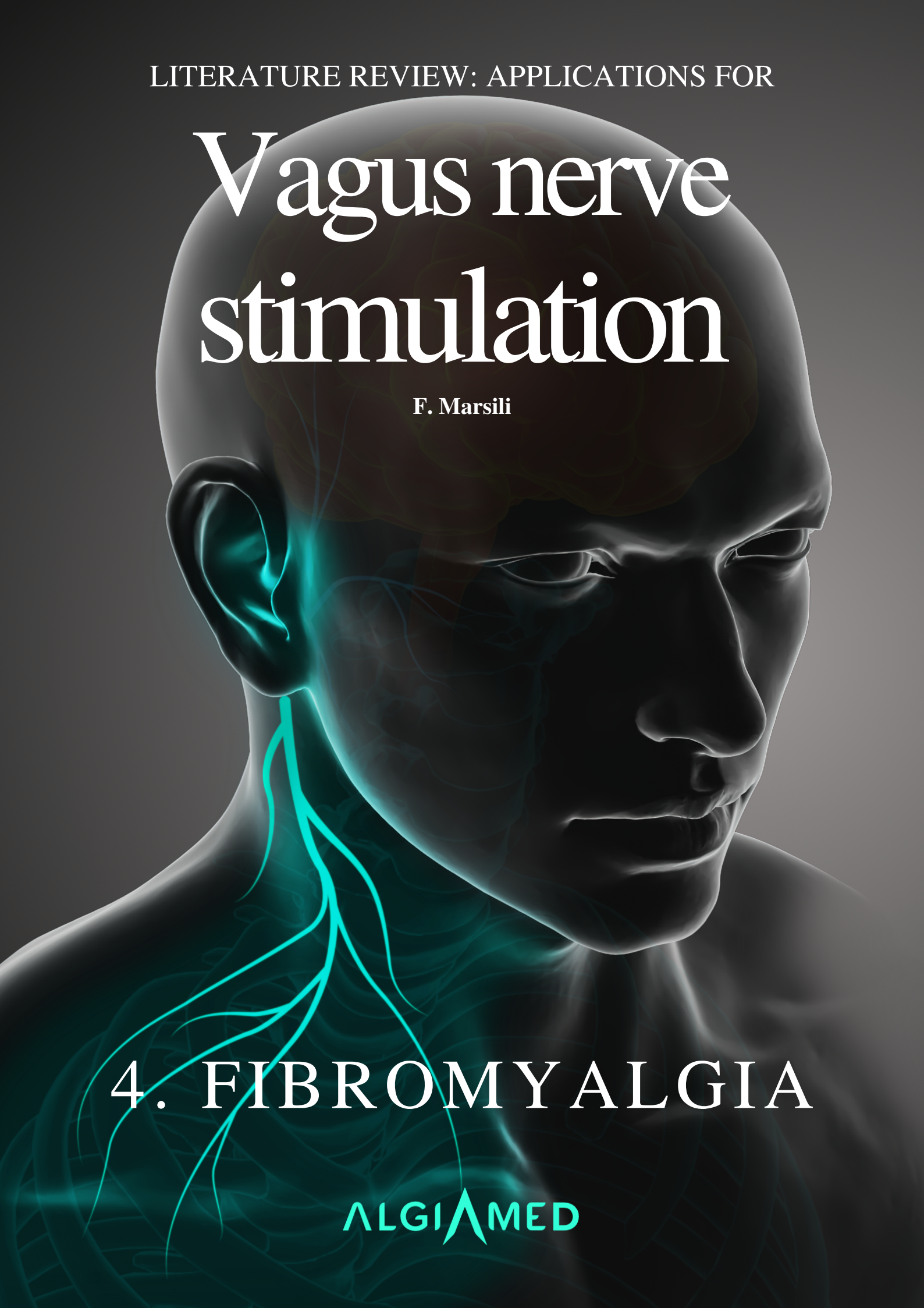
LITERATURE REVIEW: APPLICATIONS FOR

Vagus nerve stimulation

F. Marsili



4. FIBROMYALGIA

ALGIAMED

Author's choice

The papers in this collection focus on the application of Vagus Nerve Stimulation (VNS) as established therapeutic solution for difficult-to-treat conditions.

The vagus nerve is the longest cranial nerve and is widely distributed throughout the body, traversing the neck, thorax and abdomen. It is composed by motor fibres and sensory fibres from sympathetic and parasympathetic branches. [1], [2]. Afferent branches of the vagus nerve innervate brain behavioural areas involved in depressive states, and it desynchronises cortical activity with anti epileptic effects [3], [4]. Efferent branches of the vagus nerve regulate gastrointestinal secretory and motor function [5]. Recent advances in the field, have unraveled an anti-inflammatory role of the efferent vagus nerve via the Cholinergic Anti-inflammatory Pathway (CAP), a known mechanism for neural inhibition of inflammation linked to the activation of the autonomic nervous system (ANS) [6], [7].

Electrical stimulation of the VN modulates the nervous system at central, peripheral, and autonomic levels without the need for pharmacological interventions. For decades, invasive techniques of VNS have demonstrated their clinical efficacy in VN-related diseases and, to these days, efforts have been made to create a more safe, effective, and non-invasive solution to VNS.

The auricular branch is the only peripheral branch of the VN on the human body, it is part of the afferent portion of the VN that directly connects to the brainstem. Thus, auricular VN has become the most favourable access point for non-invasive VNS. Neuroimaging studies on animal models and humans have confirmed the modulatory efficacy of auricular VNS (aVNS). For examples, fMRI studies show identical activation patterns in the brain between invasive and aVNS, with significant inhibitory and anti-inflammatory effects. Due to the existence of different control systems, the anti-inflammatory effects of aVNS (i.e., release of norepinephrine and noradrenaline, and neurotrophic factors) seem to occur immediately after intervention, while neuroplastic changes only occur as a consequence of sustained regenerative efforts [7].

Colleciton 1 and collection 2 are the most extensive selections, since VNS has been standard-of-care for epilepsy and depression for decades. Collection 3 explores the possibility of using VNS for the treatment of posttraumatic stress disorders. Collection 4 focuses on fibromyalgia and collection 5 on multiple sclerosis. Collection 6 and 7 corroborates the hypothesis that VNS can be used to activate the cholinergic anti-inflammatory pathway to treat inflammatory diseases, such as inflammatory bowel disease or rheumatoid arthritis. Collection 8 and 9 focus on the use of VNS for ameliorating pain sensitivity in chronic pain conditions and for rehabilitating upper limb motor fibres after ischemic strokes, respectively. In conclusion, collection 10 opens up other possibilities for clinical applications of VNS, ranging from cardiovascular diseases, through ADHD disorders, to tinnitus.

To summarise, VNS is a novel technology and its non-invasive configuration is still under investigation. Further clinical examinations are mandatory in order to understand the underlying mechanism of VNS and to open the door to new possible therapeutic applications. However, being a non-invasive, safe, and efficient therapeutic solution, VNS is an attractive tool for further implementation and new creative clinical applications.

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4. VNS and fibromyalgia

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Safety and efficacy of vagus nerve stimulation in Fibromyalgia: A Phase I/II proof of concept trial

Gudrun Lange, PhD, **Malvin N. Janal, PhD**, **Allen Maniker, MD**, **Jennifer FitzGibbons, APN**, **Malusha Fobler, BA**, **Dane Cook, PhD**, and **Benjamin H. Natelson, MD**
UMDNJ-New Jersey Medical School, Department of Radiology, Newark, NJ (Dr Lange, Ms FitzGibbons and Ms Fobler), UMDNJ-New Jersey Medical School, Department of Psychiatry (Dr Janal), UMDNJ-New Jersey Medical School, Department of Neuroscience (Dr Natelson), Department of Veterans Affairs, New Jersey Health Care System, East Orange, NJ (Dr. Lange, Ms. FitzGibbons and Ms. Fobler), Beth Israel Medical Center, Department of Neurosurgery, New York, NY (Dr Maniker), Beth Israel Medical Center, Department of Pain Medicine & Palliative Care (Dr Natelson), New York University, College of Dentistry, Department of Epidemiology and Health Promotion, New York, NY (Dr Janal), William S. Middleton Memorial Veterans Hospital and the Department of Kinesiology, University of Wisconsin, Madison, WI (Dr Cook)

Abstract

Objective—We performed an open label Phase I/II trial to evaluate the safety and tolerability of vagus nerve stimulation (VNS) in patients with treatment-resistant fibromyalgia (FM) as well as to determine preliminary measures of efficacy in these patients.

Methods—Of 14 patients implanted with the VNS stimulator, 12 completed the initial 3 month study of VNS; 11 returned for follow-up visits 5, 8 and 11 months after start of stimulation. Therapeutic efficacy was assessed with a composite measure requiring improvement in pain, overall wellness, and physical function. Loss of both pain and tenderness criteria for the diagnosis of FM was added as a secondary outcome measure because of results found at the end of 3 months of stimulation.

Results—Side effects were similar to those reported in patients treated with VNS for epilepsy or depression and, in addition, dry mouth and fatigue were reported. Two patients did not tolerate stimulation. At 3 months, five participants had attained efficacy criteria; of these, two no longer met widespread pain or tenderness criteria for the diagnosis of FM. The therapeutic effect seemed to increase over time in that additional participants attained both criteria at 11 months.

Conclusions—Side effects and tolerability were similar to those found in disorders currently treated with VNS. Preliminary outcome measures suggested that VNS may be a useful adjunct treatment for FM patients resistant to conventional therapeutic management but further research is required to better understand its actual role in the treatment of FM.

Fibromyalgia (FM) affects 3.4% of women and 0.5% men in North America (1). Despite this prevalence, only three medications are currently approved for its use. Anecdotal data among FM practitioners suggest that many patients, however, continue to suffer pain which interferes substantially with their physical function and quality of life.

