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The Effects of Noninvasive Vagus Nerve Stimulation on Fatigue in Participants With Primary Sjögren's Syndrome

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ABSTRACT

Objectives: Fatigue is one of the most important symptoms needing improvement in Primary Sjögren's syndrome (PSS). Previous data from our group suggest that noninvasive stimulation of the vagus nerve (nVNS) may improve symptoms of fatigue. This experimental medicine study uses the gammaCore device (electroCore) and a sham device to investigate the relationship between nVNS and fatigue in PSS, and to explore potential mechanisms involved.

Materials and Methods: Forty participants with PSS were randomly assigned to use active (n = 20) or sham (n = 20) nVNS devices twice daily for 54 days in a double-blind manner. Patient-reported measures of fatigue were collected at baseline and day 56: Profile of Fatigue (PRO-F)-Physical, PRO-F-Mental and Visual Analogue Scale of abnormal fatigue (fVAS). Neurocognitive tests, immunologic responses, electroencephalography alpha reactivity, muscle acidosis, and heart rate variability were compared between devices from baseline to day 56 using analysis of covariance.

Results: PRO-F-Physical, PRO-F-Mental, and fVAS scores were significantly reduced at day 56 in the active group only (p = 0.02, 0.02, and 0.04, respectively). Muscle bioenergetics and heart rate variability showed no change between arms. There were significant improvements in digit span and a neurocognitive test (p = 0.03), and upon acute nVNS stimulation, frontal region alpha reactivity showed a significant negative relationship with fatigue scores in the active group ($p < 0.01$).

Conclusions: We observed significant improvements in three measures of fatigue at day 56 with the active device but not the sham device. Directly after device use, fatigue levels correlate with measures of alpha reactivity, suggesting modulation of cholinergic system integrity as a mechanism of action for nVNS.

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Conflict of Interest: Wan-Fai Ng has undertaken clinical trials and provided consultancy or expert advice in the area of Sjögren's syndrome to the following companies: GlaxoSmithKline, MedImmune, UCB, Abbvie, Roche, Eli Lilly, Takeda, Resolves Therapeutics, Sanofi, Novartis, and Nascient. Bruce S. Simon and Justyna Blake are consultants or employees of electroCore and hold stock options. The remaining authors reported no conflict of interest.

INTRODUCTION

Primary Sjögren's syndrome (PSS) is a chronic autoimmune disease associated with a significant negative impact on quality of life. PSS is characterized primarily by ocular and oral dryness, musculoskeletal pain, and profound fatigue.[1–4] Fatigue is a key independent predictor of poor health-related quality of life (QoL) and loss of work productivity, and patients have described fatigue as one of the most important symptoms requiring improvement.[5,6] Patients with PSS often describe physical and mental components of fatigue. Physical fatigue is frequently characterized by muscle pain or perceived lack of energy, resulting in difficulty in sustaining muscle activity. Patients reporting mental fatigue often describe symptoms such as poor concentration, memory loss, inability to retain information, and reduced cognitive ability. Indeed, we have shown that patients with PSS have more cognitive symptoms than do age-matched healthy controls as measured by the Cognitive Failures Questionnaire (CFQ). Furthermore, CFQ scores correlate with mental fatigue in PSS.[7,8]

The mechanisms underpinning fatigue in PSS are unclear. Autonomic dysfunction and immune dysregulation have been implicated. For instance, symptoms of autonomic dysfunction are common in PSS and associated with increased levels of fatigue and disease activity.[9,10] Furthermore, other factors including sleep disturbance, higher body mass index, polypharmacy, psychosocial factors, mental health conditions including anxiety and depression, pain, and circulating levels of peripheral inflammatory cytokines were reported to be predictors of fatigue in PSS.[11,12] The level of comorbidity between PSS and Chronic Fatigue Syndrome (CFS) has not been extensively studied, and it is not known whether the mechanisms underpinning symptoms of fatigue in both conditions are shared.

The autonomic nervous system (ANS) plays a key role in regulating the function of internal organs and adaptive responses to stressors. The vagus nerve is the primary parasympathetic nerve of the ANS and is a prominent component of several homeostatic axes, including the brain-gut axis, the hypothalamic-pituitary-adrenergic axis and the cholinergic antiinflammatory pathway.[13] The parasympathetic system has been linked to the regulation of a broad range of immune responses that have been well characterized in animal models. The sickness behavior model (eg, simulated in animal models using lipopolysaccharide [LPS]) is one of the strongest links between fatigue and the immune system.[14] Moreover, vagus nerve stimulation (VNS) reduces LPS-induced production of inflammatory cytokines (interleukin [IL]-1, IL-6, tumor necrosis factor alpha [TNF-α]) in mice.[15] Therefore, it is plausible that the vagus nerve may be an attractive therapeutic target for PSS.

