Home Office

NON-TECHNICAL SUMMARY

Neural basis of tactile behaviour

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

neuroscience, electrophysiology, somatosensation

Animal types	Life stages
Mice	adult, embryo, neonate, juvenile, pregnant

Retrospective assessment

> The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the projects objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

The aim is to investigate how neurons in the sensorimotor system operate during tactile exploratory behaviour.

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

Why is it important to undertake this work?

The project addresses one of the fundamental general goals of neuroscience, which is to understand how neurons work to the point that we can accurately predict their activity during behaviour. This kind of discovery research is important not only for its own sake but also because improvement in our knowledge of how neural circuits work will facilitate the development of new treatments for neurological disorders in the future. Past discoveries in this area have led to the development of brain machine interfaces which are starting to become clinically effective.

What outputs do you think you will see at the end of this project?

New information on sensorimotor function, academic publications on the topic and data from the project to be shared with the scientific community.

Who or what will benefit from these outputs, and how?

The short-term benefit will be advances in our basic knowledge of brain mechanisms of sensorimotor function.

In the longer-term, there is potential for benefits both to human health (see above) and to Artificial Intelligence (machine learning) technology. Improved understanding of how neural circuits work makes it possible to 'reverse engineer' principles of how the brain works to suggest new directions for Artificial Intelligence. For example, past advances in our understanding of the brain chemical dopamine has led to important advances in a type of Artificial Intelligence called Reinforcement Learning.

How will you look to maximise the outputs of this work?

New knowledge will be disseminated primarily through publications in scientific journals and through presentation at scientific conferences. In addition, a relatively new trend is to share the data from scientific research with other scientists to a much greater extent than was done in the past. Data, including computer code, will be shared via websites such as github.com. This brings the potential for other researchers to obtain additional insight from the data and therefore for there to be increased benefit from the experiments.

Species and numbers of animals expected to be used

- Mice: 660

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

Explain why you are using these types of animals and your choice of life stages.

Mice are the best species for this project since their brain is structured in a way that is broadly similar to the brains of other mammals (including humans). They permit the use of the most advanced and refined available research methods, whilst also having relatively low species sensitivity. This project concerns how the mature brain functions and hence focusses on adult mice.

Typically, what will be done to an animal used in your project?

Some mice will be implanted with microelectrode devices using aseptic surgical procedures under anaesthesia. Brain activity will be measured in response to sensory stimulation (eg whisker touch) after which these mice be killed.

Other mice will typically be implanted with microelectrode devices using aseptic surgical procedures under anaesthesia. After recovery, using these devices, brain activity will be measured whilst the mice freely explore their environment. In some cases, under anaesthesia, mice will: be injected with plasmids (small pieces of DNA) under anaesthesia, have their whiskers partially clipped, undergo sensory stimulation (eg whisker touch), have brain activity measured in response to sensory stimulation (eg whisker touch) or have minor repair of implants. Once the measurements are complete, these mice will be killed.

What are the expected impacts and/or adverse effects for the animals during your project?

Possible adverse effects are: blood loss (avoided by choosing implantation sites away from major blood vessels); death under anaesthesia (controlled by monitoring of vital signs); post-operative pain (controlled by administration of analgesics and regular behavioural assessment); post-operative infection (controlled by aseptic surgical technique and treatment as advised by a vet).

Expected severity categories and the proportion of animals in each category, per species.

What are the expected severities and the proportion of animals in each category (per animal type)?

Expected severity is moderate.

What will happen to animals at the end of this project?

- Killed

Replacement

State what non-animal alternatives are available in this field, which alternatives you have considered and why they cannot be used for this purpose.

Why do you need to use animals to achieve the aim of your project?

The only way to address the aim of this project is to use animals. This is because the project requires the activity of neurons to be measured with cellular resolution in behaving animals.

Which non-animal alternatives did you consider for use in this project?

in silico modelling

Why were they not suitable?

We use in silico modelling in our research to derive hypotheses of how the brain operates, and such modelling informs the work in this project. However, the data we seek from the current project itself cannot be obtained from purely in silico modelling. This would require detailed knowledge of neuronal anatomy and cellular physiology that is far beyond the state of where neuroscience is today.

Reduction

Explain how the numbers of animals for this project were determined. Describe steps that have been taken to reduce animal numbers, and principles used to design studies. Describe practices that are used throughout the project to minimise numbers consistent with scientific objectives, if any. These may include e.g. pilot studies, computer modelling, sharing of tissue and reuse.

How have you estimated the numbers of animals you will use?

Animal numbers have been peer-reviewed in a successful application for research funding and also have been reviewed by a statistician.

The numbers here have been estimated statistically in order to be confident that sufficient neural data will be obtained to meet our definition of satisfactory data.

What steps did you take during the experimental design phase to reduce the number of animals being used in this project?

A useful refinement is possible by using the latest generation of high-density microelectrode arrays ("Neuropixels"). The current version of these devices consist of ~1000 recording sites and make it possible to record from 100s of neurons simultaneously from one animal. In this way, the number of animals required in order to obtain data from a given target number of neurons is substantially reduced compared to single microelectrode technology. New versions of Neuropixels are under development (but not yet publically available at the time of writing). Thus, we anticipate further reduction benefits to be achievable within the lifetime of this project

What measures, apart from good experimental design, will you use to optimise the number of animals you plan to use in your project?

Use of latest generation of microelectrode arrays, explained above.

Refinement

Give examples of the specific measures (e.g., increased monitoring, post-operative care, pain management, training of animals) to be taken, in relation to the procedures, to minimise welfare costs (harms) to the animals. Describe the mechanisms in place to take up emerging refinement techniques during the lifetime of the project.

Which animal models and methods will you use during this project? Explain why these models and methods cause the least pain, suffering, distress, or lasting harm to the animals.

Mice. To achieve the aim of the project requires measurement of neuronal activity at cellular resolution in freely moving animals. The way to achieve this that minimises pain/harm is to implant chronic microelectrodes into the brain using aseptic procedures and analgesic drugs, with careful monitoring for the possible adverse consequences, as detailed in the protocols.

Why can't you use animals that are less sentient?

Mice are the least sentient appropriate mammalian species that are established as a model organism.

Our questions concern how the fully developed brain functions; hence study of animals at immature life stage is not applicable.

Our questions concern the neural basis of behaviour - this cannot be studied under terminal anaesthesia.

How will you refine the procedures you're using to minimise the welfare costs (harms) for the animals?

An important refinement is that this project moves our research away from procedures requiring restraint and dietry control to increasing use of "free range" procedures where the animals can move freely, where their motivation is intrinsic, and where their dietry intake is ad libitum.

What published best practice guidance will you follow to ensure experiments are conducted in the most refined way?

We are using the most advanced microelectrode arrays (see above) and the most recent, refined, published methods for using them.

How will you stay informed about advances in the 3Rs, and implement these advances effectively, during the project?

Our institute is well-connected with UK 3Rs bodies and keeps scientists here up to date. In addition, the PI is well-integrated in the research community and is highly motivated to use the latest advances (see for example comments on Neuropixels technology above).