We evaluated the possibility that periodic stimulation of the left vagus nerve by Vagus Nerve Stimulation [VNS] throughout the 24 hr day might be a safe, tolerable, and useful adjunct treatment for patients reporting continued severe pain despite receiving current best

Corresponding Author: Benjamin H. Natelson, MD, Pain and Fatigue Study Center, Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, 10 Union Square East, New York, NY 10003. bnatelson@bethisraelny.org; 212-844-6768.

medical management. Three observations guided the reasoning for undertaking this trial: first, experimental studies suggested that afferent vagal stimulation may modulate descending serotonergic and noradrenergic neurons to reduce pain (2); second, VNS has FDA approval for treatment resistant epilepsy and depression – disorders which have been treated by similar medicines as those used to treat FM (3;4) and third, VNS appeared to decrease pain perception in patients with treatment-resistant depression (5). To test our hypothesis, we initiated a Phase I/II safety and tolerability trial of VNS in a cohort of FM persons with continued substantial pain complaints despite medical treatment. While the primary purpose of this "proof of concept" trial was to assess the safety and tolerability of VNS in FM, we also collected preliminary data assessing potential treatment efficacy.

METHODS

Study participants

This was an open label, longitudinal, single-center study using VNS in a group of FM patients refractory to conventional pharmacological treatment. To be eligible, patients had to have FM, diagnosed by a physician, for at least two years, be between 18 to 60 years of age, and attain at least average scores on the vocabulary subscale of the Wechsler Adult Intelligence Scale–III (WAIS-III (6)). In addition, FM patients had to provide physician-documented evidence that the following medications had been tried to treat FM pain but either did not provide sufficient relief or were tolerated poorly: non-steroidal anti-inflammatory drugs, tricyclic antidepressants or duloxetine (an SNRI), any one anti-convulsant drug, and tramadol. Patients had to be on a stable medication regimen for at least six weeks prior to study entry and were asked to maintain this regimen throughout the initial or acute phase of the study. While reductions in dosage did not affect continuing eligibility, dosage increases or the introduction of additional drugs were not allowed during the acute phase of the study; thereafter, there were no restrictions.

Exclusions included other medical illness that could cause widespread body pain; use of antipsychotic drugs or any non-pharmacological treatment for FM within three months of enrollment; vagotomy; being in litigation at time of enrollment; reporting the onset of FM following physical trauma; positive history of psychotic depression, bipolar disorder, psychotic disorders, substance abuse/dependence within 10 years prior to study intake on diagnostic psychiatric interview [MINI (7)]; patients with non-psychotic depression were not excluded.

One hundred and twelve individuals were recruited and screened between November 2006 and May 2008. Of these, 14 women fulfilled entry criteria and provided informed consent to undergo VNS implantation, activation, current intensity ramp up, and fixed stimulation for three months. Eleven of the 14 implanted patients participated in a longitudinal study lasting an additional 8 months.

Study procedures

Timeline—After signing an IRB approved screening consent, participants visited the Pain & Fatigue Study Center on two occasions to be evaluated for study eligibility. The evaluation included a careful medical history, physical examination, and blood tests (CBC with differential, sedimentation rate, SMA-18, TSH/T4/T3 uptake, CPK, ANA, Rheumatoid factor, C6-Lyme Elisa) to rule out other possible causes of widespread pain and to allow collection of baseline data. On each of these visits, eligibility was ascertained by confirming the diagnosis of FM using ACR criteria (8). Those criteria required (a) the presence of chronic widespread pain defined as ≥ three months of pain in at least three bodily quadrants plus pain in the axial skeletal area and (b) the report of pain upon pressure of at least 11 of

18 points with a pressure of 4 kg. To determine whether a point was tender or not, we used a standardized and validated examination (9) in which a "positive" tender point was defined as a patient rating of 2 or more on a 0 to 10 pain scale (0 was none, 5 moderate and 10 worst pain imaginable) upon palpitation with 4 kg pressure. At baseline, participants were required to wear a watch-type electronic diary (Actiwatch, Respironics, Inc, Portland, OR) that polled pain intensity five times a day over 9 days (at least 37 readings required for inclusion). Eligible participants had to have a median pain intensity score of at least 5 (where 0 indicated No Pain and 10 Worst Pain Imaginable). Once eligibility was confirmed, patients signed an implantation enrollment consent approved by the IRB of UMDNJ-NJMS.

Baseline data collected on the screening visits included the SF-36 (10), the Margolis Pain Drawing (11), and reports of usual FM pain intensity during the past week, scaled the same as the electronic diary. Quantitative sensory testing (QST) assessing heat pain was conducted using the TSA 2001 apparatus (Medoc, Ltd, Ramat Yishai, Israel). Participants rated the pain intensity and unpleasantness of seven stimulus intensities ranging from 43° C to 49° C in 1° increments, each presented twice and ordered at random, on a 10 point magnitude rating scale.

After a median of 60 days following enrollment, study participants were implanted with the VNS device. After two weeks for surgical recovery, participants began a two-week stimulation adjustment period during which VNS intensity was increased to deliver as high a current as could be comfortably tolerated [target range: 1 to 2 mA] while holding all other stimulation parameters constant [pulse width = 250 μsec; frequency = 20 Hz; duty cycle = 30 sec on, 5 min off – i.e., the parameters used by Cyberonics Inc, the device manufacturer, for previous trials of VNS]. Stimulus parameters were then held constant over the next 12 weeks, referred to as the "Acute Study," although reductions in VNS current intensity due to side effects were allowed. During this phase of the study, participants could decrease medications but could neither increase dose or frequency of existing medications nor add new medications. During their 9 return visits, study participants provided data on side effects of VNS, FM and medication status, as well as usual pain ratings since their last visit; they also completed QST and self-report questionnaires. Participants who continued in the follow up study after 5, 8 and 11 months of stimulation provided these same data; they could now also request upward adjustment of current intensity due to lessening of side effects over time or diminishing pain relief after the acute study.

Assessment of safety and tolerability

Primary safety endpoints included (a) the number of participants who tolerated implantation of the VNS device, its activation and ramp up through the end of the acute study and (b) the range of VNS output current tolerated at the end of the acute study and at the 5, 8, and 11 month follow-up visits. We aimed to determine whether: a) types of adverse events were similar to those reported in patients with refractory epilepsy and treatment resistant depression and b) rates of occurrence of adverse events were similar.

Efficacy outcomes

We assessed participants for clinical improvement at each of the planned study visits. Our primary outcome measure was whether participants attained a *minimal clinically important difference (MCID+)* following VNS; this criterion has been previously employed in a 3-month drug trial in FM (12). To become MCID+, participants had to show improvement on three separate measures: a 30% improvement from baseline 'usual pain ratings in the last week' AND a Patient Global Impression of Change score rated as markedly or moderately improved [1–2 on a 7 point scale] AND an improvement of at least 6 points [0.6 SD] on the Physical Function subscale of the SF-36.

The secondary outcome measure presented in this paper – i.e., loss of FM caseness – was not an a priori hypothesis since no data exist to support the notion that this variable might change with treatment. However, we added FM caseness as a post hoc outcome measure, because of the unexpected results seen at the end of the acute study period. We defined loss of FM caseness as a patient's no longer fulfilling both 1990 ACR FM criteria -- widespread pain and at least 11 tender points on palpation. We operationalized the definition of widespread pain by considering it present if patients had pain in at least 3 bodily quadrants plus having axial pain (score of ≥ 4). Thus scores ≤ 3 no longer fulfilled the widespread pain criterion. Patients having less than 11 tender points no longer fulfilled the tender point criterion.

We report safety and tolerability data for all 14 implanted participants; outcome is reported using an intent to treat analysis.

RESULTS

Participants were all women with ages ranging from 35 to 54. Four had major depressive disorder [MDD] on entry; three were disabled. Of the remaining 10 without MDD, four were disabled.

Safety and Tolerability

All 14 study participants tolerated implantation of the VNS device, its activation and the subsequent ramp up of VNS output current. Ultimately, 100% of the study sample tolerated implantation well, while 93% tolerated ramp up and fixed stimulation during the acute study (see below).

There were 4 unanticipated/serious adverse events occurring in 3 patients. The first was not device related: participant #118 was non-compliant with the protocol requirement for not changing medication during the 16-week acute study and was hospitalized for opiate overdose. The second was device related: Participant #115 experienced a device failure necessitating surgical revision. The third, also occurring in participant #115, was not device related: Following device re-activation and ramp up of stimulus intensity, she reported such marked dyspepsia that she asked that the stimulator be turned off. Dyspepsia continued despite cessation of VNS. Data from these two participants – both of whom came into the study positive for current MDD – are not included in the preliminary efficacy analysis of the acute study. The last adverse event was classified as possibly stimulation related: Participant #121 reported stimulus-bound electric-like sensations across her chest and into her left arm that were reduced by lowering VNS intensity; this side effect of stimulation is persisting but has been well tolerated.

At the end of the acute study, current intensity ranged from 0.75 to 2 mA [median = 1.5 mA]. Thereafter, participants were free to adjust their output current, but median output current remained stable at 1.5 mA: ranges of output current at 5, 8 and 11 month stimulation follow-up visits respectively were 1.0–2.5 mA; 0.5–2.25 mA, and 1.0–2.5 mA. Despite objective evidence of improvement at the end of the acute study, one patient [#105] with MDD perceived VNS as not beneficial for her widespread pain and felt it exacerbated her pre-existing headache disorder; she requested that the stimulator be turned off and elected to have it explanted subsequent to completing the acute study.

Frequencies of observed adverse events (AEs) related to surgery, the device, or stimulation for all 14 implanted participants are listed in Table 1. Most adverse events were similar to those reported in patients with refractory epilepsy and treatment resistant depression (13); they were self limited and decreased in severity over time.