VNS, delivered using an implanted device, was first approved for treatment-resistant epilepsy in 1994.[16] Improvements in mood were noted in the original experimental cohort, which led to the investigation of VNS as a therapy for psychiatric disorders, including depression and schizophrenia.[17–19] Since their first use, implanted VNS devices have been trialed in several conditions, including drug-resistant depression, anxiety, and stroke.[17,20,21] VNS can be delivered noninvasively (nVNS), providing a safer, cheaper, and more accessible approach to explore the role of autonomic dysfunction in the pathogenesis of fatigue in PSS. Recently, a sham controlled study of auricular nVNS in systemic lupus erythematosus, conducted over 12 days, showed significant improvements in pain and fatigue in the active device group. In addition, this study showed a significant reduction in plasma levels of substance P, a proinflammatory neuropeptide involved in nociceptive signalling.[22] nVNS was also associated with fatigue improvement in 15 women with PSS.[23] Several studies have shown that nVNS may successfully alleviate symptoms in epilepsy, migraine, and cluster headache.[24]

Despite mounting evidence to suggest that nVNS can modulate symptoms of pain and fatigue in these conditions, the mechanism of action is still unclear. Because the vagus nerve modulates multiple systems within the brain and body, several possible mechanisms of action for nVNS have been explored. Several studies have shown that nVNS can mediate a reduction in inflammation; some detected neurochemical changes after nVNS; and others observed changes in vagal tone. Human studies have shown that nVNS induces a reduction in inflammatory mediators in whole blood.[25] However, in rat models of hypertension, it has been shown that nVNS attenuates neuron-derived IL-1B production.[26] It is possible that VNS targets the brain-gut axis by the modulation of inflammatory mediators. Alternatively, VNS may alter neurochemical responses; for example, in migraine, nVNS has been shown to reduce extracellular glutamate levels in rats and to reduce sensitivity to cortical spreading depression (CSD), the phenomena responsible for migraine aura and headache.[27] Neurophysiological responses may also be a factor; human studies have shown increased parasympathetic activity after nVNS measured by increased cardiac vagal tone, which would be expected if nVNS was stimulating the vagus nerve effectively.[28] It has also been suggested that VNS can result in improvement of sleep patterns, which could also explain the improvements in fatigue observed in our previous work.[29]

All these mechanisms could be implicated in the mechanism of action for the alleviation of fatigue, and it is possible that alternative mechanisms may be responsible in different individuals. In addition, overlap and interplay among these systems may contribute to the complex mechanisms underpinning the mechanism of action of nVNS in inflammatory and pain conditions in addition to fatigue. This study explores the relationship between nVNS and fatigue by comparing the effects of nVNS with those of a sham device in patients with PSS and exploring potential mechanisms involved.

MATERIALS AND METHODS

Study Participants

Forty subjects with PSS were recruited from the Newcastle Sjögren's syndrome clinic after providing written informed consent

according to the principles of the Declaration of Helsinki. Participants fulfilled the American European Consensus Group Classification criteria[30] and reported symptoms of fatigue (defined as having Profile of fatigue score > 2 of 7). After double-blind randomization to the study arms, the participants received either a noninvasive VNS device (n = 20) or a sham device (n = 20) (gammaCore®). The full inclusion and exclusion criteria and demographics are listed in Supplementary Data Supplementary Methods and Supplementary Data Tables S1 and S2.

Study Assessments

The entire assessment package, including the completion of questionnaires, ^{31}P-magnetic resonance spectroscopy (^{31}P-MRS), neuropsychologic tests, heart rate variability (HRV) measurements, electroencephalography (EEG), and venesection, were performed in the same sequence and at the same time of day for each participant. Figure 1 illustrates the study schedule.

At each scheduled visit, the following assessments were performed: European Alliance of Associations for Rheumatology (EULAR) Patient reported Outcome Index,[31] Profile of Fatigue (PROF),[32] Visual Analogue Scale of abnormal fatigue (fVAS), and the Multidimensional Fatigue Inventory.[33] The CFQ[8] was used to quantify subjective neurocognitive symptoms. Mood was assessed using Beck's Depression Inventory (BDI)[34] and Bond and Lader Visual Analogue Scale (BLVAS).[35] Cardiac dysautonomic symptoms were assessed through the Composite Autonomic Symptom Scale (COMPASS 31)[36] and using the Orthostatic Grading Scale (OGS).[37] In addition, the number of discharges from the nVNS device was also recorded.

