before and after using taVNS in the severity of post exertional malaise, pain, gut problems, urinary problems,

mental health, and the ability to leave the house. 67.2% of respondents would recommend taVNS to other people with ME, however, 4.3% of respondents would not, and short and long-term negative effects were reported. Participants who had difficulty controlling the intensity of the stimulation and difficulty with application were more likely to experience short-term harmful effects. This suggests the need for support from experts in the correct application of taVNS. The open questions also identified one person who had a major crash after the use of taVNS. This is concerning and further research is needed to identify why some people experience more long-term harmful effects.

It is not possible to clearly attribute improvements or deterioration to the use of taVNS, given baseline fluctuations in symptom severity[3], in addition to other factors cited for symptom changes such as over-exertion, vaccination or infection, stress, diet, medication, and relaxation and pacing techniques. Randomized controlled trials are needed to identify a causal relationship between taVNS and any positive or negative effects.

For taVNS to become a clinically relevant therapy, it is important to understand both mechanism of action and optimal modalities[10]. The parameters for taVNS application are thought to influence autonomic processes, but no optimal parameters have been determined[9]. Frequently adopted settings in research are a pulse width between 200uS and 300uS at a rate of 25 Hz[9]. The median settings reported in this survey were 200uS at 30Hz. Output intensity was not identified in this survey but it must be noted that not all TENS devices are suitable for taVNS as it is not possible to set the low levels of intensity required. It is not clear from the survey responses whether the TENS devices were appropriate for taVNS and 40% had difficulty with discomfort from the electrodes, while 43% had difficulty with the application of electrodes, so this needs to be considered when determining the effects of taVNS. In addition, the cognitive difficulties associated with ME may have led to problems setting up the TENS devices such as incorrect programming. This could have affected the negative

responses seen in the survey and highlights the need for appropriate support for people with ME in the use of taVNS.

There are currently no approved treatments specifically for ME[1] and management tends to be symptom specific. Without widely available treatments, it is not uncommon for people with ME to explore interventions independently, such as remedies for pain relief[12] or dietary supplementation[13]. Thus people with ME have also been exploring taVNS for symptom relief, given its success in other areas of healthcare[14]. This is concerning as there is no evidence of its effectiveness in people with ME, and this survey has identified potential negative effects and a need for support when setting up and using the devices.

Trials of direct stimulation of the vagus nerve have been conducted in a wide range of conditions including epilepsy, depression, anxiety, pain and migraine[9] and Long Covid[15] but only two studies have been published on ME. A randomised placebo-controlled study using an intranasal mechanical stimulation[16] with 30 people with ME reported a 30% reduction in overall symptoms, but not fatigue, after eight weeks in comparison to a placebo. However, this study required participants to attend a clinic twice a week, and reported that many suffered PEM and subsequent deterioration. The second study involved trialling non-invasive vagus nerve stimulation using a device held to the neck for 11 people with ME, in addition to participants with fibromyalgia and rheumatoid arthritis[17]. Although the study reported a significant reduction in daytime sleepiness, abnormal fatigue, anxiety and depression, the report was under-powered and had a short treatment period of only 24 days. More research is needed to identify the benefits and risks of taVNS in order to ensure safe clinical practice.

Limitations

This survey did not confirm a diagnosis of ME from a health care professional, although the patient information sheet and all literature advertising the study identified a diagnosis of ME

as part of the inclusion criteria. In future surveys, published ME criteria will be part of the participant information leaflet so participants can check that if their symptoms fit formal ME criteria. As this was an exploratory survey, it could not establish the safety and efficacy of taVNS, which requires a randomized clinical trial.

Conclusion

This survey aimed to explore the experiences and attitudes of people with ME towards taVNS. Although there are limitations of this approach, the survey suggested that some proportion of individuals with ME may experience significant benefits from using taVNS, including a reduction in symptom severity and an improvement in the ability to leave the house. However, others have experienced negative effects, and this highlights the need for controlled intervention studies to clearly identify safe parameters of taVNS for people with ME.

Conflict of Interest

The authors declare no conflicts of interest.