Surgery and stimulation related adverse events not reported previously, but observed here included mild (n=1) to moderate (n=2) dry mouth and moderate (n=1) to severe (n=2) increases in fatigue. While rates of occurrence for voice alteration for FM patients were similar to those of patients with treatment resistant MDD and epilepsy (64% versus 58 and 54%, respectively), rates of neck/facial pain, headaches, and dyspnea were greater in the FM sample (50%, 21%, and 50%, respectively versus 13–16%, less than 5%, and 14–16%, respectively). These observations in this small sample suggest that individuals with treatment resistant FM, a chronic pain disorder, may be more sensitive to pain related to vagus nerve stimulation. However, this increased sensitivity did not result in termination of stimulation.

Efficacy

A priori outcome measure—Table 2 indicates the time points when individual participants became MCID+ [light grey shading]. At the end of the acute study, five [36%] of the 14 implanted participants had become MCID+, and in the follow up study, two, eight, and seven of the 14 implanted participants [14%, 57%, and 50% respectively] had become MCID+ at the 5, 8 and 11 month stimulation visits. Two participants were MCID+ across all 4 assessment times; one study patient was MCID+ at the end of the acute study and then again at the 8 and 11 month stimulation follow up visits; three patients became MCID+ at the 8 month and 11 month time points – suggestive of progressive improvement over time. Less successful outcomes included one participant who was MCID+ only at the end of the acute study and a second one who was MCID+ only at the end of the acute study and at the 8 month assessment.

A posteriori outcome measure—At baseline, each of the 14 women had tenderness in 4 bodily quadrants as well as in axial skeletal areas [noted in Table 2 as 5 within parentheses], and tender point counts ranged from 12 to 18 [median = 17.5]. Table 2 also shows the points in time when individual participants ceased fulfilling both criteria for FM caseness – that is, when participants had three or fewer quadrants of pain and had fewer than 11 tender points [thick outlined boxes]. These numbers increased over the course of the study from two at the end of the acute study to five at the end of the follow-up study. There was an association between MCID status and FM status: participants no longer fulfilled criteria for FM at 14 of the 22 time points [63.6%] where participants were MCID+, while only one no longer fulfilled criteria for FM at the 23 time points [4.3%] where participants were MCID- [Fisher's test = 0.001, 2-tailed]. Concordance between the two outcome measures seemed to improve over time. While only two of the five MCID+ participants no longer fulfilled the two criteria for FM at the end of the acute study, five of the seven MCID + participants no longer fulfilled both criteria for FM at the end of the follow-up study.

The overall decrease in pain sensitivity is supported by the QST results obtained prior to device activation and at each of the subsequent study visits for the 11 patients completing the follow up trial [see Figure 1]. As expected, reported pain intensity increased as the actual temperature of the probe increased, ANOVA for repeated measures $F_{2,26} = 14.1$, $p = 0.001$. Results also showed that there was a significant and progressive decrease in pain intensity reported to each of the three temperatures over the course of the study, ANOVA for repeated measures $F_{5,77} = 9.3$, $p = 0.001$.

DISCUSSION

In general, FM patients had the same types of side effects to VNS as those reported in patients with treatment-resistant epilepsy and depression – most often stimulus-bound voice alteration, neck pain, nausea, and dyspnea; these side effects tended to dissipate with time.

Dry mouth and increased fatigue were two AEs not previously reported and present in this study population. While implantation surgery was tolerated well, two patients did not complete the acute study [one due to problems tolerating stimulation and the other due to study violations]; a third patient requested device explantation due to treatment inefficacy. This non-completion rate does not differ from that reported at the end of the one year trial of VNS for major depression [270 completers of 295 implanted (14); fishers test NS]. Eleven women completed the follow up study. No late emerging AEs were observed.

While the primary purpose of this study was to assess the safety and tolerability of VNS in FM, a secondary goal was to do a preliminary evaluation of its efficacy. We assessed the MCID and another measure added at the end of the acute study phase – the existence of the diagnosis of FM consistent with 1990 ACR FM criteria (2), i.e., FM caseness. We had not considered loss of FM caseness (2) as a possible outcome measure when we designed the study because no published treatment had been efficacious enough to affect diagnosis, but since we found this to occur in certain VNS-treated patients, we realized that using loss of FM caseness as an outcome variable might be useful for clinicians in judging the potential efficacy of VNS.

Both outcome measures showed substantial improvement over time. At the end of the acute study, five of the 14 participants became MCID+ and two no longer fulfilled both diagnostic criteria for the 1990 ACR FM case definition (2). In contrast to studies using reduction in pain alone to indicate the therapeutic efficacy of a drug in treating FM, only this and one other published trial used the more demanding MCID to determine a positive therapeutic effect (12). Importantly, no study has ever reported sufficient improvement in pain that treated patients no longer fulfill criteria for the diagnosis of FM (2).

This therapeutic effect seemed to increase beyond the acute trial. At the end of the 11 month study, seven patients were MCID+ and parallel improvement was seen in terms of FM caseness (2): five patients no longer fulfilled either the widespread pain criterion or the tender point criterion for the diagnosis of FM (2), and a sixth patient continued to have wide spread pain but had fewer than 11 tender points (dark grey shading in Table 2). We were surprised by the robustness and ubiquity of response to the VNS treatment. While it is true that “improvement in tender point threshold appears to be a difficult outcome to achieve” (4), our results suggest that an FM treatment can reduce tender point threshold to the degree that the point tested is no longer tender.

However, tender point count was not a reliable predictor of continued therapeutic success over time as can be seen with #102 as an example (see Table 2). She had widespread pain throughout the trial and had as few as five tender points at one visit; but, then, number of tender points increased thereafter. The best predictor of outcome seemed to be reduction in painful quadrants to three or lower. For every patient except #121 at her 8 month visit, this reduction in bodily pain boded well for continued clinical improvement.

The reduction in QST/psychophysical response to heat pain stimuli suggests that VNS had an effect on the sensitivity of the nociceptive system. Patients reported large decreases in pain ratings from the pre-stimulation baseline to the end of the acute study phase, and these changes persisted throughout the remaining study visits. These data suggest that VNS may tune down the pathophysiological processes responsible for central sensitization, thus providing a potential mechanism as to how VNS can reduce widespread musculoskeletal pain in FM. The results of the entire QST battery are currently being prepared as a separate manuscript.

Since this is an uncontrolled pilot study, an obvious question is whether this positive therapeutic effect is specific to VNS itself or is a placebo effect secondary to extraneous

factors related to being in a treatment trial necessitating surgery, feeling a sensory stimulus throughout the day, and having high hopes for a good therapeutic outcome. Some data do exist to show that non-specific [i.e., placebo] effects can last for many months in trials requiring surgery. But studies reporting that outcome were for episodic events – syncope (15) or angina (16) – very different conditions from one with chronic pain. One trial on Parkinsonian patients has been cited as showing a long-lived placebo effect, but not one which improved patients' neurological impairment or their objective function (17); another with sham surgery for knee pain did produce a 10% reduction in pain over one year (18). Thus, published data indicating a prolonged effect of nonspecific factors in reducing chronic symptoms are sparse.

Some evidence for an initial non-specific effect may be seen from the data of one participant, subject #124, who became MCID+ at the end of the acute study but at no time point thereafter. However, the continued improvement over time shown by some patients and the fact that more patients attained outcome criteria over time argues against a non-specific or placebo explanation for the therapeutic benefit; such an incrementing response has been reported for VNS treatment of refractory epilepsy (19). Nevertheless, a controlled trial is needed to determine the specificity of these effects.

Acknowledgments

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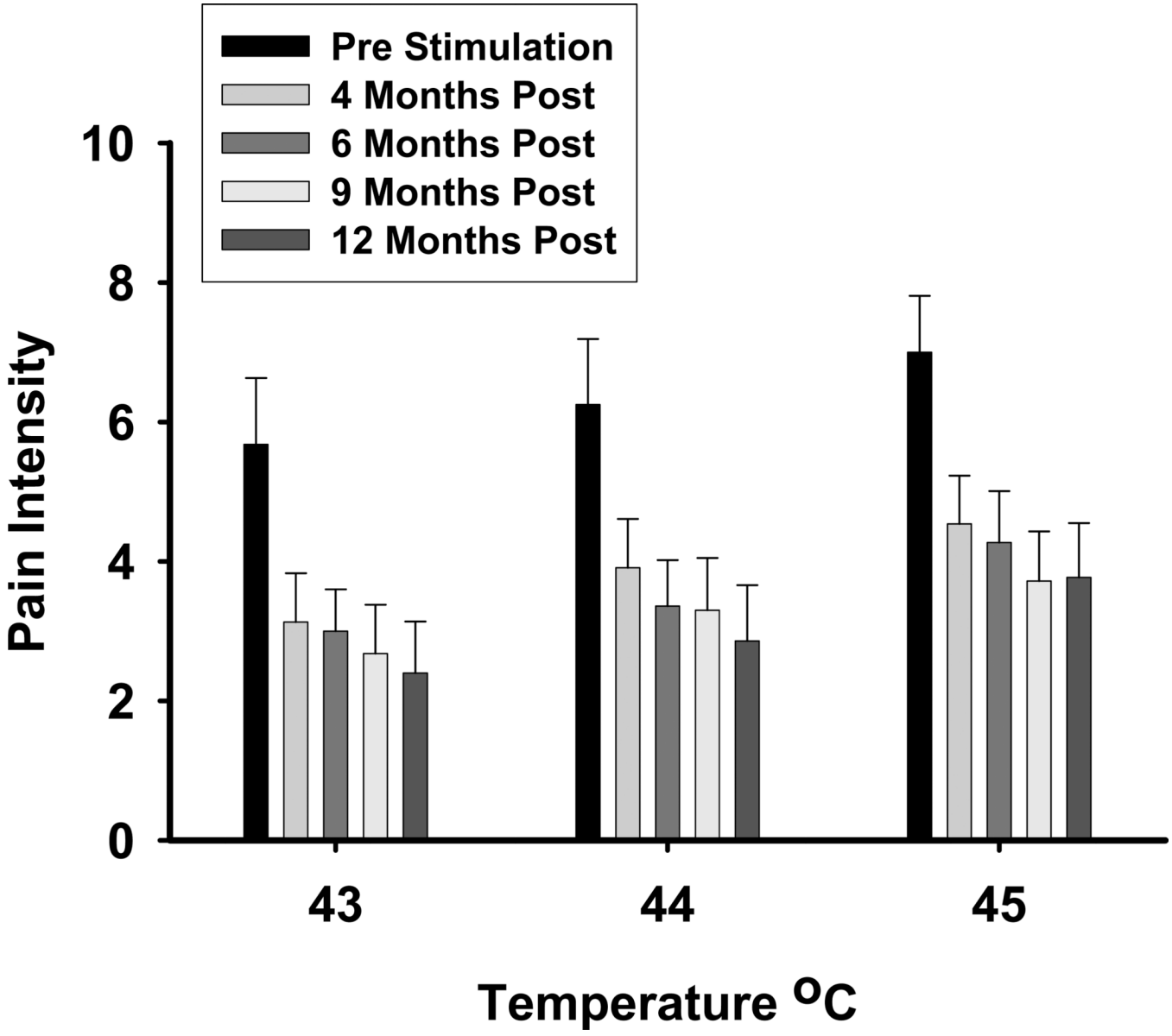