All participants completed the neurocognitive assessments at baseline and at follow-up visits 2 and 3. The assessments included both paper and computer-based tests. Paper questions included Pre-morbid IQ National Adult Reading Test[38] (only completed at baseline), trail making test, digit symbol tests, Rey-Auditory Verbal Learning Test,[39] Stroop, digit span, and verbal fluency tests. The computer-based assessments included a psychomotor vigilance test.

Noninvasive Vagus Nerve Stimulation

VNS was delivered through the gammaCore nVNS device. The gammaCore signal consists of five 5000-Hz pulses repeated at a rate of 25 Hz for a maximum of 120 seconds per dose. The waveform of the electric pulses approximates a sine wave with peak voltage limited to ± 30 Volts and a maximum output current of 60 mA, which is well tolerated by participants. The amplitude of the stimulation is adjusted by the patient using buttons located on the device. The gammaCore nVNS device has been shown in several studies to effectively stimulate the vagus nerve.[40–42] Data from studies in migraine, cluster headache, and airway reactivity show the benefits of nVNS are similar to those reported for implantable VNS and noninvasive auricular stimulation.[43–45]

After a 2-minute stimulation with gammaCore, Brock et al showed a sustained elevation of cardiac vagal tone that lasted up to 24 hours.[28] A recent study of CSD in a rat model of migraine showed that chronic nVNS stimulation was not superior to a single dose.[27] The sham device appears identical to the gammaCore in look, weight, visual and audible feedback, and user controls. It delivers a similar buzzing sensation to the skin without stimulating the vagus nerve.

Electroencephalography

Eyes-closed and eyes-open resting-state EEG recordings were performed. Further details of electrode placement and data acquisition are available in Supplementary Data Supplementary

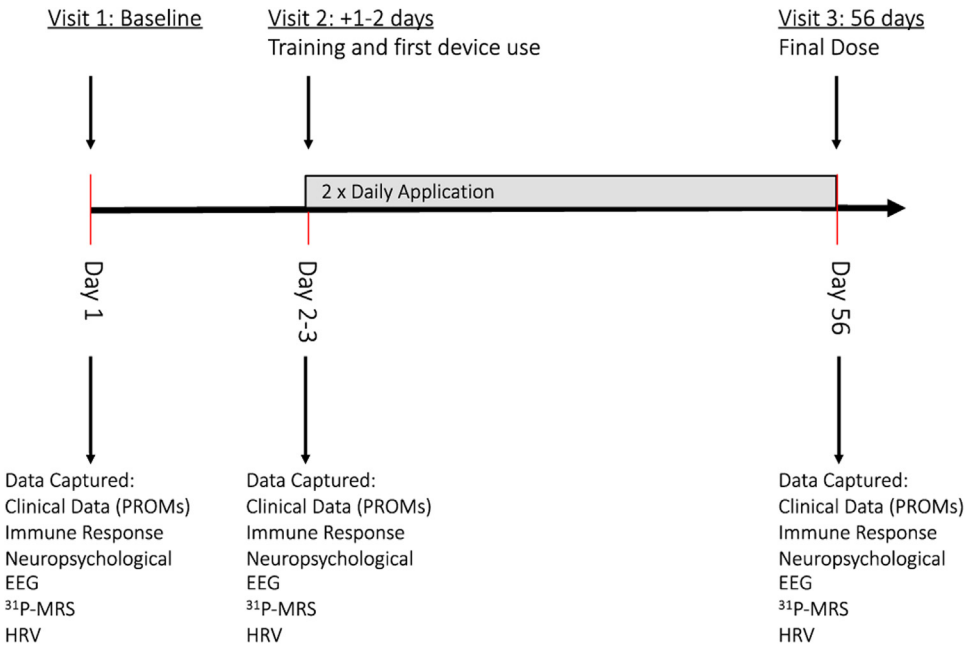

Figure 1. Study assessment schedule. Participants were trained to use the nVNS device during visit 2 and instructed to use it twice daily as per manufacturer's protocol (120 seconds over each carotid artery morning and evening). At Day 56, the subjects were asked to use the device 90 minutes before attending the unit. Thus, data collected from these scheduled visits represented baseline values, changes after "acute" nVNS, and changes after "prolonged" nVNS. [Color figure can be viewed at www.neuromodulationjournal.org]

Materials. In healthy individuals, opening the eyes results in a decrease in alpha power, particularly in the occipital lobe.[46] Alpha reactivity was calculated as the relative reduction in alpha power when changing from an eyes-closed to eyes-open state. Alpha reactivity represents the integrity of the cholinergic system, with a lower value representing a cholinergic deficit. Reduced alpha reactivity is associated with cognitive impairment and mental fatigue.[47]

