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NON-TECHNICAL SUMMARY

Synaptic organisation of neuronal circuits for perception and behaviour

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

Neurons, Synapse, Neuronal networks, Behaviour, Learning

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?

We aim to improve our understanding of the organization of the neuronal circuits in the brain that are responsible for representing sensory information. In particular, we wish to find out how nerve cells in sensory areas of the brain communicate in order to represent and integrate information from our different senses to guide behaviour, for example, during the selection of relevant targets. We also wish to find out how these representations are altered when visual or auditory perception improves as a result from learning.

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?

Improving our understanding of the neuronal basis for perception and behaviour is in the first instance a matter of considerable fundamental scientific interest. By generating fundamental new knowledge about the structure and function of specific brain areas we will not only advance our knowledge of brain mechanisms in health, but also help understand what may go wrong in neurological disorders which are currently poorly understood and represent a heavy burden in society. Indeed, the estimated annual cost to the UK of mental disorders is £100 billion. The difficulty in designing better treatments for neurological disorders has highlighted the urgent need to improve basic knowledge of neuronal circuits.
The data collected during this research program will also be used to build, refine and test biologically accurate models of brain circuits. A lasting benefit of this animal research will be to provide computer models that can be used by other scientists in their future research. Such models can generate new hypotheses through predictions and enable neuroscientists to a better understanding of complex neural systems.

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?

In order to gain understanding and test causality, complex systems need to be dismantled and probed invasively. These experiments can thus only be done in reduced model systems. Our system of choice is mice and we will use approximately ~6500 mice over 5 years in procedures other than simple breeding and maintenance. We may breed and/or maintain up to 5000 mice, some of which will be the same ones as in the additional procedures. Due to the statistical nature of genetics, around half of the animals bred under this protocol will not undergo other regulated procedures but will be reintroduced to the breeding stock or terminated humanely.

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?

Part of the project will involve the raising of genetically altered mice to allow us to study the functions of particular molecules in sensory processing. These animals are expected to be no different in the way they behave from wild-type controls. The behavioural testing procedures we will use to measure sensory abilities in head fixed or freely moving animals are painless. In some cases, it will be necessary to motivate the animals to perform these tasks by rationing their food or water during testing. This may result in temporary weight loss, but this will always be monitored carefully and extra food or water provided if this occurs. The ability of modern techniques to monitoring or altering neuronal activity in particular regions of the brain make it possible to carry out almost all of this work in a manner that should cause only temporary pain or discomfort to the animals under study. For example, surgical operations for implantation of ultrafine microelectrodes or for inserting genes into the brain will be carried out under general anaesthesia, in aseptic conditions, and with appropriate post-operative care. Adverse effects may occur, but the incidence is likely to be low and methods of control (e.g. analgesia) and the most refined experimental techniques will always be used to mitigate them. Chronic implants for recording neural activity or for delivering flashes of light for the purpose of altering that activity are small and light- weight and do not materially affect the animal’s quality of life. Animals will be killed humanely at the end of the experiment.

Replacement

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

Because this project investigates the neuronal circuit organization for multisensory integration and behaviour and how this changes during learning, it can only be carried out using *in vivo* approaches. Moreover, a key aim of this project is to try to account for changes in sensory perception at microscopic level in terms of the underlying circuitry. This requires the use of post-mortem histological measurements, which would not be ethical or practical to carry out in humans. Finally, computer modelling does form an important component of our work, but this relies on the information provided by the animal studies and cannot replace them.

Reduction

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

Calculations are carried out to determine the necessary number of animals for each experiment, ensuring significance of our results but also minimizing the number of animals used. We are additionally able to keep animal numbers to a minimum by using cutting edge methods that yield large amounts of data and experimental designs that allow multiple measurements to be made from each animal.

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.

We will use mice for this study because they are particularly suitable for cellular imaging studies and the availability of transgenic animals expressing genetically-encoded fluorescent proteins in particular neurons enables long-term imaging of their structure and function. Besides their neuronal circuit organization shares many similarities with that of humans. Previous research in rodents also provides a platform to build on. State-of-the-art recording and analytical methods will be used to interrogate neuronal function. We will constantly monitor international and local developments in refining surgical and experimental procedures.

The data obtained from these experiments will be used to refine computer models of the brain that will help guide subsequent experiments and contribute to a reduction in the number of animals needed.