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PAuSing-pCF [COV-LT2-0022]

Title: Percutaneous Auricular Nerve Stimulation for Treating Post-COVID Fatigue

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Plain English Summary

Fatigue is a very common symptom of Long COVID and estimated to affect ~2% of the UK population; post-Covid Fatigue (pCF) not only has a devastating impact on the lives of patients and carers but has significant economic implications for society, which in the USA is estimated to cost $2·6 trillion.

Whilst the causes of fatigue are multi-factorial, many of the symptoms of fatigue correlate with features consistent with overactivity of the sympathetic nervous system (resembling a chronic stress response), it has been hypothesized that vagus nerve (parasympathetic) underactivity might be the underlying cause of fatigue, and that stimulation of the vagus nerve might therefore reduce fatigue.

The vagus nerve can be easily and safely stimulated via an electrode clipped to the ear, using transcutaneous auricular vagus nerve stimulation (taVNS). We randomly assigned 114 participants with pCF, focussing on people diagnosed with COVID19 but not requiring hospital in-patient treatment, to receive daily home-based taVNS for 16 weeks: one group received active stimulation and two groups received sham or placebo stimulation respectively. After 8 weeks, all participants received active taVNS. Fatigue was assessed using questionnaires and lab-based tests to measure changes in brain circuits, muscles, and heart.

Assessments were performed at baseline, 8 weeks, and 16 weeks. Across all participants, primary analysis of questionnaire scores showed no significant differences between interventions. However, in participants meeting minimum adherence criteria (≥1 h/day on ≥50% of days), questionnaire scores and peripheral muscle fatigue improved significantly after 8 weeks of active taVNS, but not after sham or placebo.

These findings provide evidence that taVNS is a promising therapeutic approach for managing persistent fatigue in pCF and support the hypothesis that vagus nerve dysfunction contributes to fatigue.

Executive Summary

Study aims: The primary objective of the PAuSing-pCF study was to establish whether transcutaneous electrical stimulation of the auricular nerve (transauricular vagus nerve stimulation; taVNS), self-administered by a handheld battery-powered transcutaneous electrical nerve stimulation (TENS) device, reduces symptoms of fatigue associated with Long COVID (post-COVID Fatigue). Secondary aims were to explore:
1. Whether neurological endophenotype could predict response to taVNS, thus permitting a stratified approach to treatment.
2. What the optimum duration and dose of taVNS are.

Background: Long COVID is a common complication of SARS-CoV-2 infection, affecting individuals with both severe and mild COVID-19. Long COVID (or post-COVID syndrome; PCS), is defined by the National Institute for Health and Care Excellence (NICE) as a multi-system condition with a range of debilitating symptoms - signs and symptoms continue or develop after acute COVID-19, continue for more than 4 weeks, and are not explained by an alternative diagnosis. Currently, ~3.1% of the UK population have PCS. Whilst symptoms remit spontaneously for some, many individuals with PCS have persistent problems, for which there are no evidence-based treatments and limited understanding of underlying mechanisms. The commonest symptom of PCS is fatigue; post-COVID fatigue (pCF) affects around 71% of those with PCS, equivalent to 2.3% of the UK population, and encompasses physical exhaustion, increased effort perception, and cognitive dysfunction ("brain fog"). Previously, our research group provided preliminary evidence that in Sjögren's syndrome, a chronic autoimmune condition associated with fatigue, non-invasive vagus nerve stimulation (VNS) can reduce fatigue. Here, we investigated the effects of 16 weeks of self-administered transcutaneous auricular (taVNS) on fatigue symptoms and related physiological, neurophysiological, and behavioural measures in otherwise healthy individuals with pCF.