Muscle Bioenergetics

^{31}P-MRS provides a useful objective measure to distinguish patient-reported physical fatigue from mental fatigue. Previously, we have shown that ~50% of patients with CFS experience profound acidosis within their muscles when undertaking moderate exercise and a significant delay in recovery of muscle pH to baseline levels.[48] The cumulative acid exposure, as determined by the "area under the curve" for pH change during exercise testing, was almost 50-fold higher than in sedentary healthy controls. Analysis of ^{31}P-MRS muscle bioenergetics and acid homeostasis was performed in 32 participants (14 active, 18 sham) as previously described,[49] and the phosphocreatine (PCr) recovery interval was calculated. The PCr recovery interval is the recovery time between the maximum drop in absolute pH values (acidosis) after moderate exercise and the time at which muscle acidosis returns to baseline.

Ex vivo Immune Response

Blood samples were drawn at baseline, visit 2 (90 minutes after directly observed nVNS), and visit 3 (90 minutes after self-administered nVNS). EDTA-treated whole-blood samples were stimulated with LPS (2ng/mL) for 24 hours. Serum levels of proinflammatory (IL-1, IL-6, TNF-α, interferon gamma) and antiinflammatory (IL-10, transforming growth factor beta) cytokines in response to LPS stimulation were measured in all 40 participants. Cytokine levels in the supernatant were measured using enzyme-linked immunosorbent assay. Whole-blood immune cell subsets at baseline and day 56 were measured using flow cytometric analysis.

Heart Rate Variability

In 24 participants (11 active, 13 sham), we assessed HRV using the Task Force® Monitor (TFM), which provides noninvasive beat-to-beat hemodynamics measurements.[50] In addition, the TFM derives power spectra of HRV. HRV power spectra are calculated in two frequency bands: high frequency (HF) (0.15–0.40 Hz) and low frequency (LF) (0.04–0.15 Hz), which are used along with LF/HF ratio to provide indices of cardiovascular autonomic balance. Broadly, the LF bands are mediated predominantly by sympathetic modulation of sinoatrial node and vasomotor function, whereas HF bands are mediated by the vagal (parasympathetic) modulation of cardiovascular activity. LF and HF are therefore potentially quantitative indicators of autonomic tone, and the LF/HF ratio reflects sympatho-vagal balance.[51,52]

Statistical Analysis

Ten participants (seven active, three sham) were excluded from analysis (Supplementary Data Table S2 shows details). Of these, seven participants (six active, one sham) either withdrew or were lost to follow-up. Each device is loaded with a predetermined number of nVNS doses, and the number of doses discharged can be observed on the device. Three participants (one active, two sham) were excluded because their devices recorded very few discharges (fewer than 50) at the end of the study, indicating improper device application throughout the study. One participant (active device) developed polymyalgia rheumatica during the study period and was therefore excluded from the remainder of the study. One participant (active device) withdrew from the study owing to unwanted side effects of the device (the sensation when using the device). The primary aim of this study is to analyze the effects of nVNS on changes in fatigue, so the study was powered to detect these changes. The sample size estimation was based on the comparison of fatigue scores in the active and sham device, to give a power of >80% to detect a difference of one standard deviation in fatigue scores on a two-tailed test at the 5% level of significance. This equates to a difference in fatigue scores of 1.0 unit on the ProF-physical fatigue and 1.1 units for the slightly more variable mental fatigue scores. We judged the magnitude of these detectable differences to be clinically useful. At the 5% level of significance on a two-tailed test, this gives a recommended sample size of $n = 17$ per group. The sample size was increased to 20 for pragmatic reasons to accommodate potential participant withdrawal or other losses from the study. In addition, exploratory analyses were performed to identify candidate mechanism(s) involved. Because this study is not a medical device intervention study, an "intention-to-treat" statistical approach is not considered appropriate.

Preprocessing of the EEG recordings was performed after acquisition, using the EEGLAB toolbox version 13 (MATLAB 8.5; The MathWorks Inc, Natick, MA).[53] Further details of alpha reactivity calculations are available in Supplementary Data Supplementary Methods. Alpha reactivity was calculated at each time point: at baseline, at visit 2 after first stimulation (acute), and at visit 3 after daily nVNS including the morning of the visit (prolonged). To compare alpha reactivity between the two groups for each of three conditions (baseline, acute nVNS, and prolonged nVNS), repeated-measures ANOVA analysis was used. Pearson's product moment correlation analysis was performed between three measures of fatigue (PRO-F-Physical, PRO-F-Mental, and fVAS scores) and alpha reactivity, for each of the three cortical regions (frontal, central, posterior) and for each condition (baseline, acute VNS stimulation, chronic VNS stimulation). This analysis was performed separately for the active and sham groups. Bonferroni correction was applied for multiple comparisons between the three stimulation conditions ($\alpha = 0.017$).