Figure 1.
Mean pain intensity ratings (± SEM) across the duration of the study. Data are plotted in months following surgical implantation of VNS.

Table 1

Study participant adverse event profile

Observed Surgery Related AEs (N=14)	**Mild**	**Moderate**	**Severe**
Dyspnea		3	
Voice Alteration	1	1	
Infection/Fever		1	
Incision pain	1	1	
Skin irritation	1	1	
Nausea		2	
Neck pain			1
Sleep difficulties/Insomnia		2	
Surgery-related complications such as upper respiratory infection		1	
Observed Device or Stimulation Related AEs (N=14)	**Mild**	**Moderate**	**Severe**
Agitation/anxiety/panic		1	
Chest pain			1
Device migration	2		
Decreased appetite/weight loss	1		
Dyspepsia		1	2
Dysphagia	2		
Dyspnea	3	4	
Ear pain	1	2	
Facial pain	1	3	1
Gastritis		1	
Headache	2	1	
Increased coughing	1		
Mania, hypomania, and related symptoms	1		
Nausea and vomiting	2	3	
Neck/throat pain	1	3	3
Sleep disturbances/difficulties, including worsening of pre-existing obstructive sleep apnea, insomnia		4	
Tinnitus			1
Tooth pain		1	
Voice alteration	5	4	
AEs potentially specifically related to Fibromyalgia (N=14)	**Mild**	**Moderate**	**Severe**
Surgery related			
Dry mouth	1		
Fatigue		1	
Headache		1	
Neck numbness		1	
Device and stimulation related			
Abdominal pain		1	

Observed Surgery Related AEs (N=14)	**Mild**	**Moderate**	**Severe**
Depression worsening		1	1
Dry mouth	1	2	
Excessive production of saliva	1		
Fatigue		1	2
Nasal congestion	1		
Neck numbness		1	
Photophobia		1	

Table 2

Efficacy outcome measures: Tender points (# quadrants of Pain) Across the Study

ID	Baseline Average	Acute Study End	After 5 Months of Stim.	After 8 Months of Stim.	After 11 Months of Stim.
102	12 (5)	9 (5)	5 (4)	10 (5)	14 (5)
104	18 (5)	2 (4)	4 (5)	1 (1)	8 (2)
105	14.5 (5)	6 (4)	STOP	STOP	EXPLANT
106	18 (5)	11 (5)	8 (0)	5 (2)	7 (3)
107	16 (5)	12 (5)	8 (5)	6 (3)	3 (3)
108	17 (5)	4 (1)	4 (3)	7 (0)	6 (0)
111	15.5 (5)	0 (1)	8 (5)	9 (5)	9 (4)
114	18 (5)	16 (5)	16 (5)	8 (4)	13 (5)
115	18 (5)	DEVICE PROBLEM THEN SIDE EFFECTS→ STOP			
117	18 (5)	18 (5)	5 (0)	2 (2)	5 (2)
118	13.5 (5)	STUDY VIOLATION; EXCLUDED			
119	18 (5)	18 (5)	18 (5)	18 (5)	18 (5)
121	18 (5)	18 (4)	18 (5)	18 (3)	18 (5)
124	15 (5)	15 (4)	14 (4)	11 (4)	15 (4)

Light grey filled cell indicates MCID+

Thick black outlined cell indicates no longer fulfilling EITHER widespread pain OR tenderness criteria for FM

Dark grey filled cell indicates patient who at last visit did not fulfill tenderness criterion for FM

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GENERAL & SELECTED POPULATIONS SECTION

Feasibility of Auricular Field Stimulation in Fibromyalgia: Evaluation by Functional Magnetic Resonance Imaging, Randomized Trial

Anna Woodbury, MD*,† Venkatagiri Krishnamurthy, PhD*,† Melat Gebre, MD* Vitaly Napadow, PhD‡ Corinne Bicknese, MD* Mofei Liu, MSPH§ Joshua Lukemire, MS§ Jerry Kalangara, MD*,† Xiangqin Cui, PhD*,†,§ Ying Guo, PhD§ Roman Sniecinski, MD, MSCR* and Bruce Crosson, PhD*,†

*Emory University School of Medicine, Atlanta, Georgia; †Atlanta Veterans Affairs Health Care System, Atlanta, Georgia; ‡Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; §Emory University Rollins School of Public Health, Atlanta, Georgia, USA

Correspondence to: Anna Woodbury, MD, Department of Anesthesiology, Emory University SOM, 1365 Clifton Road, Atlanta, GA 30322, USA. Tel: 404-778-5582; Fax: 404-686-4475; E-mail: anna.woodbury@va.gov, anna.woodbury@emory.edu.

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Trial registration: US National Institutes of Health ClinicalTrials.gov Id: NCT03008837

Abstract

Objective. To evaluate the feasibility of recruitment, preliminary efficacy, and acceptability of auricular percutaneous electrical nerve field stimulation (PENFS) for the treatment of fibromyalgia in veterans, using neuroimaging as an outcome measure and a biomarker of treatment response. **Design**. Randomized, controlled, single-blind. **Setting**. Government hospital. **Subjects**. Twenty-one veterans with fibromyalgia were randomized to standard therapy (ST) control or ST with auricular PENFS treatment. **Methods**. Participants received weekly visits with a pain practitioner over 4 weeks. The PENFS group received reapplication of PENFS at each weekly visit. Resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) data were collected within 2 weeks prior to initiating treatment and 2 weeks following the final treatment. Analysis of rs-fcMRI used a right posterior insula seed. Pain and function were assessed at baseline and at 2, 6, and 12 weeks post-treatment. **Results**. At 12 weeks post-treatment, there was a non-significant trend toward improved pain scores and significant improvements in pain interference with sleep among the PENFS treatment group as compared with the ST controls. Neuroimaging data displayed increased connectivity to areas of the cerebellum and executive control networks in the PENFS group as compared with the ST control group following treatment. **Conclusions**. There was a trend toward improved pain and function among veterans with fibromyalgia in the ST + PENFS group as compared with the ST control group. Pain and functional outcomes correlated with altered rs-fcMRI network connectivity. Neuroimaging results differed between groups, suggesting an alternative underlying mechanism for PENFS analgesia.

Key Words: Percutaneous Electrical Nerve Stimulation (PENS); Fibromyalgia; Alternative Therapies; Rehabilitation Medicine; Chronic Pain; Magnetic Resonance Imaging (MRI)

Introduction

Fibromyalgia is a chronic pain syndrome that consists of chronic widespread pain, decreased physical function, fatigue, psychoemotional and sleep disturbances, and various somatic complaints and affects approximately 8 million people in the United States [1]. It is estimated that fibromyalgia costs the US population over $20 billion per year in lost wages and disability [2, 3]. In Gulf War–Era veterans, the incidence of fibromyalgia is significantly higher in deployed personnel, making the veteran population a unique group in which to study fibromyalgia and its treatments [4]. Although the pathophysiologic mechanisms leading to development of the disease are not well established, there is sufficient evidence to support the idea that fibromyalgia is a disorder of autonomic nervous system dysfunction [5] and central (brain and spinal cord) pain-processing mechanisms [6]. One nonpharmacologic method for modulating autonomic nervous system dysregulation and treating pain is vagal nerve stimulation (VNS), which can be performed using the ear [7, 8]. The neuro-stim system (NSS) is a device approved by the Food and Drug Administration (FDA) for pain that targets the auricular branches of several cranial nerves, including the vagus via percutaneous electrical neural field stimulation (PENFS) [9, 10], providing a nonpharmacologic alternative for pain treatment.

Chronic, clinical pain is more difficult to study than experimental, evoked pain due to daily symptom fluctuations and lack of a controlled environment. Resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) is a specific type of neuroimaging that has evolved as an objective tool with the potential to reduce some of the variability in measuring parameters in chronic pain. It is capable of indexing functional connectivity between specific brain areas in patients with chronic pain and reflects changes that occur during their treatment [11]. This imaging approach has also been used to develop biomarkers for clinical pain intensity [12]. In a study of 17 participants with fibromyalgia, changes were found in insular connectivity to the default mode network (DMN) that correlated with changes in pain scores following treatment [13]. Based on this prior work, we aimed to assess a similar number of participants for this feasibility study using a novel nonpharmacologic treatment for fibromyalgia: auricular PENFS.

