

## 1. Study Title.

### **Neurophysiological characterisation of post-COVID fatigue**

## 2. What is the purpose of the study?

Despite the high severity of the COVID virus in a substantial minority of those infected, most people only suffer from mild initial symptoms, which typically resolve without the need for hospitalisation. However, there is increasing evidence that even after mild disease, many people (typically >20%) continue to suffer from symptoms such as fatigue and muscle weakness. This is often referred to as Long COVID, and can be quite detrimental to quality of life and productivity. As a novel disease, the neural mechanisms behind post-COVID fatigue (pCF) remain unclear – symptoms of fatigue and weakness could be caused by problems in several different brain areas and this uncertainty is hampering our ability to make more rational decisions on the best interventions and treatments. Our aim is to use observational and electrophysiological methods to examine and characterise the neural mechanisms behind pCF, and to monitor their progression over time.

You are being invited to take part in this study. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

## 3. Why have I been chosen?

We have asked you to help us either as a normal, healthy volunteer or as someone who has had a verified COVID-19 test and who is now potentially experiencing some of the longer term effects such as fatigue. If you have any history of neurological disease (for example epilepsy or Parkinson's disease), any implanted devices (e.g. a pacemaker), or are pregnant, you should decline to participate in this study. If you have never had COVID but belong to one of the high risk categories, you should also not participate. People sensitive to loud noises should also not participate. You do not need to tell us the reason for your decision.

## 4. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. Please feel free to ask any questions at any time. If you decide to take part, you are still free to withdraw at any time and without giving a reason.

## 5. What will happen to me if I take part?

You will be asked to attend our laboratories within the Medical School at Newcastle University, where we can discuss any further queries you may have regarding the study. Please wear loose clothing for easy access to the upper arm and lower leg. Once you are happy to proceed and have signed the consent form we can begin. We may first ask you to fill in a brief questionnaire to allow us to quantify your self-assessment of fatigue on the day of your visit. We will then carry out the experimental part of the study, which will take up to 3 hours. We will use adhesive electrodes stuck to the skin on the hand, arm and lower leg to record the electrical activity produced when your muscles are active. To record activity from your brain we will use similar electrodes on your scalp. We will ask you to perform a task with your hand or arm or leg, in which you will be asked to respond to lights or sounds by moving in a particular way (e.g. pressing a lever upon instruction or asking you to move your ankle). We may also measure responses to different types of stimuli described in the paragraphs below. Stimuli will be given while you are at rest and also while you are making a movement.

One of the stimuli we might test in the experiment is a brief loud sound. We have carefully calibrated these so that the duration and level of sound is not harmful to your hearing – perhaps comparable to a car horn sounded next to you in the street. You will notice that the person running the study wears ear protectors during the experiment: this is because they often conduct multiple studies per week, giving them a higher level of exposure than the person volunteering. People especially sensitive to loud sounds might find them unpleasant, and in that case should not participate in the study.

We also need to measure your reflex responses and for this we need to give a test with electrical stimulation of a muscle or nerve. We will place adhesive electrodes on the skin and pass a weak electric current through them. This is not painful or harmful, but can feel a little strange if you haven't experienced this before, and can be akin to 'pins and needles', and will make your muscles twitch involuntarily. Please let the experimenter know if you find the stimuli unpleasant, and they will stop the study.

We will measure the strength of connections between your brain and spinal cord using magnetic brain stimulation. A coil will be placed over your head, and a rapid magnetic field produced which can stimulate the part of your brain controlling movement. Again, this is painless and harmless (it feels like a tap on the head); it will make your muscles twitch. Most subjects tolerate this type of brain stimulation without problems, but please let the experimenter know if you find the stimuli unpleasant and want to stop.

Please ensure that your posture is comfortable at the start of the experiment as small discomforts at the start can become very unpleasant after you have been sitting in the same place for some time. The experiments will be carried out by research staff that are fully trained and competent in the procedures to be used. We are not medical doctors.

One of the aims of the study is to test how these measurements change over time and in order to do this, some of you will be asked to visit the lab more than once (every ~4 months, 3 times) so that we can repeat the measurements described above. If you are chosen for the repeat visits, we will also ask you to fill in a brief online questionnaire once a month regarding your fatigue symptoms. This will be brief and take less than 5 minutes of your time to complete – you will be given a unique number, so as to avoid having to enter any of your personal information online, but if you prefer a paper questionnaire instead, please let us know and we can offer that to you in printed form, and we can then digitise the answers in the lab.