All other statistical analysis was performed in R Statistical Software Version 4.0.3 or JMP Pro Statistical Visualization Software (version 15; SAS Institute Inc, Cary, NC).[54] Changes in fatigue scores (fVAS, PRO-F-Physical, and PRO-F-Mental) were analyzed by analysis of covariance (ANCOVA) testing for differences between sham and active VNS groups after adjustment for baseline fatigue scores. Similarly, changes in TNF-α and IL-6 levels were analyzed, testing for differences between the two groups after batch correction and adjustment for baseline levels by ANCOVA. To perform a manipulation check for the two arms of the study, we asked the participants the question 'Which device do you think you have?' There was no significant difference in expectation between the active and sham arms.

RESULTS

Effects of nVNS

Fatigue

There were statistically significant reductions in the PRO-F-Physical, PRO-F-Mental, and fVAS scores between baseline and

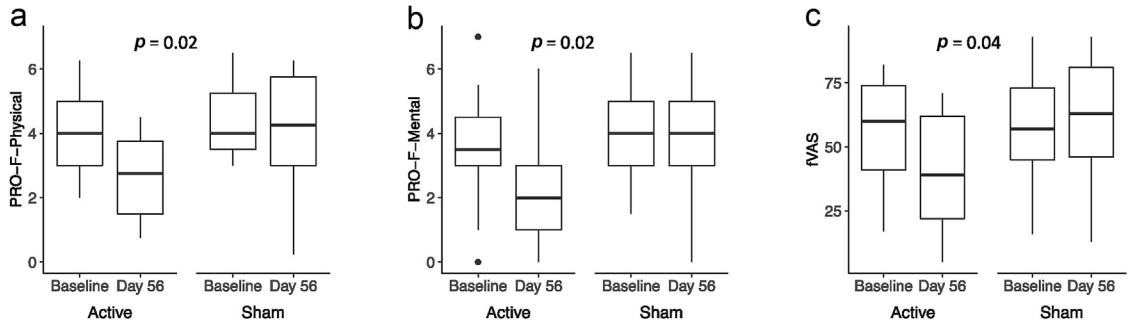

Figure 2. Box plots showing the changes in PRO-F-Physical (a), PRO-F-Mental (b), and fVAS (c) between baseline and day 56 for active and sham experimental arms. *p* Values are for the effect of experimental arm in an ANCOVA with baseline measures as a covariate. PRO-F measures have a maximum score of 7; fVAS has a maximum score of 100.

day 56 in the active device group ($p = 0.02$, $p = 0.02$, and $p = 0.04$, respectively). No reduction in fatigue was observed in the sham device group for any fatigue measure (Fig. 2a–c). For the active arm, the median reductions in PRO-F-Physical, PRO-F-Mental, and fVAS scores were 28%, 25%, and 20%, respectively, further summary statistics are provided in Supplementary Data Table S3.

Other Patient-Reported Outcome Measures

Other patient-reported outcome measures (PROMs) studied did not change significantly between baseline and the end of the study or between the active and sham groups. COMPASS 31 and OGS are tools for evaluating symptoms of autonomic dysfunction. COMPASS 31 provides a broad assessment of dysautonomic symptoms, whereas OGS assesses orthostatic hypotension only. COMPASS 31 and OGS showed nonsignificant changes from baseline to day 56 between study arms ($p = 0.08$ and 0.28, respectively). BLVAS showed no significant change from baseline to day 56 between arms (alertness $p = 0.61$, calmness $p = 0.79$, contentment $p = 0.92$). Similarly, CFQ showed no change from baseline to day 56 between study arms ($p = 0.29$). Individuals who fulfilled The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for depression were excluded from recruitment to this study; however, 38% of baseline BDI scores indicated mild-to-moderate severity of depressive symptoms (median scores of 12 for both active and sham groups). There was no difference in baseline BDI between groups (Supplementary Data Fig. S1, $p = 0.59$).

Neurocognitive Tests

We observed a small significant improvement in backwards digit span in the active group compared with the sham group ($p = 0.03$) and trends toward improvement in total digit span ($p = 0.06$). We observed no significant changes in any other cognitive tests before and after device use in either group. Supplementary Data Tables S4 and S5 and Supplementary Data Figure S2 provide further details of the results.