Methods: A total of 114 participants (85 females), aged 18-65, suffering from pCF by self-report (continuing symptoms of fatigue>4 weeks post-infection) were recruited to the study. None had a history of neurological or psychiatric disorders, nor cardiac disease prior to SARS-CoV-2 infection. The diagnosis of COVID-19 was verified (by polymerase chain reaction, lateral flow or antigen tests) in all participants; none required hospitalisation following initial infection. The study was designed as a single-site, single-blind, sham-controlled and placebo-controlled, randomized trial, with all participants moving to the

active intervention (open label) after 8 weeks. This gave all participants the opportunity to benefit from the active taVNS intervention.
Participants were randomized to one of three experimental groups:

- Intervention-1 (active taVNS): Clip electrode was attached to the tragus and connected to the TENS device to stimulate the auricular branch of the vagus nerve.
- Intervention-2 (sham control): Clip electrode was also attached to the tragus, but the electrode was inactive.
- Intervention-3 (placebo control): Clip electrode was attached to the earlobe and connected to the TENS device thus stimulating afferents of the greater auricular nerve.

Neurophysiological, behavioural and fatigue assessments were repeated at baseline (week 0), after 8 weeks and at the end of the study (week 16).
Participants were required to self-administer electrical stimulation to the external ear to activate nerves running beneath the surface of the skin. A FlexiStim transcutaneous electrical nerve stimulation (TENS) device was used for this purpose.
The stimulation parameters were set for each participant and the stimulus current strength was set just above perceptual threshold to ensure the subject was aware of the stimulation, but also so that the intensity was not uncomfortable or painful. Participants were asked to apply the intervention three times per day. Minimum acceptable TENS usage was defined as ≥1h/day (the length of one stimulation cycle) on at least 50% of days. To monitor adherence, a data logger, which recorded how often and how long the device was switched on, was attached to the TENS device. For patient-reported outcomes (PROs), participants were asked to fill out questionnaires online, over the course of the 16-week trial. The questionnaires consisted of a Fatigue Visual Analogue Scale (VAS) and the Fatigue Impact Scale (FIS).
The following physiological measures were acquired in the lab: cortical excitability testing using transcranial magnetic brain stimulation; galvanic skin response; StartReact; stop-signal reaction time; electrocardiogram; and twitch interpolation. Biometric data were also collected from participants. These included blood oxygen saturation, tympanic temperature, height, weight and full body composition.

Results: The primary outcome, as outlined in the statistical plan, compared the mean differences in the change in VAS scores from baseline to week 8, between participants treated with taVNS and the two control groups (sham and placebo stimulation). The intention-to-treat analysis showed that these differences were not statistically significant (taVNS vs sham p=0.59 and taVNS vs placebo p=0.81).

However, because of the very low levels of adherence, we also completed a per-protocol analysis in a subgroup of participants who met minimum adherence

criteria (≥1h TENS on ≥50% of days). This analysis included data from the remaining 59 participants (45 females, 49.8 ± 10.2 years) of the 114 participants recruited (24 dropped out during the study and a further 31 were excluded from analysis for not meeting minimum TENS usage); 24 were randomized to active taVNS, 19 received sham stimulation and 16 were allocated to the placebo group. The control cohort consisted of 52 healthy participants, with no symptoms of fatigue (37 females, 46.1 ± 9.3 years).

The 28 electrophysiological measures that were significantly different in pCF versus control participants at baseline, as well as the FIS and VAS scores, were analysed before and after 8 weeks of daily taVNS usage. Of the 33 total measures (28 electrophysiological measures and 5 questionnaire scores), 6 measures improved significantly after 8 weeks of taVNS. Participants improved significantly in all questionnaire scores, including the primary outcome measure of the study (visual analogue scale VAS $p<0.001$), the total score of the fatigue impact scale (FIS; $p<0.001$), as well as all subscores of the fatigue impact scale (FIS_Physical $p<0.001$, FIS_Social $p<0.001$, FIS_Cognitive $p<0.001$). The results of twitch interpolation showed significantly decreased levels of peripheral fatigue (TI_PeriphFatigue $p=0.001$), which, in contrast to subjective assessments, is an objective electrophysiological measure of improvement. All other measures remained unchanged after 8 weeks of taVNS.

There was additional improvement in VAS when using active taVNS open-label for another 8 weeks (16 weeks total), though less pronounced than over the first 8 weeks (decrease of 7.0 ± 10.4 points, $p=0.003$, $d=0.437$). There was no further reduction in FIS scores or peripheral fatigue after 16 weeks of taVNS.

Finally, analysis of our cross-sectional baseline data showed that those with pCF >200 days had significantly more fatigue and showed increased cortical excitability, slower reaction times and increased peripheral muscle fatigue compared to those with pCF <200 days.