We hypothesized that PENFS results in greater pain and functional improvements than standard therapy (ST) and that these improvements can be correlated with altered brain connectivity as evaluated by rs-fcMRI. To test this hypothesis, we conducted a feasibility study in which we randomized veterans with fibromyalgia (2010 American College of Rheumatology criteria) [14] to ST control or ST with PENFS and evaluated post-treatment changes in pain, function, and rs-fcMRI.

Methods

Study Procedure

We conducted an open-label, randomized, controlled trial. Study participants were prescreened using a chart review of patients at the Atlanta Veterans Affairs Health Care System and then were invited via a phone call for a face-to-face screening session to determine if they met the inclusion criteria. Baseline assessments and rs-fcMRI were obtained by a blinded investigator prior to initiation of the intervention. Participants were re-assessed at 2, 6, and 12 weeks post-treatment. Follow-up rs-fcMRI was also obtained at 2 weeks post-treatment to assess changes in connectivity.

Participants

Twenty-one adult male and female veterans with a diagnosis of fibromyalgia were block randomized and stratified by sex to ST or PENFS in addition to ST. The inclusion criteria were as follows:

Age, 20–60 years (limit set to minimize brain structural changes due to aging).
Diagnosis of fibromyalgia by the American College of Rheumatology 2010 criteria [15].
Right-handedness (to provide consistency in brain structure and function).
Pain score of 4 or greater on the Defense and Veterans Pain Rating Scale (DVPRS) in the 3 months prior to enrollment.
Intact skin in area of PENFS treatment.
Ability to safely tolerate MRI.

The exclusion criteria were as follows:

Pregnancy.
History of seizures or neurologic conditions that alter the brain.
Claustrophobia, MRI-incompatible implants, or other conditions incompatible with MRI.
History of uncontrolled psychiatric illness, autoimmune disease that leads to pain, or skin conditions that can increase risk of infection at the PENFS site.

All participants provided written informed consent approved by the Institutional Review Board of Emory University and the Veterans Affairs Research & Development Committee.

Assessments of Pain and Function

Participants who met the study criteria returned for baseline assessments, including rs-fcMRI, collection of biobehavioral information, arm curl, 30-second chair stand, DVPRS, and documented baseline analgesic consumption. Arm curl tests measured the total number of bicep curls a veteran could do on the left and right arms in 30 seconds (5-lb weight for women; 8-lb weight for men). The 30-second chair stand test measured the total number of full sit-to-stands a veteran could do in 30 seconds. The DVPRS is a validated measure of pain for military and veteran populations and includes pain interference questions in the realms of "activity," "sleep," "mood," and "stress" [16]. Participants were

asked to evaluate on a scale of 0 to 10 the level of their pain and the level to which pain interfered with their "activity," "sleep," "mood," and "stress," with 0 representing no pain or interference and 10 representing the worst pain.

Intervention

Participants were stratified based on sex and block randomized to either ST or ST plus PENFS using the NSS device. PENFS treatment consisted of a series of four weekly treatments as described in the following section. Participants were assessed for changes in pain and function at 2, 6, and 12 weeks post-treatment.

Patients randomized to PENFS had the NSS (Innovative Health Solutions, Versailles, IN) applied; a battery pack (external auricular device) was secured via adhesive to the back of the ear to provide continuous stimulation at preprogrammed frequencies and intensities through electrodes that were sterilely, percutaneously placed at neurovascular bundles. The device was placed in the clinic, and the participants wore the device home continually until it was replaced at each weekly visit over 4 weeks. The external auricular device of the NSS is an FDA-cleared neuromodulating generator targeting acute and chronic pain with a frequency of 1–10 Hz, a pulse width of 1 millisecond, an amplitude of 3.2 V, an impulse of 100 mW, a length of stimulation of 120 hours, and a duty cycle of 2 hours on and 2 hours off.

All PENFS electrode placement points were located through transillumination, with one grounding electrode applied to the posterior concha and three electrode points to stimulate the respective auricular nerve endings (greater auricular, auricular branch of vagus, and auriculotemporal; Figure 1). The NSS uses a needle array instead of a single pin to help provide a field effect. Due to the effects of "field stimulation," the external auricle and its cranial nerve branches, including the vagal branch, receive stimulation [9].

ST consisted of medication management with neuropathic pain medications (gabapentin, pregabalin, duloxetine, tricyclic antidepressants, and so on), nonsteroidal anti-inflammatory medications (ibuprofen, meloxicam, and so on), topicals (lidocaine/prilocaine cream, menthol/salicylate, and so on), muscle relaxants (tizanidine, cyclobenzaprine, baclofen, and so on), and referral to acupuncture and physical therapy, tailored to the individual patient based on comorbid conditions and patient preference. Patients were evaluated weekly over 4 weeks in parallel to the weekly interventions performed on the PENFS treatment group.

MRI Acquisition

Blood oxygen level–dependent (BOLD) rs-fcMRI images were acquired on a 3 T Siemens Trio 3 T MRI scanner with a 32-channel phased-array head coil using a single-shot gradient-echo echo planar imaging (EPI) sequence with the following MRI parameters:

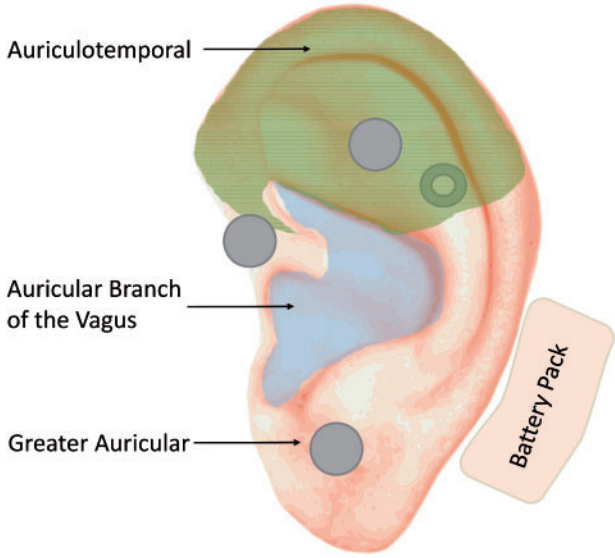


Figure 1. Depiction of the auricle showing nerve distributions and sample NSS placement. Electrode placement is shown using gray dots. The gray donut depicts one electrode array placed on the posterior pinna. Wire harnesses are not depicted. The battery pack is depicted with its usual placement posterior to the auricle.

Field of view (FOV) of 220 mm.
Repetition time/echo time (TR/TE) of 2,000/25 milliseconds
Multiband acceleration factor of 3.
Flip angle (FA) of 60°.
Matrix size of 110 × 110.
Slice thickness of 2 mm.
Generalized autocalibrating partial parallel acquisition (GRAPPA) factor of 2.
Partial Fourier of 6/8.
Thirty-four phase-encoded reference lines.
Seventy-two interleaved axial slices covering the entire brain.Three hundred fifty scan volumes to yield 9 minutes of resting-state fMRI data for stable estimation of connectivity networks.

A 1-mm^3 isotropic high-resolution T1-weighted anatomical image for spatial normalization to Montreal Neurological Institute (MNI) template space was acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TE of 2.89 milliseconds, TR of 2,300 milliseconds, FOV of 256 mm^2 × 256 mm^2, FA of 8°, and matrix size of 256 × 256. To correct for EPI geometric distortions, a pair of spin echo EPI scans with opposite phase-encoding directions ("top up") [17] were acquired that were designed with the same echo spacing and bandwidth as the task fMRI (echo spacing [ES] of 0.69 milliseconds and bandwidth [BW] of 2,272 Hz/px). The participant's head was comfortably stabilized using foam pads to minimize motion during and between scans.

Image Processing

The BOLD EPI images were processed systematically with a combination of Analysis of Functional NeuroImages (AFNI), FMRIB Software Library (FSL), and Matlab (Natick, MA) in-house scripts [18, 19]. To systematically delineate the clinical intervention-based connectivity changes, we used a highly validated and optimized rs-fcMRI pipeline developed by our group [20] tailored to pain studies [13, 21–23]. The rs-fcMRI volumes were corrected for slice timing, bulk head motion, and EPI distortion [17]. In parallel, the T1-weighted MPRAGE images were skull stripped using Optimized Brain Extraction Tool (optiBET) [24] and spatially transformed to an MNI-152 standard template using FSL's linear (FLIRT) and nonlinear (FNIRT) spatial transformation algorithms. The EPI distortion–corrected rs-fcMRI images were then de-noised for various artifacts (such as cardiac and respiratory, hardware, susceptibility and motion artifacts) using standard FSL tools (FIX) that employ independent component analysis (ICA)–based de-noising methodologies. The de-noised images were then co-registered with the T1-weighted MPRAGE using FSL's boundary-based registration algorithm (epi_reg) and then warped to MNI space using the MPRAGE-to-MNI transformation warp images. To reduce influence from cerebrospinal fluid pulsatility and resulting partial volume effects near the edge of the ventricles, we masked the ventricles in the rs-fcMRI time course. We then temporally filtered the rs-fcMRI time course using a Chebyshev II low-pass filter cutoff frequency of 0.32 Hz, and then the signal intensity across neighboring voxels for each volume was spatially smoothed using a Gaussian filter full width at half maximum (FWHM) of 4 mm. From the motion parameters captured during the global head motion correction, frame-to-frame displacement was computed [25], and time points from the rs-fcMRI time series were censored at a threshold of 0.3 mm. For whole-brain connectivity analyses using a seed-based approach, a sphere (5-mm radius) centered at the seed MNI coordinates was used to generate an average seed time course to cross-correlate with the time courses of all other voxels [26]. The Fisher z transform was applied to the cross-correlation values to normalize the distribution.