Muscle Bioenergetics

PCr recovery interval can be measured using ^{31}P-magnetic resonance spectroscopy during and after dynamic exercise. Impairment of PCr recovery may suggest metabolic changes to energy production in muscle fibers. These data showed no significant changes in PCr recovery interval between arms (median PCr/ADP ratio: active = 1.20, sham = 1.24, $p = 0.59$), and recovery interval did not change after device use ($p = 0.47$, Supplementary Data Fig. S3). In addition, these data suggest that PCr recovery in individuals with PSS from both groups are within the healthy range; therefore, physical fatigue in PSS is unlikely to be due to metabolic defect.

Ex Vivo Immune Response

After stimulation of whole blood with LPS, we observed significant differences in IL-6 production between the active and sham arms of the study (Supplementary Data Fig. S4). The change in IL-6 levels between day 1 and day 56 was significantly different between the sham arm and the active arm ($p = 0.02$), the sham arm showing a trend toward increased IL-6 (active group median decrease -168 pg/mL, sham group median increase 452 pg/mL). No differences were observed in TNF-α production ($p = 0.80$). There were no significant changes in whole-blood immune cell subset response between the active and sham groups, as determined by ANCOVA after adjustment for baseline levels (Supplementary Data Fig. S5).

Evidence of Active nVNS

Electroencepholgraphy

We did not find any significant differences in alpha reactivity between the two groups after acute or chronic nVNS. However, in the active group after acute stimulation, we found a significant negative correlation between fVAS score and alpha reactivity in the frontal (Fig. 3, $r = -0.91$ $p < 0.01$) and central regions (Supplementary Data Table S6.2, $r = -0.79$, $p = 0.02$), with a similar trend in the posterior cortical region (Supplementary Data Table S6.2, $r = -0.71$, $p = 0.05$). In contrast, no correlation was found between the measures of fatigue and alpha reactivity for any regions in the sham group.

Heart Rate Variability

We observed no significant changes in measures of HRV before and after device use in either group.

DISCUSSION

In line with our pilot study,[23] the key analyses in this study showed a significant reduction in three patient-reported measures of fatigue with the active device but not the sham device. Physical and mental fatigue based on the PRO-F measures were improved

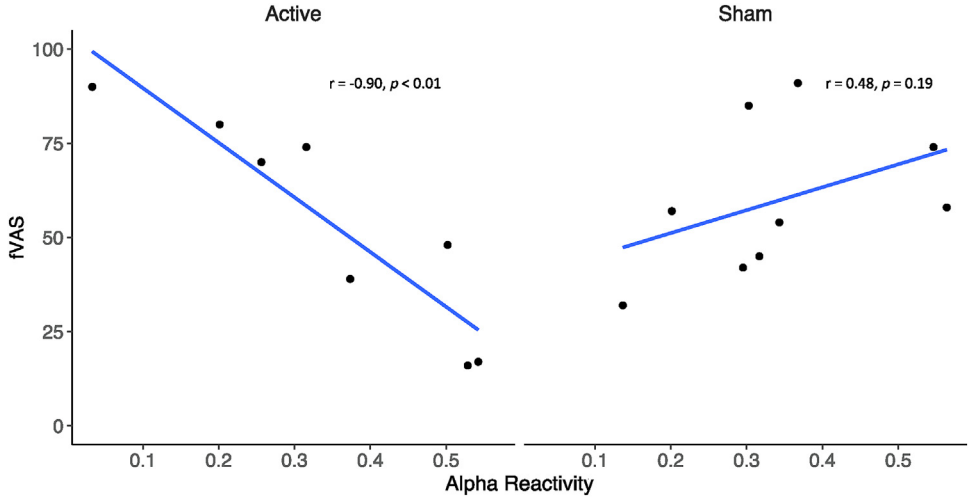

Figure 3. Alpha reactivity, frontal cortical region. A significant negative correlation was observed between fVAS and alpha reactivity after acute stimulation at visit 2 in the active group ($p < 0.01$). A significant negative correlation was also observed in the central region, and a similar strong trend was observed in the posterior region in the active group (Supplementary Data Table S6.2). No significant correlations were observed in the sham arm. Sham group $n = 9$, active group $n = 8$. Seventeen study participants completed EEG recordings at visit 2; nine from the sham device group and eight from the active device group. [Color figure can be viewed at www.neuromodulationjournal.org]

by the end of the study period, as was fVAS. Although there are no consensus definitions on clinically meaningful improvement in fatigue, we observed a greater than 20% decrease in each fatigue score in the active device group. In contrast, we saw no significant improvement in any other outcome measure. Although one participant withdrew from the study owing to unwanted side effects, there were no serious device-related adverse events.

