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Pausing post-COVID fatigue

Submission date
06/05/2022

Recruitment status
No longer recruiting

Registration date
12/05/2022

Overall study status
Completed

Last Edited
11/03/2024

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English Summary

Background and study aims
Fatigue is a very common symptom of Long COVID. Feedback from those with post-COVID fatigue (pCF) has highlighted the devastating impact it has on their lives and the need for novel therapeutic options.
As with all forms of post-viral fatigue, the causes of pCF are likely to be multi-factorial. However, as a post-infectious phenomenon, inflammatory/immune processes are likely to be important. Fatigue encompasses not only the perception of increased physical effort and extreme tiredness but also cognitive/mental fatigue (problems with thinking, remembering and concentrating). As part of a separate study, we have recently shown that such symptoms in pCF are associated with measurable changes in the nervous system.
There is increasing evidence that COVID-19 can affect the autonomic nervous system. Interestingly, most of the changes could be mediated by the vagus nerve. If true, stimulation of the vagus nerve might help to prove that the changes we have observed have a mechanistic role in pCF.
The vagus nerve controls many of the unconscious functions of the body. However, it also provides access for modulating abnormal brain networks and neuroinflammatory pathways by electrical nerve stimulation. For example, the surgical implantation of devices for stimulating the vagus nerve is a long-established approach for managing difficult to treat epilepsy. Non-invasive vagus nerve stimulation (nVNS), delivered through electrodes placed on the skin of the neck, avoids the risks of surgery, and is now also recognized to be an effective treatment for certain headache disorders. More recently, small studies in patients who have chronic immune-mediated diseases associated with fatigue have shown that nVNS significantly reduces the symptoms of fatigue. If nVNS can improve symptoms of fatigue in chronic immune-mediated diseases it should in theory also be effective in pCF.
Whilst most studies have stimulated the vagus nerve non-invasively via electrodes placed on the neck, the vagus can also be activated by stimulating the skin of the ear. Transcutaneous auricular vagus nerve stimulation (taVNS) is potentially an easier and more reliable approach to activating the vagus nerve and can be self-administered safely at home. Moreover, taVNS can be delivered with a handheld battery-powered transcutaneous electrical nerve stimulation (TENS) device purchased without prescription over the counter, or online.
This study will:
1. Probe the mechanisms of pCF in adults by testing whether taVNS self-administered using a TENS device can reduce symptoms of fatigue (assessed by questionnaires) and normalise changes in the peripheral and central nervous system that are hypothesized to mediate fatigue;

and
2. Provide trial evidence as to whether taVNS is an effective intervention for pCF.

Who can participate?
Members of the public who have a verifiable positive COVID-19 diagnosis but who did not require hospitalisation and who are at least 2 weeks after diagnosis. They will be screened for symptoms of fatigue.

What does the study involve?
Fatigue and biometric/neurophysiological/behavioural assessments are completed and blood samples collected (week 1). Participants will be fitted with wearable technology and smartphones for collecting data will be provided, and baseline ambulatory data collected for 7 days. During this 7-day period, participants will be randomly allocated to one of the three experimental groups – active tragus stimulation, sham tragus stimulation (control 1) and active pinna/greater auricular nerve stimulation (control 2). At the Week 2 visit fatigue assessments will be repeated, taVNS parameters will be set and equipment, consumables and instructions for the assigned intervention provided in a box. In weeks 3-4 wearable devices (patches and smartphones) will be collected and the fatigue assessments repeated. At the Week 8 visit neurophysiology, behavioural and fatigue assessments will be repeated, and participants receiving active VNS will continue for a further 8 weeks and those initially in the control arms will cross over to the active intervention for the last 8 weeks of their participation in the study; thus all participants will have the opportunity to experience the active VNS intervention. At Week 12 fatigue assessments will again be completed and at the Week 16 visit, all assessments will be repeated.

What are the possible benefits and risks of participating?
Members of the public with post-COVID fatigue may benefit from an improvement in fatigue syndromes. Participants will help with basic research. There are no associated risks in participating.