Statistical Analysis

Analysis of sample characteristics for the groups was conducted to assess comparability of the samples. Categorical variables such as sex and biobehavioral data were assessed using Fisher's exact test, but continuous variables such as age were assessed using two-tailed t tests. All reported P values are two tailed and considered significant at the 0.05 level, family-wise error (FWE) corrected. To quantify brain connectivity, rs-fcMRI data were analyzed with both a seed-voxel and pairwise connectivity via the partial correlations approach [25].

Primary Outcome (rs-fcMRI as a Biomarker of Treatment Outcomes)

Seed-Voxel Functional Connectivity Approach. Prior studies regarding fibromyalgia and pain have identified altered network connectivity using seeds in the inferior parietal lobule (IPL), right dorsolateral prefrontal cortex (R-dlPFC), dorsal anterior cingulate cortex (dACC), insula, right temporoparietal junction (R-TPJ), medial prefrontal cortex (mPFC), and sensorimotor network (SMN) [11, 21, 23, 27–31]. These areas were carefully chosen to avoid extending into white matter, into cerebrospinal fluid, or outside the brain. Based on this existing data, seed-based resting connectivity analyses between relevant areas were performed. The seeds were spherical, 1 cm in diameter, and centered on the MNI peak coordinates of regions of activity defined from prior published studies [11, 21, 23, 27–31]. The same seeds were eroded to include only gray-matter voxels using the Johns Hopkins University International Consortium of Brain Mapping white-matter atlas [32]. We then correlated the averaged time series from the seed regions using AFNI.

Connectivity Analysis via Partial Correlations. To evaluate the feasibility of using fcMRI as a biomarker in PENFS treatment outcomes, we evaluated the association between the participants' DVPRS scores and brain connectivity (using partial correlations) and tested for significance. Following the aforementioned processing steps, we used correlation coefficients to investigate the association between the baseline resting SMN–DMN connectivity and post-PENFS changes in pain levels. Pairwise connectivity between node pairs was assessed via partial correlation. Partial correlation has shown great promise in accurately detecting true brain network connections measuring the direct connectivity between two nodes and avoiding spurious effects in network modeling [33]. We estimated partial correlations using *DensParCorr*, a statistical R package that implements an efficient and reliable statistical method for estimating partial correlation in large-scale brain network modeling [34]. To examine the relationship between brain connectivity (via partial correlation) and DVPRS scores, we first obtained the partial correlation connectivity matrix using the *DensParCorr* package for each participant. Then, for each pair of regions of interest (ROIs), we calculated the correlation between the participants' connectivity and DVPRS scores to assess their association.

Secondary Outcome (Improvements in Clinical Pain and Function)

Participants were measured at baseline, 2 weeks, 6 weeks, and 12 weeks. Mixed-effect linear regression was used to model each outcome separately. The model predictors included treatments (treatment vs control), time (the four time points), and the interaction of treatment and time,

Table 1. Demographic and medical characteristics of study population

Characteristics	PENFS Treatment (n = 12)	Standard Therapy Control (n = 9)	*P* Value
Age, mean years	50 ± 9.78	48.56 ± 10.08	0.68
Gender			
Female	6 (50%)	6 (67%)	0.47
Male	6 (50%)	3 (33%)	—
Race			
Caucasian	7 (58%)	4 (44%)	0.55
African American	5 (42%)	5 (56%)	—
Ethnicity			
Hispanic	1 (9%)	1 (11%)	0.84
Non-Hispanic	10 (83%)	8 (89%)	—
Unknown	1 (8%)	0 (0%)	—
Baseline pain scores, mean DVPRS	6.42 ± 1.64	8 ± 1.52	0.04*
Baseline sit-to-stand	8.67 ± 4.48	6.44 ± 3.21	0.22
Baseline bicep curls			
Left	18.92 ± 7.20	15.33 ± 7.66	0.29
Right	18.58 ± 6.51	14.89 ± 7.27	0.24

PENFS = percutaneous electrical nerve field stimulation; DVPRS = Defense and Veterans Pain Rating Scale.
*$P<0.05$. Means are reported with 95% confidence intervals (mean ± 1.96 standard deviation).

Table 2. Change in pain score (Defense and Veterans Pain Rating Scale [DVPRS]) and function following therapy

Time Point	Total Cohort	Outcome Variable	Treatment (PENFS)	Control (Standard Therapy)	*P* Value
2 weeks	16 (9 PENFS)	DVPRS	–0.9 ± 3.5	–1.4 ± 7.4	0.80
		Sit-to-stand	2.7 ± 6.6	0.3 ± 8.1	0.24
		Bicep curls (left)	4.6 ± 12.7	1.7 ± 13.7	0.42
		Bicep curls (right)	4.2 ± 10.0	0.7 ± 15.1	0.32
6 weeks	14 (8 PENFS)	DVPRS	–1.1 ± 4.0	–0.5 ± 2.1	0.52
		Sit-to-stand	3.1 ± 9.7	0.3 ± 8.1	0.27
		Bicep curls (left)	6.1 ± 13.1	–1.8 ± 12.4	0.04*
		Bicep curls (right)	6.0 ± 14.4	0.8 ± 13.2	0.2
12 weeks	14 (9 PENFS)	DVPRS	–1.3 ± 4.0	–0.1 ± 3.3	0.27
		Sit-to-stand	1.7 ± 8.7	1.4 ± 7.7	0.91
		Bicep curls (left)	5.8 ± 13.2	0.0 ± 15.5	0.21
		Bicep curls (right)	4.6 ± 13.3	0.2 ± 11.4	0.24

PENFS = percutaneous electrical nerve field stimulation.
*$P<0.05$. Means are reported with 95% confidence intervals (mean ± 1.96 standard deviation).

with subject as a random effect. The significance level was set at 0.05. Data analysis was conducted with R version 3.6.3 on the RStudio platform. The ggplot2 package was used to generate trend plots, and the lmerTest package was used to fit the mixed-effect linear regression model.

Results

A total of 21 participants were block randomized to either PENFS treatment or ST control (ST; n=9) or ST with auricular PENFS (ST + PENFS; n=12). Baseline demographic characteristics such as age, gender, race, and ethnicity did not significantly differ between the groups. However, due to the small sample size, and as a product of chance randomization, study participants assigned to the PENFS treatment group had significantly lower pain scores at baseline than the ST control group (Table 1).

Two participants complained of minor irritation at the site with PENFS treatment. No major adverse events were reported. All participants randomized to the PENFS treatment group completed both imaging evaluations and the 4-week and 12-week follow-up visits in addition to the baseline visits. However, we excluded three PENFS treatment participants from analysis; two participants experienced extenuating circumstances (cervical disc herniation and loss of home) during the study period; the third participant received an fMRI that could not be adequately processed due to anatomical variations in the participant's brain, unrelated to exclusion criteria. Two participants in the ST control group did not present for their follow-up fMRI. Therefore, these individuals were excluded from analysis, leaving us with a total cohort of nine PENFS treatment participants and seven ST control participants for analysis. Not all individuals presented for all follow-up visits, but all participants included in

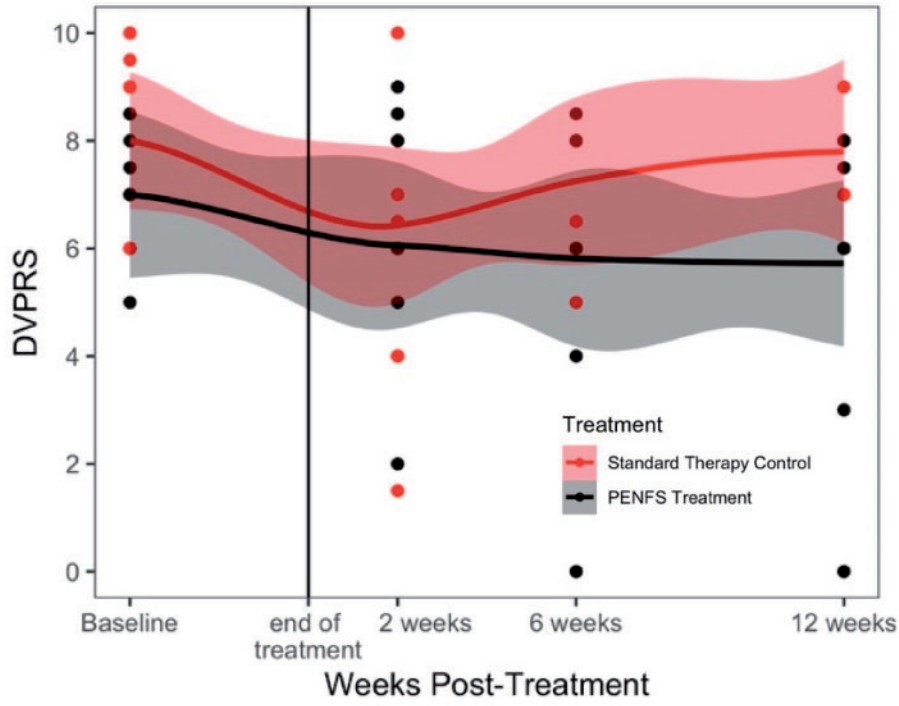


Figure 2. Pain scores over time in PENFS treatment and standard therapy control groups. Participants were assessed at baseline, and at 2, 6, and 12 weeks following the 4-week intervention (PENFS treatment + standard therapy vs. standard therapy control). Individual subjects are represented by dots, some of which overlap. The confidence intervals are shown in shading around each mean, which is represented by a solid line. All pain measures were obtained using the Defense and Veterans Pain Rating Scale (DVPRS). There was a trend towards improved pain scores in the PENFS treatment group as compared to the standard therapy control group at 12 weeks post-treatment.