We explored several biophysiological variables to identify candidate mechanisms of action for future follow-up studies. We observed weak associations between self-reported mental fatigue and neurocognitive test scores (Supplementary Data Fig. S6) and we found small improvements in digit span associated with active device use. Owing to the ten excluded participants, the power to detect differences in neuropsychologic assessments in this study may be limited. Formal neurocognitive assessments in PSS have yielded mixed data, but several studies reported impaired performance in various neurocognitive domains, particularly verbal memory, which strongly associates with mental fatigue scores. A previous study showed objective evaluation did not corroborate self-assessment of memory difficulties. Such discordance reflects the individual differences in subjective "metacognitive" awareness (ie, perception of one's own cognitive ability and performance) relative to objective neurocognitive functioning—an important predictor of QoL and general functioning. In this study, many of the participants performed well at baseline, and it is possible that potential improvements related to a reduction in fatigue would be minimal owing to a ceiling effect. Therefore, further investigation is required to determine whether the neuropsychologic assessments used in this study are sufficiently sensitive to reflect changes in mental fatigue state.

BDI has utility in assessment and monitoring of the severity of depressive symptoms; it is not a diagnostic tool, so clinical depression was excluded on the basis of DSM-5 criteria.[55] Analysis of BDI showed no significant improvement in depressive symptoms for either device. This supports the assertion that improvements in fatigue observed in other PROMs are not secondary to improvements in mood state.

The exact mechanism of action of nVNS upon self-reported fatigue and potentially the immune system is unclear. Previously, we have described a reduction in inflammatory cytokine release upon LPS stimulation of whole blood after VNS device use. These changes in stimulated cytokine release did not correlate with improvements in fatigue, however. In this study, we were not able to replicate reduction of proinflammatory cytokines in the nVNS arm. Instead, we observed a slight increase in IL-6 production after LPS stimulation in the sham group, which was not observed in the active group. We did not observe these differences in unstimulated samples. It is worth noting that the relationship between systemic proinflammatory cytokines and fatigue is complex,[10,56] and further investigations into the connection between nVNS, fatigue and inflammatory cytokines are warranted.

It has been hypothesized that changes in muscle bioenergetics may play a role in fatigue in PSS, as has been observed in CFS.[48] However, we observed no differences in PCr recovery intervals in the active or sham groups before or after nVNS, which suggests that dysregulation of muscle bioenergetics is not responsible for the symptoms of fatigue observed in PSS.

We also evaluate the effect of nVNS on cardiovascular autonomic systems and neurophysiology. More specifically, we assessed surrogate measures of autonomic tone and cholinergic drive by measuring HRV and alpha reactivity, respectively. Although increased HRV has been associated with parasympathetic influence,[57] we saw no differences in HRV measures over time or between study arms. The association between HRV and vagus nerve activity is widely disputed, and these results were consistent with the manufacturer's expectations. Confounding factors influencing this association could include the location of VNS; for example, stimulation of the auricular branch of the vagus nerve has been shown to affect HRV in some studies; however, others show

no effect.[58,59] We did, however, observe a relationship between alpha reactivity and fatigue scores after acute nVNS stimulation, which was in line with our expectations. The relationship between fatigue and alpha reactivity was not observed after acute stimulation with the sham device, suggesting that this effect was related to nVNS. Indeed, it has been established that VNS including nVNS modulates EEG microstates and brain activity[60]; therefore, the relationship between fatigue and alpha reactivity observed deserves further investigation in the future.

This study has limitations. Firstly, not all participants completed the study, and a significant proportion of study participants did not complete all the investigations owing tovarious reasons, including patient choice (mostly because of the study intensity), noncompliance, and staff or equipment availability. The resultant data set available for analysis has reduced our statistical power, so we took care to avoid overinterpretation of results. Future studies would benefit from a much larger sample size because the variability in the participants' neck physiology may also result in variable VNS. It is possible that the participants could perceive whether they had been equipped with an active or sham device, which would not be possible with surgically implanted devices because they would be completely indistinguishable. However, the sham device is identical to the active device in appearance and user controls, and we found no evidence of "unblinding" from the participants' answers to the manipulation check question.

CONCLUSIONS

In conclusion, we observed reduction of self-reported fatigue among patients with PSS after nVNS; the mechanisms underpinning the association are not clear but may involve changes in neurocognitive performance and neurophysiology parameters. Our data support further investigation into the role of nVNS as a treatment for fatigue in patients with PSS.