Where is the study run from?
Newcastle University (UK)

When is the study starting and how long is it expected to run for?
February 2022 to March 2025

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Dr Mark Baker
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Study website
http://www.covidfatigue.co.uk/

Contact information

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Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
PAuSing-pCF-Protocol-v2.0

Study information

Scientific Title
Percutaneous auricular nerve stimulation for treating post-COVID fatigue

Acronym
PAuSing-pCF

Study hypothesis
Does vagus nerve stimulation via the auricular branch (taVNS), self-administered using a transcutaneous electrical nerve stimulation (TENS) device, affect symptoms of fatigue and physiological, neurophysiological, behavioural, and immunological correlates of fatigue in otherwise healthy members of the public with post-COVID fatigue (pCF)?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/04/2022, Faculty of Medical Sciences Research Ethics Committee (Newcastle University, Medical School, Framlington Place, NE2 4HH, UK; Tel: not provided; res.policy@ncl.ac.uk), ref: 2284/18447

Study design
Single-centre interventional double-blinded randomized sham/placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Home

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Condition
Post-COVID fatigue

Interventions
In this study, participants will be required to self-administer electrical stimulation to the external ear to activate nerves running beneath the surface of the skin. A FlexiStim (TensCare, Epsom, UK) transcutaneous electrical nerve stimulation (TENS) device will be used for this purpose. These devices are commercially available over the counter (OTC), or online without prescription, and having been specifically developed for safe use without training and with only minimal written instructions participants should find these TENS devices straightforward to use.

The research assistant (RA; or research team member) will set up the stimulation parameters for the TENS device and train the participant to use the device at the end of their visit to the laboratory, after completing laboratory assessments. The RA will first explain to each participant that, 'the aim of the study is to test the effects on fatigue of stimulating different parts of the ear lobe at different levels of stimulation'. The RA will then set stimulus parameters during the TENS demonstration by determining sensory threshold and pain/discomfort threshold for tragus, pinna and earlobe stimulation and instructing the participant to set the TENS at a specified current setting whenever it is used.

To activate the auricular branch of the vagus nerve (taVNS) a clip electrode connected to the TENS system will be attached to the left tragus. Fabric sleeves, cut to the correct length to cover the two prongs of the ear clip electrode, ensure that the electrode gel (Spectra 360 Electrode Gel, Parker Laboratories Inc, NJ, USA) applied in between the ear clip electrode, or that the saline used to moisten the sleeves, makes a good electrical contact with skin of the tragus. To activate the greater auricular nerve (C2/C3 nerve roots; positive control) clip electrode will be attached to the left earlobe/pinna to stimulate this external ear region.

The stimulation parameters will be set for each participant using the electrical muscle stimulation (EMS) program on the TENS machine and the same parameters will be used for tragus and earlobe/pinna stimulation. The stimulation protocol will begin with a two-minute warm-up at a frequency of 6 Hz and pulse width of 200 μs. This will be followed by a 60-minute train, which alternates 30 seconds at 25 Hz and 300 μs with 60 seconds at 4 Hz and 200 μs. Finally, there will be a 3-minute cooldown stimulation protocol of 3 Hz and 200 μs. The stimulus current strength will be set just above the perceptual threshold to ensure the subject is aware of the stimulation, but also so that the intensity is not uncomfortable or painful.

To ensure participants are blinded, for each intervention participants will only be required to power the TENS device ON (stimulator settings will be pre-set for each participant and the same settings used for all interventions). Instructions for delivering intervention-1, intervention-2 or intervention-3 (according to the randomization procedure) will be provided in a sealed envelope with the device to each participant. The three interventions will be as follows:

Intervention 1: Clip electrode attached to the tragus and connected to the TENS device to stimulate the auricular branch of the vagus nerve i.e. active nVNS.

Intervention 2: Clip electrode, incorporating a hidden resistor to shunt stimulus current, is attached to the tragus such that the auricular nerve is not stimulated when the TENS device is powered on i.e. controlling for mechanical pressure exerted by the clip electrode on the tragus.

Intervention 3: Clip electrode attached to the earlobe and connected to the TENS device thus stimulating afferents of the greater auricular nerve (C2/C3 nerve roots) i.e. Controlling for non-specific effects of electrical stimulation.

Before the participant starts the allocated intervention, the RA will also explain to each participant that, 'because different current strengths are being tested, they may not feel the stimulation'. Participants will be asked to apply the treatment three times per day: after waking, after lunch and at bedtime.