#### **6. What precautions are being taken to reduce the chances of COVID transmission during my visit?**

If prior to your visit if you display any of the cluster of symptoms related to the disease (such as persistent coughing, fever, loss of smell or taste, diarrhoea, muscle pain) you will be asked to reschedule your visit for at least 2 weeks in the future. Before (and after) your visit all contact surfaces will be wiped down with disinfectant. In the lab, whenever possible a 2 meters distance will be kept between yourself and the experimenter, but for instances where this is not possible (such as during placement of electrodes), appropriate PPE will be worn by experimenter (surgical mask, gloves and apron) and by yourself (face mask). Both you and the experimenter will be expected to wash your hands at the start and end of the session. New PPE will be used for every participant. Even if you have recently recovered from COVID, and are potentially less likely to be vulnerable to infection, we will still follow exactly the same procedures.

#### **7. What are the possible disadvantages and risks of taking part?**

The methods which we will use are straightforward, and safe. Many are routinely used by doctors for diagnosing and treating their patients. None of the methods to be used will cause any harm.

#### **8. What are the possible benefits of taking part?**

There will be no benefit to you for taking part. The information which we gain by doing this study could lead to important advances in understanding the neural mechanisms behind post-Covid fatigue, and could help guide treatments for this in the future.

#### **9. What if something goes wrong?**

If you are harmed by taking part in this research project, you may be entitled to compensation under an insurance policy held by the University of Newcastle. If you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you should in the first instance contact Prof. J. Veltmann, Director of the Institute of Biosciences, University of Newcastle, The Medical School, Framlington Place, Newcastle, NE2 4HH.

#### **10. Will my participation in this study be kept confidential?**

All information which is collected about you during the course of the research will be kept strictly confidential. Upon your first visit you will be given a unique identifier number that will be used for all of your data storage and management. A paper document (that never leaves the lab) will match the unique identifier to any identifiable information of you, and this document will be destroyed at the conclusion of the study (3 years). Any information about you which leaves the laboratory will have your name and address removed so that you cannot be identified from it. You will be given a copy of this information sheet to take away with you, and may wish to show it to your GP if you want to discuss your participation in the study with him or her.

#### **11. What will happen to my data collected during this study?**

Your data will be digital (both the questionnaire answers and electrophysiological recordings) and will contain no identifiable information that can be related back to yourself. Your data will be stored on the Newcastle University's secure servers for no more than 10 years – the first 3 years will be the duration of this study plus an additional 7 years, to allow completion of any outstanding publications, and should the data be of further interest to ourselves or other for related COVID research. After that time, we would aim to upload the data onto an open access repository (such as <https://openneuro.org/>) for others to access. If you wish for your research data to be deleted at the conclusion of the 10 years please let us know at any point prior to that time.

#### **12. What will happen to the results of the study?**

The results of this study will be published in scientific journals. If you would be interested in seeing a copy of the final paper, please let us know and we will send you one when it is published.

#### **13. Who is organising and funding the research?**

This work is funded by the Medical Research Council as part of their Rapid Response Rolling Call to deal with the COVID pandemic.

#### **14. Who has reviewed the study?**

This study was approved by the Faculty of Medical Sciences Research Ethics Committee, part of Newcastle University's Research Ethics Committee. This committee contains members who are internal to the Faculty. This study was reviewed by members of the committee, who must provide impartial advice and avoid significant conflicts of interests.

#### **15. Contact for further information**

This sheet provides basic information about the experiment. We will explain more as we go along; please feel free to ask questions. The person conducting the study is Dr Anne Baker. The head of the laboratory in which these experiments are carried out is Dr Demetris Soteropoulos. Please contact the team on [covidfatigue@newcastle.ac.uk](mailto:covidfatigue@newcastle.ac.uk) if you have any queries about the study. If this does not resolve your query, please contact Dr Soteropoulos (0191 208 8547; email [demetris.soteropoulos@ncl.ac.uk](mailto:demetris.soteropoulos@ncl.ac.uk); postal address Henry Wellcome Building, Medical School, Framlington Place, Newcastle upon Tyne, NE1 4HH). Thank you for giving your time to this study.

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