KEY MESSAGES

What Is Already Known About This Subject?

- The vagus nerve has been implicated in pathological fatigue in the context of immune-mediated diseases and chronic fatigue syndrome
- Preliminary work shows improvements in fatigue symptoms after twice-daily noninvasive vagal nerve stimulation (nVNS) over a 26-day period.

What Does This Study Add?

- The findings in this study corroborate previous evidence that nVNS may improve symptoms of fatigue in PSS.
- After acute nVNS stimulation, apparent cholinergic activity, measured by alpha reactivity, is found at a high level in participants with low levels of fatigue.

How Might This Impact on Clinical Practice or Future Developments?

Vagus nerve stimulation may be a useful strategy to improve fatigue in PSS.

Patient and Public Involvement

Patients have been involved at all stages of the research, including identifying research topics, study design, research participation, and dissemination. The results of our pilot study were presented at the Northeast Sjögren's Syndrome Association meeting to discuss study design and collect feedback. Patients also participated in the review of the main summary of the grant application.

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Authorship Statements

Emmanuella Traianos performed ex vivo experiments using the blood samples. Jessica Tarn, Evelyn Evans, Mryto Stylianou, and Alexis Collins performed data analysis. Jessica Tarn, Evelyn Evans, and Wan-Fai Ng drafted the manuscript. Victoria Macrae organized the execution of the study, including conduct of the study visits. Wan-Fai Ng, Julia Newton, John Paul Taylor, Andrew Blamire, Mark R. Baker, Peter Gallagher, and Stuart Watson conceptualized the study. All authors contributed to the interpretation of the data and reviewed the manuscript. All authors approved the final version of the manuscript.

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SUPPLEMENTARY DATA

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COMMENT

The vagus nerve is an important component of the neuro-endocrine-immune axis. It plays a pivotal role in maintaining the homeostatic regulation of the visceral functions through its efferent connections that constitute the cholinergic anti-inflammatory pathway. There are several mechanisms through which stimulation of the vagus nerve leads to reduction in inflammation (1. Bonaz B, Picq C, Sinniger V, Mayol JF, Clarençon D. Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatory pathway. *Neurogastroenterol Motil*. 2013;25(3):208-221.). The idea that stimulating the vagus nerve may increase cholinergic activity, dampen the inflammatory response and decrease fatigue in rheumatological diseases/chronic musculoskeletal diseases (including Sjogren's syndrome) has been documented in prior studies (2. Courties A, Berenbaum F, Sellam J. Vagus nerve stimulation in musculoskeletal diseases. *Joint Bone Spine*. 2021;8.8(3):105149.). There is evidence for anti-inflammatory effect of noninvasive vagus nerve stimulation in rheumatoid arthritis (3. Drewes AM, Brock C, Rasmussen SE, et al. Short-term transcutaneous non-invasive vagus nerve stimulation may reduce disease activity and pro-inflammatory cytokines in rheumatoid arthritis: results of a pilot study. *Scand J Rheumatol*. 2021;50(1):20-27). Transcutaneous auricular vagus nerve stimulation has been shown to have a positive effect on the cognitive reappraisal of emotions and has been proposed as a potential tool in the treatment of a major depressive disorder (4. De Smet S, Baeken C, Seminck N, et al. Non-invasive vagal nerve stimulation enhances cognitive emotion regulation. *Behav Res Ther*. 2021;145:103933). Noninvasive VNS as a therapeutic tool is increasingly being studied in other conditions including epilepsy, chronic headaches, chronic fatigue syndrome, chronic pain and, gastrointestinal disorders including irritable bowel syndrome. This study does have a sound methodology and looks at several variables including heart rate variability, pro and anti-inflammatory cytokine levels, alpha reactivity in EEG, performance on cognitive tasks such as trail making test, digit symbol tests, Rey-Auditory Verbal Learning Test, Stroop, digit span, verbal fluency tests, and psychomotor vigilance test. Interestingly small improvements in digit span were noted in the study that could reflect positive changes in cognitive processing. Since there is a close association between mood and cognition, excluding patients with clinical depression certainly provided more validity to the finding by reducing confounding. It needs to be ascertained if longer duration of treatment or changes in frequency of stimulation has any added cognitive benefits. Improvements in alpha reactivity (which is a marker of cholinergic integrity) together with the marked reduction in self-reported fatigue underscores the potential therapeutic benefits of using (noninvasive vagus nerve stimulation) to address fatigue in Sjogren's syndrome. As rightly pointed out by the authors, a larger study population and dataset would help in further improving the statistical power and the validity of the findings.

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