Participants will be randomized initially to one of three groups, one active and two control interventions, which they will self-administer for 8 weeks as part of a double-blind, sham /placebo-controlled study design. Balanced randomization will be performed independently by the statistical team. Participants receiving active VNS will continue for a further 8 weeks and those initially in the control arms will crossover to the active intervention for the last 8 weeks of their participation in the study; thus, as suggested by patients in our current pCF study, all participants will have the opportunity to experience the active VNS intervention.

Intervention Type
Device

Phase
Phase II

Drug/device/biological/vaccine name(s)
FlexiStim (TensCare, Epsom, UK) transcutaneous electrical nerve stimulation (TENS) device

Primary outcome measure
Fatigue assessed using a visual analogue scale (VAS) at Week 1, Week 2, Week 4, Week 8, Week 12, Week 16

Secondary outcome measures
1. Ongoing levels of fatigue (Fatigue Impact Scale [FIS], Functional Assessment of Chronic Illness Therapy – Fatigue [FACIT-F], VAS), mood (Generalised Anxiety Disorder Assessment [GAD-7], Patient Health Questionnaire [PHQ-9]) and musculoskeletal pain (Brief Pain Inventory), measured with questionnaires at Week 1, Week 2, Week 4, Week 8, Week 12, Week 16
2. Biometric data measured using wearable technology (Axivity AX6 & Vitalpatch) for 7 days at each of the three assessment periods (Week 1, Week 8, Week 16)
3. Maximal M-wave measured by median nerve stimulation from the abductor pollicis brevis muscle at Week 1, Week 8, Week 16
4. Intracortical inhibitory circuits assessed by measuring motor evoked potentials elicited via transcranial magnetic stimulation (TMS) during recruitment curves, paired-pulse and short-interval intracortical inhibition paradigms at Week 1, Week 8, Week 16
5. Grip force measured with a handgrip dynamometer at Week 1, Week 8, Week 16
6. Galvanic skin responses measured by placing two metal plates on the lateral and medial surfaces of the index finger at Week 1, Week 8, Week 16
7. Reaction time measured using a StartReact paradigm and measure stop-signal reaction time at Week 1, Week 8, Week 16

8. Heart rate and its variability measured with single-channel ECG at Week 1, Week 8, Week 16
9. Molecular biomarkers measured using serum PAXgene RNA samples at Week 1, Week 8, Week 16

Overall study start date
28/02/2022

Overall study end date
01/03/2025

Eligibility

Participant inclusion criteria
1. Members of the public (adults) who have a verifiable positive COVID diagnosis (COVID+) but who did not require hospitalisation and who are at least 4 weeks after diagnosis, will be recruited via the trial website (http://covidfatigue.org.uk/), social media and radio advertisements. They will be screened for symptoms of fatigue using an electronic implementation of the Fatigue Impact Scale
2. Aged ≥18 and <65 years
3. Able to provide written informed consent in English
4. No previous diagnosis of neurological or psychiatric disorder
5. No cardiac disease (e.g., cardiomyopathy, myocardial infarction, arrhythmia, prolonged QT interval, etc)
6. No implanted device (e.g., pacemaker)
7. Not pregnant
8. Fluent in English

Participant type(s)
Other

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
Both

Target number of participants
96

Participant exclusion criteria
1. Previous diagnosis of neurological or psychiatric disorder
2. Cardiac disease (e.g., cardiomyopathy, myocardial infarction, arrhythmia, prolonged QT interval, etc)
3. Implanted device (e.g., pacemaker)

4. Pregnant
5. Not fluent in English

Recruitment start date
15/05/2022

Recruitment end date
30/04/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Newcastle University
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Sponsor type
University/education

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ROR
https://ror.org/01kj2bm70

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
01/03/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publicly available repository. Data will be uploaded to https://data.ncl.ac.uk. Data generated by this project will be in the form of computer files holding surface EMG signal waveforms recorded in response to stimuli. These files will be recorded by the Spike2 software package. Data will be made available after the researchers publish the papers arising from the study. Data will be stored on https://data.ncl.ac.uk for at least 10 years and available to be downloaded by anyone. Raw data is uploaded in anonymous form and participants be asked to give consent for this at the beginning of the study.

IPD sharing plan summary
Stored in non-publicly available repository