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NON-TECHNICAL SUMMARY

Development and function of neural circuits underlying perception and behaviour in the mammalian brain

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

neuroscience, neurons, neurophysiology, development

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

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?

Animal behaviour emerges as the product of coordinated activity of neurons with different patterns of gene expression, synaptic connections, and activity. The aim of this project is to link these levels of analysis and provide a mechanistic explanation for how the brain generates 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?

All the richness of animal behaviour is the product of input-output transformations carried out by individual neurons connected into intricate networks. These neurons come in hundreds of distinct cell types, generated during brain development through the activity of different combinations of genes. The rules according to which different cell types select their input and output connections forms the backbone of the neuronal networks of the brain. Yet we still do not know how these connections are established, and how the resulting networks of neurons give rise to patterns of activity underlying cognition and behaviour.

This project will advance our understanding of how different specialised classes of neurons act together to give rise to perception, memory, decision-making and other elements of high level brain function, and how the specialised properties of these neuronal populations are influenced by cell-type specific gene expression programmes. Although understanding how genes guide the specification of input and output connections of neurons is important in its own right, it will also provide key insights into how disruption of genes leads to circuit deficits underlying the symptoms of neuropsychiatric disorders linked to perturbation of neuronal connectivity, including autism and schizophrenia.

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

This project will advance our understanding of how networks of neurons within the brain process information to give rise to behaviour and how their connections are established during brain development. This knowledge will be disseminated through presentations at scientific conferences and peer-reviewed publications. In addition, any new techniques, reagents, or software tools generated as a part of this project will be made freely available to other researchers in the field.

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

Experiments in this project will help reveal how the organisation and function of animal brains enables perception, memory, decision-making and other aspects of cognition. This knowledge will be valuable for several reasons. The neocortex of different mammalian species follows similar principles in its organisation. Therefore, studying how the mouse cortex contributes to these high-level brain functions will advance our understanding of how they are carried out in the human brain.

This project will also investigate how the circuits that carry the computations responsible for cortical functions are established during development. Currently, there is a major gap in our understanding of how molecular mechanisms influence, which synaptic connections neurons make in cortical circuits, ultimately defining the computations carried out by them. It is proposed that many neurodevelopmental disorders, most prominently autism spectrum disorders, are “connectopathies” – consequences of disrupted neuronal connectivity. Experiments in this project will disrupt individual genes during cortical development to identify their role the establishment of neuronal connections. This knowledge will reveal the molecular programmes that orchestrate the development of healthy cortical connectivity and provide insight into how their perturbations give rise to neurodevelopmental disorders.

In addition, in pursuit of the goals above we will develop a new platform that will allow us to systematically examine the consequences of knock-out of many individual genes in parallel. This platform could be applied to other research questions and in other brain regions and so could serve to accelerate research seeking to identify potential targets for treatment of neuropsychiatric or neurodegenerative diseases.

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

Whenever possible, we will seek to maximise the utility of data and tools generated as a part of this project through collaboration with other experimental or theoretical groups, and online distribution of raw data and software tools. We will also make use of preprint platforms, such as bioRxiv, to rapidly disseminate our findings to a broad audience.

Species and numbers of animals expected to be used

- Mice: 17350

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.

The overall organization of the brain is similar across mammals. Therefore, insights gained through studying the structure and function of the mouse brain will help understand how the neural circuits within the human brain give rise to perception, memory, decision-making and other aspects of cognition. In addition, the availability of genetically altered mice makes it possible to measure and manipulate neural circuits with unprecedented precision. Most experiments will be conducted in adult mice. In experiments aiming to understand how the nervous system develops and require access to the fetal or neonatal nervous system, pregnant mice and their embryos or neonates will be used. In addition, mouse embryos or oocytes will be used when required for the development and maintenance of genetically altered mouse lines.

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

To provide access to the brain in experimental procedures in this project, animals will undergo surgeries under deep anaesthesia, during which devices for recording activity of nerve cells or delivery of substances into the brain may be implanted. All animals will receive pain relief and will be closely monitored during recovery. In most cases, animals will undergo one or two surgical procedures, with sufficient time between surgeries to allow for complete recovery.

