Home Office

NON-TECHNICAL SUMMARY

State-dependent neural processing

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

brain, neuron, hormones, pregnancy, state

Retrospective assessment

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

Objectives and benefits

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

What's the aim of this project?

The aim of this project is to understand how processes in the rest of the body influence information processing in the brain. Brain networks control instinctive behaviours such as parenting, feeding and aggression, but the animal's current (internal) state profoundly affects their function. Hungry animals for instance will be strongly attracted to food, whereas animals that have recently eaten typically ignore of even avoid food. We will (i) perform behavioural experiments to uncover which behaviours are affected by state changes such as pregnancy, (ii) determine which brain areas and neurons are affected by

these states, (iii) record and manipulate the activity of these identified neuronal populations and (iv) aim to identify the cellular mechanisms by which state changes can permanently remodel the brain.

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.

What are the potential benefits that will derive from this project?

The main benefit that will arise from this project is knowledge about how internal states affect the brain, and more generally about how the brain processes information. Internal states such as pregnancy, hunger, or aggression are highly similar between mice and humans, and so are the brain networks controlling many basic behaviours. Therefore, the results of this project will give fundamental insight into the function of the human brain. Gaining knowledge about how internal states and hormones affect the function of the healthy brain is essential for understanding what goes wrong in the diseased brain, such as in types of depression or –anxiety that frequently occur after giving birth. This project will also increase our knowledge of mouse animal behaviour, and in particular will identify states that can profoundly alter brain function and behaviour – this can be used to refine future animal experiments. Moreover, we will develop new tools (e.g. maps that visualise where hormones bind in the brain) that will be of interest to scientists across a broad range of neurobiology.

Species and numbers of animals expected to be used

What types and approximate numbers of animals will you use over the course of this project?

This work will use less than 7000 laboratory mice over 5 years. Mice are an ideal model for this programme, since their parental, aggressive and feeding behaviours are strongly affected by the animal’s current state, and because a large range of cutting-edge techniques are available for recording and manipulation neurons in the mouse brain.

Predicted harms

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

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?

In order to record from neuron networks in the brain, mice undergo surgery under deep anaesthesia to implant recording devices, fixed externally to their skull. They are cared for after surgery and receive pain relief until they recover completely and adapt to the devices; there are no pain receptors in the brain so complications may only arise if the device detaches from the skull, in which case it is repaired or the animal is killed. In a subset of experiments, the mice are then exposed to (social) situations in which a threatening stimulus can be present (e.g. an unfamiliar mouse intruding into their space) and the simultaneous activity in their brain is recorded. In some studies, the function of specific neurons may

knocked out by using chemicals (such as pharmacological drugs or by removing cells) in order to confirm which regions are responsible for certain behaviours. In some cases, the hormonal state of the animal might be altered surgically (e.g. ovariectomy) or chemically (e.g. stimulation with pregnancy hormones), which might lead to mild transient distress/pain. Mice will always be fully recovered before entering further experimental/behavioural studies. In all these studies, it is critical that the mice exhibit natural behaviours so it is essential that the surgical procedures do not, in themselves, cause adverse effects which interfere.
Repeated exposure to threatening stimuli may increase generalised anxiety but the recording sessions will be limited in duration and frequency to ensure no lasting harm. At the end of experiments, or if mice show signs of ill health, distress or suffering, they will be humanely killed. Brain tissue will be collected from animals post mortem in order to study the relationships between behaviour, neuron recordings and anatomy.
Since anatomical, recording and behavioural experiments will be performed from animal at different stages of gestation (as well as after gestation), we will carefully determine any adverse on the pregnant animal, as well as possible adverse effects on unborn or newborn pups.
In some behavioural experiments, pups (age typically P2-4) will be exposed to females of different reproductive stages (e.g. virgin female, lactating female). Although the vast majority (>95%) of females will either ignore the pups or be parental, a subset of animals might start showing aggressive behaviour, in which case the animals will be immediately separated. In the rare case that a pup should be wounded during such interactions, it will be immediately and humanely killed.

Replacement

State why you need to use animals and why you cannot use non-animal alternatives.

This project aims to understand how processes in an animal’s body influence information processing in the brain. This requires studying the intact brain in mice. It is therefore impossible to avoid the use of animals for addressing these questions, because other approaches such a neuronal cell cultures do not replicate the connectivity structure and of the brain, and preclude behavioural measurements. However, as the project – and thus our knowledge – advances, we will increasingly be able to use computer models as a replacement for subsets of experiments.

Reduction

Explain how you will assure the use of minimum numbers of animals.

We will use several state-of-the-art methods simultaneously, together with powerful data analyses, to get the maximal amount of data and information collected from each animal. In addition, the statistical power of each experiment will be increased by collecting functional, anatomical and cellular data from the same animal. Also, in most procedures the experiment and control can be performed in the same animal, which further increases statistical power and reduces the number of animals used.

Refinement

Explain the choice of species and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.

All experiments will be done in mice. To minimise harmful effects, we will use recording and stimulation techniques that are well established and with which we have expertise. All experiments in the brain will target specific areas so that effects on other areas and functions are minimal. Surgeries will be done under aseptic conditions with appropriate anaesthesia and pain management. Experiments in awake animals will only be performed if the animals are stress-free and experience no visible discomfort.