Table 3. Change in pain interference scores related to activity, sleep, mood, and stress following therapy

Time Point	Total Cohort	Outcome Variable	Treatment (PENFS)	Control (Standard Therapy)	*P* Value
2 weeks	16 (9 PENFS)	Activity	−1.2 ± 3.5	0.9 ± 8.9	0.3
		Sleep	−1.6 ± 5.8	−0.4 ± 11.3	0.63
		Mood	−1.0 ± 5.1	−0.6 ± 10.5	0.85
		Stress	−1.4 ± 3.6	0.0 ± 9.7	0.5
6 weeks	14 (8 PENFS)	Activity	−1.2 ± 4.5	1.2 ± 3.1	0.04*
		Sleep	−1.6 ± 5.5	1.8 ± 4.2	0.02*
		Mood	−1.4 ± 5.3	1.8 ± 4.5	0.03*
		Stress	−1.8 ± 4.4	1.7 ± 3.6	0.01*
12 weeks	14 (9 PENFS)	Activity	−1.6 ± 4.7	1.0 ± 7.2	0.2
		Sleep	−1.7 ± 4.6	2.2 ± 5.9	0.04*
		Mood	−2.1 ± 4.3	1.8 ± 7.3	0.08
		Stress	−1.9 ± 3.3	1.8 ± 6.4	0.06

PENFS = percutaneous electrical nerve field stimulation.
*P values less than 0.05 are considered statistically significant. Means are reported with 95% confidence intervals (mean ± 1.96 standard deviation).

the analysis were present for baseline assessments, preimaging and postimaging studies, and at least one follow-up visit. Missing data were not imputed and were not used for analysis to avoid distortions related to imputation in the small sample size. There were no significant differences in pain scores between the treatment or control group over time (Table 2). The PENFS treatment group displayed significant improvements in left-sided bicep curls as compared with the ST control group at 8 weeks following therapy (P=0.04); no other statistically significant differences were noted.

Although no significant differences were found in the pain scores between the two groups following treatment, there was a trend toward continued pain relief in the PENFS treatment group as opposed to the ST control group at 6 weeks and 12 weeks following treatment, whereas the ST control group appeared to return to baseline at 12 weeks (Figure 2). Outcomes related to function tended to improve in both groups following treatment, with similar results by week 12.

No statistically significant difference was found between groups at 2 weeks immediately following

treatment. At 6 weeks, participants in the PENFS group reported significantly improved pain interference with activity, sleep, and mood compared with participants who received ST alone (Table 3). At 12 weeks, participants in the PENFS group continued to report significant improvements in pain interference with sleep as compared with the ST group, although the effects on activity, mood, and stress diminished. Additional graphs of outcomes from Table 2 and Table 3 can be found in the Supplementary Data.

Table 4. Decreased connectivity following standard therapy (control group, right posterior insula seed)

Brain Region	Cluster Size (No. of Voxels)	Voxel (x, y, z)
Lobule VIII of cerebellum (L)	170	–38, –60, –52
Inferior parietal lobule (L)	111	–46, –54, 34
Crus II of cerebellum (L)	87	–12, –82, –42
Crus II of cerebellum (R)	78	50, –46, –42
Putamen (L)	78	–28, 8, 6
Posterior cingulate cortex (L)	61	–12, –44, 24
Lobule VIII of cerebellum (R)	47	26, –60, –46

L = left; R = right.

Coordinates are reported in Montreal Neurological Institute (MNI) space (mm), and regions are grouped according to the cluster to which they belong. All regions were located based on connectivity to the right posterior insula seed and reflected decreased connectivity (P=0.05). Regions are listed in order of descending cluster size.

Table 5. Increased connectivity following percutaneous electrical nerve field stimulation (PENFS) treatment (PENFS group, right posterior insula seed)

Brain Region	Cluster Size (No. of Voxels)	Voxel (x, y, z)
Middle occipital gyrus (R)	170	42, –88, 0
Midbrain (L)	71	–8, –32, –10
Anterior insula (L)	58	–36, 14, –16
Lobule IX of cerebellum (R)	41	2, –56, –58

R = right; L = left.

Coordinates are reported in Montreal Neurological Institute (MNI) space (mm), and regions are grouped according to the cluster to which they belong. All regions were located based on connectivity to the right posterior insula seed and reflected increased connectivity (P=0.05).

Neuroimaging outcomes were analyzed using seed-voxel analysis based on a priori hypotheses with a carefully selected group of seeds implicated in pain and emotional regulation. With conservative motion scrubbing, as described in the *Methods* section, an average of 5.9%±10.9% of data was censored across all participants and all scans. The groups did not significantly differ in regard to motion, nor did motion significantly differ between baseline and follow-up within each group, and each participant had at least 4 minutes of data remaining after censoring, in alignment with the recent recommendations made by Parkes et al. [35]. In the ST control group, decreased connectivity (post-treatment vs pretreatment) was found from the right posterior insula to the bilateral lobule VIII of the cerebellum, left IPL, bilateral crus II of the cerebellum, left putamen, and left posterior cingulate cortex (PCC) following treatment (Table 4). This corresponds with decreased pain scores initially following treatment (Table 2).

In the PENFS treatment group, increased connectivity (post-treatment vs pretreatment) was found from the right posterior insula to the right middle occipital gyrus, left midbrain, left anterior insula, and right lobule IX of the cerebellum following treatment (Table 5). This corresponded with decreased pain scores initially following treatment (Table 2).

Using a right posterior insula seed, a difference of the differences (post-treatment vs pretreatment for treatment vs control) was measured, reflecting increased connectivity in the PENFS group as compared with the control group to areas associated with descending modulation of pain (Table 6; Figure 3). Decreased connectivity was found in the PENFS group as compared with the control group from the right posterior insula to the right IPL, an area of the DMN (Table 6). We must emphasize that this is a difference of change scores; thus, the baseline rs-

Table 6. Between-group differences in connectivity following treatment

Brain Region	Cluster Size (No. of Voxels)	Voxel (x, y, z)	Direction of Change (PENFS vs Control)
Lobule VII of cerebellum (R)	203	44, –50, –42	Increased
Lobule VII of cerebellum (L)	200	–38, –60, –52	Increased
Inferior frontal gyrus (L)	197	–58, 26, 8	Increased
Superior frontal sulcus (R)	188	24, 14, 42	Increased
Middle temporal gyrus (R)	164	58, 0, –28	Increased
Putamen (L)	150	–28, 8, 8	Increased
Superior frontal gyrus (L)	115	–28, 68, 6	Increased
Anterior cingulate (L)	108	–18, 44, –2	Increased
Brain stem (L)	77	–6, –32, –6	Increased
Inferior parietal lobule (R)	42	56, –42, 56	Decreased

PENFS = percutaneous electrical nerve field stimulation; R = right; L = left.

These connectivity measures are the result of a difference of differences (post-treatment vs pretreatment for PENFS minus post-treatment vs pretreatment for standard therapy control). Coordinates are reported in Montreal Neurological Institute (MNI) space (mm), and regions are grouped according to the cluster to which they belong. All regions were located based on connectivity to the right posterior insula seed (P=0.05).

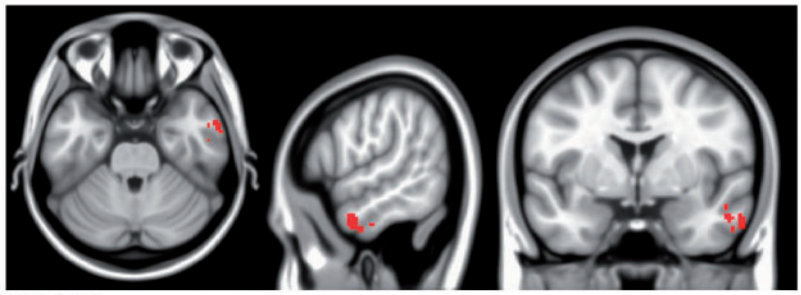
Figure 3. Changes in Connectivity for PENFS Treatment Group Relative to Standard Therapy Control Group: Right Posterior Insula Seed. Seed-based analysis was performed using a right posterior insula seed, and changes in the standard therapy group (post-pre) were subtracted from changes in the PENFS group (post-pre). These changes were then analyzed using a 3 dimensional T-test. The PENFS group exhibited changes in connectivity (P=0.05) between the right posterior insula seed and areas depicted. Increased connectivity was found to bilateral cerebellar areas (left cerebellum lobule VIIB/Crus II and right cerebellum lobule VIIB/Crus I-II) post-treatment compared to the standard therapy control group. Other areas displaying increased connectivity included the left inferior frontal gyrus, right superior frontal sulcus, middle temporal gyrus, left putamen, left anterior cingulate cortex, and left brainstem. Decreased connectivity was found to the right inferior parietal lobule. These changes in connectivity reflect a comparison of between (intra-) group changes following treatment.

fcMRI was subtracted from the post-treatment rs-fcMRI for both groups, and then the difference from the ST control group was subtracted from the difference from the PENFS treatment group, resulting in the absolute differences found in Table 6.

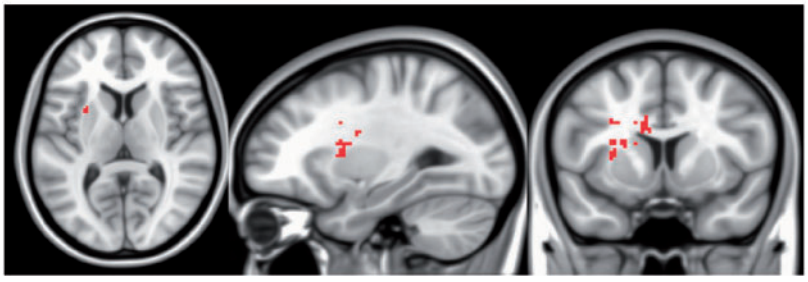
Figure 3 highlights the difference of differences between the results of treatment for the PENFS group as compared with the ST control group using a right posterior insula seed. The figure reflects the increased connectivity from the right posterior insula to areas of the cerebellum implicated in pain and emotional regulation, as well as changes in connectivity to other areas involved in the descending modulation of pain.