In some experiments the animals may be head-fixed to allow recording of neural activity and/or reliable presentation of sensory stimuli. In these cases, mice will be habituated to head fixation and the experimental setup to minimise stress and discomfort.

In some experiments, to motivate animals to perform complex behavioural tasks, animals' access to food or water may be restricted, and food or water rewards will be provided during the experiments. In these cases, the animals’ weight and health status will be carefully monitored, and ad libitum food or water will be provided if any adverse effects are observed.

At the end of experiments or if mice show signs of unexpected ill health, distress or suffering which cannot be ameliorated with minimal veterinary or husbandry intervention they will be humanely killed.

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

Pain resulting from surgical procedures may reach moderate severity for short periods of time immediately following surgery. Animals will be closely monitored for signs of pain after surgery and appropriate analgesia will be provided.

Head fixation is expected to result in only mild stress during initial habituation to the experimental apparatus.

Animals under food or water restriction will typically maintain around 85%, but at least 80% of their normal body weight.

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)?

57% of mice are expected to experience mild severity, while 43% are expected to experience moderate severity.

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

- Killed
- Used in other projects

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?

We are still far from understanding how the circuits of neurons within the brain give rise to perception, memory, decision-making and other aspects of cognition, or how the disruption of these circuits leads to disease. Achieving this understanding requires measuring and manipulating neural circuits in ways that are not possible in humans. Instead, we will focus on mice, which are genetically tractable allowing highly precise measurements and manipulations of neural circuits and the development of disease models, and whose brains are organized according to similar principles to humans.

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

Computer simulations

In vitro brain organoids

Why were they not suitable?

Computer simulations of neural networks require precise knowledge of the structure of connections between nerve cells and their properties. We still lack sufficient data to reproduce using simulations the behaviour of even the simplest nervous systems, such as those of nematode worms, least of all of the much more complex mammalian brains.

In vitro brain organoids have the potential to recapitulate much of the cellular diversity of the nervous system. However, this project is focused on studying how neurons within the brain process information from the environment and contribute to behaviour, which is only possible in vivo.

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?

The numbers of animals are estimated based on our prior experience breeding genetically altered mouse lines and with experimental approaches used in the project.

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

Using our extensive experience with experimental techniques and statistical expertise, we will ensure that we use the minimal number of animals to achieve our scientific objectives. We will use state-of-the-art methods to measure neural activity of many brain areas or neurons in parallel and develop sophisticated data analyses approaches to extract the maximum amount of value from these results. Whenever possible, we will use within experiment comparisons to maximise statistical power and minimise the impact of external variables. Finally, as a part of this project we will seek to develop new methods that will allow us to measure or manipulate gene expression or neural activity in many populations of neurons in parallel in the same animal, greatly reducing the total number of animals.

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

Pilot studies will be used to test the efficiency and applicability of new tools and techniques before employing them broadly to pursue the scientific objectives of the project. Computer modeling will be broadly applied to refine experimental hypotheses. Whenever possible, post-mortem brain tissue will be re-used and shared. Raw experimental data will be stored and re-used for new analyses, whenever possible.

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.

This project will exclusively use mice. Surgical procedures will be conducted under deep anaesthesia following aseptic technique and mice will be carefully monitored following surgery to ensure complete and uneventful recovery.

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

While mammals, including mice, share the basic principles of brain organization with humans, the brains of other vertebrates and invertebrates are distinct. For example, the neocortex, which plays a key role in high level cognitive function, is present only in mammals. Carrying out experiments in this project solely in terminally anaesthetized animals is not feasible since studying perception and behaviour necessitates the use of awake animals.

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

Appropriate analgesia will be used during surgical procedures and mice will be closely monitored during recovery. In experiments involving head-fixation, mice will be gradually habituated to the experimental setup to minimise stress.

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

We will follow the guidelines set out in LASA Guiding Principles on Preparing for and Undertaking Aseptic Surgery.

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

We will strive to continuously improve our procedures with the help of the biological research facility staff, the Named Information Officer, Named Animal Care and Welfare Officers and the Named Veterinary Surgeons. We also consult the websites of NC3RS and RSPCA to keep up with the latest advance.