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Table 1: Survey items

Length of ME/CFS symptoms in years
Gender
Age group
Region of living
Additional diagnoses.
Predisposing factors do you believe led to the onset of your ME/CFS
Reasons to trial taVNS
Support (if any) for trial of taVNS
Currently using taVNS or have stopped
The device used for taVNS?
Settings
Type of electrodes
Locations on the ear
Locations on other parts of the body
The side of the body used
Any changes to Settings, Location, and Electrodes since starting taVNS
Duration of taVNS use.
Issues with your equipment.
Satisfaction
Changes in the following SYMPTOM (Improved, No change, Worse)
Post-exertional Malaise (fatigue and worsening of symptoms following exertion)
Brain Fog (eg difficulty concentrating, remembering, and processing information)
Pain (eg muscles, joints, headache etc.)
Sleep problems (eg unrefreshing sleep, insomnia, daytime sleeping etc)
Neurosensory issues (eg sensitivity to sound, touch, movement, visual problems etc)
Sensitivities to food, chemicals, medications, odours
Physical weakness (eg muscle weakness, poor coordination, muscle twitching etc)
Flu-like symptoms (eg sore throat, sinusitis, swollen lymph nodes etc)
Gut problems (eg diarrhoea, bloating, abdominal pain, nausea)
Urinary problems (eg urinary urgency, incontinence)
Cardiovascular problems (eg inability to sustain upright posture, rapid heart rate etc)
Problems with temperature regulation (eg cold extremities, sweating)
Mental health issues (eg low mood, anxiety, irritability
Changes in the following ACTIVITY (Improved, No change, Worse)

Showering and dressing
Cooking and preparing meals
Ability to leave the house
Engaging in 30 minutes of physical activity (eg playing with children, cleaning, walking)
Engaging in 30 minutes of social interaction (eg phone call, video call, face to face)
Engaging in 1 hour of mental activity/work
Ability to engage in part-time work/study (20 hours)
Ability to engage in full-time work/study (38 hours)
Short-term or intermittent harmful effects experienced associated with taVNS
Longer-term harmful effects from taVNS, persisting 4 weeks or more.
The overall severity of ME/CFS symptoms at BASELINE prior to commencing use of taVNS and NOW after using taVNS.
Rating the effect of taVNS on ME/CFS
Willingness to continue with taVNS
Recommending taVNS to other people with ME/CFS

Table 2. Demographics of the survey population

Demographic	N	(%)
Age group (years)		
19 – 34	15	(12.9%)
35 – 50	46	(39.7%)
51 – 70	52	(44.8%)
71 – 90	3	(2.6%)
Sex (female)	99	(85.3%)
Country of origin		
UK including NI	70	(60.3%)
Europe	18	(15.5%)
Australasia and Oceania	16	(13.8%)
North America excluding Canada	12	(10.3%)
Length of time with symptoms of ME/CFS in years		
0 – 4	22	(19.0%)
5 – 9	33	(28.4%)
10 - 20	25	(21.6%)
>20	36	(31.0%)
Additional diagnoses (some participants selected more than one option	16	(13.80%)
No	67	(57.8%)
Postural Orthostatic Tachycardia Syndrome or Orthostatic Intolerance (POTS or OI)	30	(25.9%)
Dysautonomia or Short Fibre Neuropathy (SFN)	28	(24.1%)
Mast Cell Activation Syndrome or Mast Cell Activation Disorder (MCAS or MCAD)	24	(20.7%)
Fibromyalgia	21	(18.1%)
Migraine	16	(13.8%)
Orthostatic Hypotension or Neurally Mediated Hypotension (OH or NMH)	12	(10.3%)
Autism Spectrum Disorder (ASD)	10	(8.6%)
Ehlers-Danlos Syndrome or Spectrum Disorder (EDS or SD)	8	(6.9%)
Long Covid	32	(27.6%)
Other		

ME/CFS Predisposing factors (some participants selected more than one option)		
An infectious illness	91	(78.4%)
Psychological stress	50	(43.1%)
Physical trauma	17	(14.7%)
Genetic factors (other family member affected)	16	(13.8%)
Immunisation	10	(8.6%)
Exposure to heavy metals	10	(8.6%)
Exposure to toxic chemicals	11	(9.5%)
Blood transfusion	2	(1.7%)
Surgery	11	(9.5%)
Unknown	12	(10.3%)
Other	11	(9.5%)