Key findings: (including headline messages relevant to policy makers):
a. Aetiology. Vagus nerve dysfunction contributes causally to pCF.
b. Phenotype. If symptoms of fatigue do not improve/remit after 200 days, significant/persistent
changes in the underlying pathophysiology of fatigue are observed in patients with pCF.
c. Therapy. Self-administered taVNS improves fatigue in pCF, if used for a minimum of 1 hour per day on alternate days (50% of the time) on average.

Conclusions and recommendations for further research:
a. Vagus nerve dysfunction causes myopathy, which can be ameliorated by taVNS. This observation requires further investigation. An understanding of the

mechanisms by which the vagus nerve causes cellular/subcellular changes in muscle should reveal new therapeutic targets for pCF (and other forms of fatigue) and provide a scientific basis for the dose/duration of taVNS.
b. Guidance for the design of future clinical trials in pCF. Patient stratification. Our findings that pCF phenotype changes over time, particularly after 200 days, has implications for other studies aiming to investigate mechanisms behind pCF and the development of treatment approaches. A key challenge for future trials will be to balance recruitment to ensure even representation of pCF phenotypes. Without stratification of symptom duration/physiological profile, treatment effects risk being diluted or misinterpreted. Adherence. Whilst our findings may be peculiar to the use of devices as interventions in pCF, until the evidence is available, the possibility of low adherence should be considered when designing clinical trials in pCF and adherence should be monitored. The reasons why participants with pCF struggle to adhere to trial interventions should also be explored. Objective trial endpoint. Peripheral (muscular) fatigue, measured using the twitch interpolation protocol, is a robust/quantifiable biomarker of fatigue and should be incorporated as an endpoint in future clinical trials in pCF/post-infection fatigue.
c. Vagus nerve stimulation as a therapy for fatigue. Our preliminary results should be confirmed in larger clinical trials of taVNS in pCF (and other forms of post-infection fatigue), including an exploration of taVNS dose/duration.

Dissemination plans: Results will be disseminated via our study website (from pre-print servers) and submitted to international medical scientific journals for publication. Once published, Newcastle University Press Office will prepare a press release.

Expected influence/impact: The results of this study should influence/inform policy given the prevalence of pCF and its contribution to economic inactivity in the UK. Further funding for research into mechanisms/therapies for fatigue would be beneficial. The impact on service providers is perhaps a more realistic goal (NHS fatigue clinics will have to deliver taVNS) but wider stakeholders, including those with myalgic encephalomyelitis/chronic fatigue syndrome and other forms of post-infection fatigue will also benefit.

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Glossary

FIS	Fatigue Impact Scale
NICE	National Institute for Health and Care Excellence
pCF	post-COVID fatigue
PCS	post-COVID syndrome, now known as Long COVID

taVNS	Transcutaneous auricular vagus nerve stimulation
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual Analogue Scale
VNS	Vagus nerve stimulation

Key Publications

1. M. Shahmandi et al (2026) Effect of Percutaneous Auricular Nerve Stimulation on Fatigue in Adults with Post-COVID Fatigue (PAuSing-pCF): Results of a Randomised, Sham-Controlled Trial. *NIHR Open Research*
2. M. Germann et al (2025) Percutaneous Auricular Nerve Stimulation for Treating Post-COVID Fatigue (PAuSing-pCF): a single-site, single-blind, sham-controlled, randomized, interventional, crossover study protocol. *medRxiv*
3. M. Germann et al (2025) Evidence of Accumulating Neurophysiologic Dysfunction in Persistent Post-COVID Fatigue. *medRxiv*
4. M. Germann et al (2025) Percutaneous Auricular Nerve Stimulation for Treating Post-COVID Fatigue (PAuSing-pCF). *medRxiv*
5. N.Y. Aboagye et al (2025) Feasibility of predicting next-day fatigue levels using heart rate variability and activity-sleep metrics in people with post-COVID fatigue. *Frontiers in Digital Health.*
6. N.J. Maffitt et al (2024) Recovery of neurophysiological measures in post-COVID fatigue: a 12-month longitudinal follow-up study. *Scientific Reports.*