Table 7 presents statistically significant correlations between post-treatment changes in DVPRS pain scores and brain connectivity measured by partial correlations between ROIs. Although the sample size is too small for multiple comparisons to be feasible, the effect sizes

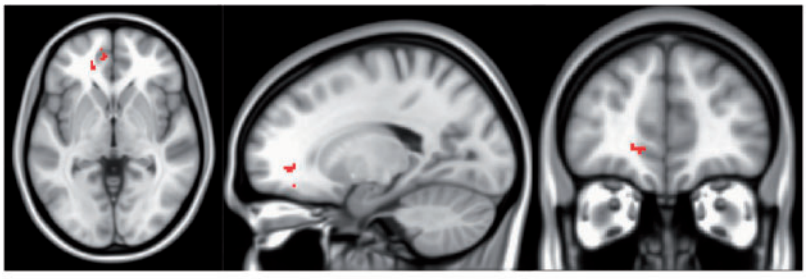
Middle Temporal Gyrus



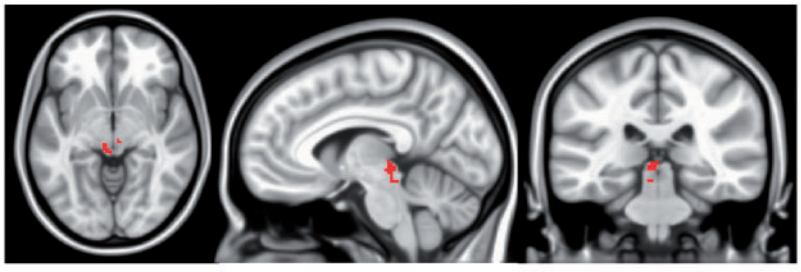
Left Putamen



Left Anterior Cingulate Cortex



Left Brainstem



Right Inferior Parietal Lobule

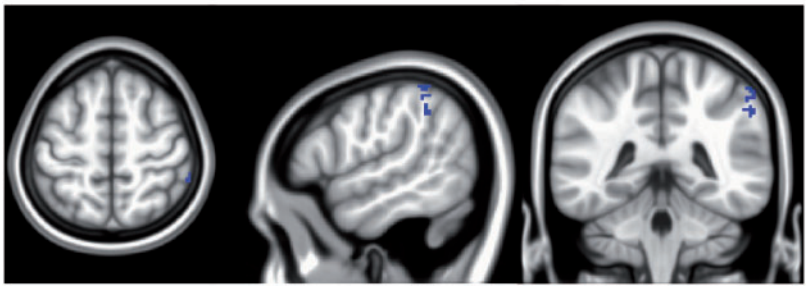


Figure 3. Continued.

Table 7. Connectivity between regions of interest (ROIs) statistically significantly correlated with Defense and Veterans Pain Rating Scale (DVPRS) scores

ROI 1	ROI 2	Correlation Between Brain Connectivity and DVPRS Scores	*P* Value
Right posterior insula	Left posterior insula	0.46	0.009*
Left posterior insula	Dorsal anterior cingulate cortex	0.364	0.044*
Left posterior insula	Left cerebellar lobule VI	–0.398	0.027*
Right dorsolateral prefrontal cortex	Left posterior cingulate cortex	0.421	0.018*
Right putamen	Right posterior cingulate cortex	0.383	0.034*
Left sensorimotor cortex I	Left cerebellar lobule VI	–0.483	0.006*
Medial prefrontal cortex	Left cerebellar lobule VI	0.408	0.023*

*$P<0.05$. All reported correlations exhibit effect sizes of medium strength or higher. Further details can be found in the corresponding heat map.

of the significant correlations reported are all medium or higher [36, 37]. A decrease in connectivity between the right posterior insula and left posterior insula was significantly associated with a decrease in DVPRS pain scores. Similarly, a decrease in connectivity between the left posterior insula and the dorsal anterior cingulate cortex (dACC) was associated with a decrease in DVPRS pain scores. Decreased connectivity from the right dorsolateral prefrontal cortex (dlPFC) to the left PCC was associated with a decrease in DVPRS pain scores. Decreased connectivity from the right putamen to the right PCC was associated with a decrease in DVPRS pain scores. Decreased connectivity between the medial prefrontal cortex (mPFC) and lobule VI of the left cerebellum was associated with a decrease in DVPRS pain scores. However, increased connectivity from the left sensorimotor cortex (S1M1) to lobule VI of the left cerebellum was associated with a decrease in DVPRS pain scores, and increased connectivity between the left posterior insula and lobule VI of the left cerebellum was associated with a decrease in DVPRS pain scores (Table 7). Supplementary Data depict a heat map of partial correlations between DVPRS and connectivity between selected ROIs implicated in pain and fibromyalgia. A heat map of *P* values is also shown.

Discussion

In our open-label neuroimaging feasibility study of 21 veterans with fibromyalgia who were randomized to either ST or ST with PENFS treatment, results reveal a trend toward improved pain and function in the PENFS group, along with meaningful changes in resting-state functional connectivity in pain-related areas. Participants who received PENFS reported significant ($P<0.05$) long-term (12 weeks) improvements in pain interference with sleep as compared with ST alone and significant improvements in function (left bicep curl) and all pain interference measures at 6 weeks. Other outcomes related to pain and function revealed a trend toward long-term improvement for the PENFS group over the ST group, although this was not statistically significant.

It was exciting to note that PENFS-related improvements in pain scores were present even at 12 weeks following the completion of treatment and correlated to changes in inter-network connectivity (i.e., salience network [SN], SMN, and DMN), which differed between groups. This suggests that PENFS may promote neuromodulation across brain areas and networks, resulting in neuroplasticity and longer-term pain relief following an initial input through a separate mechanism from ST, perhaps through VNS-induced neural plasticity, as reflected by changes on rs-fcMRI [38].

Results of our ST control group (Table 4) are consistent with results of prior studies evaluating rs-fcMRI in fibromyalgia, reflecting a decrease in connectivity between the insula and areas of the DMN associated with decreasing pain scores [11, 13, 29]. In contrast, the PENFS treatment group exhibited increased connectivity between the right posterior insula seed and the right middle occipital gyrus, left midbrain, left anterior insula, and right lobule IX of the cerebellum following treatment associated with decreased pain scores (Table 5), suggesting a different mechanism of action for PENFS-related treatment effects as compared with ST. These areas may provide new targets for neuromodulatory interventions in future studies of pain treatment, and their role in pain modulation requires further exploration. The difference of differences between the two groups (post-treatment vs pretreatment for the PENFS group vs the ST group) suggests modulation of the executive control network in relation to the cerebellum for the PENFS group as compared with the ST control group (Table 6). The executive control network (or frontoparietal control network) includes the superior frontal gyrus/sulcus, inferior frontal gyrus, middle temporal gyrus, and IPL and is thought to contribute to goal-based, deliberate action [39]. The cerebellum is one of the most commonly implicated areas of the brain in relation to pain and emotional processing [40–43]. This suggests that PENFS may exert an effect on modulating the emotional and executive control centers related to pain processing and may, in this way, decrease the interference of pain in daily activities.

Separate from the seed-based approach to evaluate differences in functional connectivity within and between

groups, we also sought to evaluate the correlation of connectivity between ROIs and overall changes in DVPRS scores to build on the use of neuroimaging as an outcome measure for pain. A partial correlations approach designed for neuroimaging analysis was used to correlate changes in DVPRS scores with changes in connectivity between a priori–identified ROIs (Table 7). Statistically significant correlations between post-treatment changes in DVPRS pain scores and brain connectivity were found for both intra-network and inter-network connectivity for the salience network, the somatomotor network, and the DMN.

In our proof-of-principle study, despite the small sample size, it was exciting to see consistent results that corroborated prior studies as well as novel PENFS-related findings. Our study had several limitations in addition to small sample size: lack of participant and provider blinding and lack of a placebo control group may result in a placebo-related effect; baseline differences in pain scores as a result of randomization may bias results toward the null. ST treatment was heterogeneous to allow for tailored treatments based on patient comorbidities, side effects, and prior treatment failures, but this may have resulted in increased variability. Effects of smoothing in rs-fcMRI data may also result in overlap of certain ROIs, potentially decreasing the accuracy of the results. Multiple comparison correction is too stringent to be feasible for the pairwise connectivity association analysis due to the small sample size of the current study and the large number of pairs of connections. However, the effect sizes of the significant correlations reported (Table 7) are all medium or higher [36, 37], indicating the statistical and clinical relevance of the identified associations.

Although our data are suggestive of an initial neural input resulting in a possible long-term neuromodulatory effect, further investigation is warranted. Future work may include a randomized, double-blind, placebo-controlled trial involving sham vs true PENFS and the utilization of advanced analyses such as hierarchical ICA. The utilization of brain-stem imaging and heart rate variability data may also aid in determining whether PENFS is acting through modulation of the vagal nucleus or through a different mechanism. Given that clinical pain scores continued to decrease at 12 weeks' follow-up, subsequent studies should also aim to evaluate long-term rs-fcMRI neural changes, as our rs-fcMRI data only evaluated immediate post-treatment effects as compared with baseline.

Conclusions

Overall, the results of this small open-label feasibility trial suggest a potential positive effect of PENFS as compared with ST alone and provide questions for further research and hypothesis generation. The clinical efficacy of PENFS for fibromyalgia should be explored in a larger randomized, double-blind, placebo-controlled trial. Neuroimaging outcomes should additionally be evaluated at later time points to evaluate the long-term neuromodulatory effects of PENFS.

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Supplementary Data

Supplementary Data may be found online at http://painmedicine.oxfordjournals.org.

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