Table 3. Characteristics of taVNS use

Variable	N	(%)
Current user		
Yes	84	(72.4%)
Stopped using taVNS	32	(27.6%)
Reasons for stopping		
Difficulties using the equipment	4	(3.4%)
No improvement	12	(10.3%)
Unwanted negative effects	16	(13.8%)
Length of time using taVNS		
0 - 1 month	34	(29.3%)
1 - 3 months	19	(16.4%)
3 - 6 months	26	(22.4%)
6 - 12 months	25	(21.6%)
1 year +	10	(8.6%)
Missing	2	(1.7%)
Support		
No support	24	(20.7%)
Equipment supplier	20	(17.2%)
Health care professional	10	(8.6%)
Other taVNS users	39	(33.6%)
Friends/family	7	(6.0%)
Facebook group	37	(31.9%)
Other	12	(10.3%)
Type of electrodes (participants selected more than one option)		
Electrode supplied with custom taVNS device (eg Parasym, Gammacore, Nemos)	23	(19.8%)
Double clip	36	(31.0%)
Two single clips	12	(10.3%)
Single clip with adhesive pad	50	(43.1%)
Two adhesive pads	1	(0.9%)
Other	4	(3.4%)
Locations on the ear (participants selected more than one option)		
Tragus	98	(84.5%)
Cymba Concha	15	(12.9%)

Cavum Concha	16	(13.8%)
Lobe	5	(4.3%)
Antihelix	5	(4.3%)
Helix	3	(2.6%)
Triangular fossa	4	(3.4%)
Ear not used	0	(0.0%)
Other	1	(0.9%)
Locations on other parts of the body		
Neck	4	(3.4%)
Shoulder	45	(38.8%)
Other	1	(0.9%)
Missing	66	(56.9%)
Issues with your equipment		
No issues with the equipment	39	(33.6%)
Discomfort from electrode (eg pressure, pain)	46	(39.7%)
Difficulty with application of electrode (eg not staying in place)	50	(43.1%)
Difficulty controlling the intensity of stimulation	15	(12.9%)
Other	16	(13.8%)
Satisfied with equipment		
Not at all satisfied	12	(10.3%)
Neither satisfied or unsatisfied	8	(6.9%)
Mildly satisfied	11	(9.5%)
Moderately satisfied	39	(33.6%)
Very satisfied	44	(37.9%)
Other	2	(1.7%)

Table 4. Severity of ME/CFS symptoms before and after using taVNS and harmful effects

Severity of symptoms	before using taVNS N (%)*		after using taVNS N (%)*	
Mild symptoms	9	(7.8%)	13	(11.2%)
Moderate symptoms	57	(49.1%)	56	(48.3%)
Severe symptoms	46	(39.7%)	47	(40.5%)
Very severe symptoms	9	(7.8%)	3	(2.6%)
Missing	2	(1.7%)	6	(5.2%)
Harmful effects associated with taVNS use	**Short-term or intermittent**		**Longer-term > 4 weeks**	
No harmful effects	47	(40.5%)	99	(85.3%)
Irritation at the site of stimulation (eg tingling, pain, redness, itching, skin breakdown)	41	(35.3%)	10	(8.6%)
Light-headedness / dizziness	9	(7.8%)	2	(1.7%)
Fatigue	10	(8.6%)	3	(2.6%)
Shortness of breath	3	(2.6%)	2	(1.7%)
Voice alteration / hoarseness	1	(0.9%)	1	(0.9%)
Abnormal heart rhythm	6	(5.2%)	2	(1.7%)
Insomnia	10	(8.6%)	2	(1.7%)
Anxiety	8	(6.9%)	1	(0.9%)
Headache	17	(14.7%)	3	(2.6%)
Other	30	(25.9%)	4	(3.4%)

*some participants selected more than one option

Table 5: A Logistic regression model for probabilities of developing short-term or intermittent harmful effects (N: 116)

Variable	Factor	Coefficient (*B*)	X^2 (1)	p-value	Odd ratio (*OR*)	95% CI for *OR*	
						Lower	Upper
Short-term or intermittent harmful effects^	Difficulty controlling the intensity of stimulation	.985	4.986	.026	2.447	1.116	5.369
	Left side	-1.296	4.617	.032	.274	.084	.892
	Constant	1.082	3.484	.062	2.951		

^ This model was statistically significant ($\chi 2$ (2) = 15.0, p < .01). It explained 11.6% of the variance in Short-term or intermittent harmful effects (Nagelkerke R2), and correctly classified 63.8% of cases. (Hosmer and Lemeshow test: $\chi 2$ (2) = .075, p-value = 0.963). Individuals who used taVNS on the left side were less likely to develop short-term or intermittent harmful effects.