Home Office

NON-TECHNICAL SUMMARY

Neural basis of spatial cognition and memory in the hippocampus

Project duration

5 years 0 months

Project purpose

- (a) Basic research
- (b) Translational or applied research with one of the following aims:
    - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants.
    - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants.

Key words

Hippocampus, space, memory, navigation

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 will determine how particular brain cells that act like an internal Global Positioning System [GPS] system connect and communicate with each other to allow us to navigate and to remember places. Importantly, we will study the relationship between the hippocampus (the area of the brain which acts as an internal GPS system and is crucial for remembering new events and navigating) and Alzheimer's disease, the most common type of dementia. Alzheimer's disease is associated with an ongoing decline of brain function which severely affects memory, thinking skills and other mental abilities. The hippocampus is one of the first areas affected by the disease.

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?

An understanding of how different parts of our GPS system communicate to create internal maps of the environment will provide fundamental insights into the relationship between mind and brain. The ability to artificially manipulate these brain GPS cells to remember and imagine previously unvisited places would be an important breakthrough in our attempt to build devices which would help to restore and maintain one's ability to remember places and events associated with these places. Finally, the brain GPS is one of the first areas impaired during Alzheimer's disease. Identifying what goes wrong and how this is reflected in our ability to navigate will help identify methods for early diagnosis and effective treatment.

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?

250 rats & 3000 mice, 2000 of which used for breeding.

Over 5 years

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?

We will measure and manipulate brain cell activity in navigating rats and mice in order to understand how different activity patterns enable an animal to perceive space, learn and remember environments and navigate to a goal location. Rodents will have tiny electrodes or optical lenses implanted and, in some cases, drugs injected into their brains or damage made to small areas of the brain. All surgical interventions are made under deep anaesthesia and animals are given painkillers before, during and after the surgery to minimise pain and discomfort. Mice usually show signs of full recovery within a few hours; to assess this we look at whether they are eating normally and displaying their usual behaviours (e.g. running on their toy wheels, building nests in their cages). It takes around 1 to 5 days for the rats to reach a comparable level of recovery, during which animals mostly rest and sleep. After recovery, animals will explore real and virtual environments. They will be freely foraging in differently sized and shaped enclosures looking for sweet rice, or will navigate to a reward location in different mazes and corridors. Some environments will be presented in virtual reality, using screens, projectors and other sensory stimuli. In these cases, an animal will have a small head post permanently fixed to its skull. It will be head-fixed via this post to stationary metal bars while it is running on a cylinder or an air-suspended ball in front of two screens displaying the virtual enclosures (or similar). Head fixation allows us to use light to measure and manipulate the activity of the specific identified brain cells, which is essential for studying memory-related processes. Before we carry out the actual experiment, the animals are given two to three days to get used to running on the ball to lower their stress levels. When animals are first head-fixed, they produce more urine/faeces, indicating that they dislike it; however, they stop responding this way several minutes after their first exposure to head fixation. Food rewards are then used to encourage navigation; the animals usually perform the task adequately after two to five days of experience. Once familiar with head-fixation, mice willingly explore virtual environments, similar to what they do on running wheels in their home cages. Behavioural experiments usually involve training the animals to seek sweetened food rewards (e.g. soya milk, sweet rice) and are carried out in such a way as to minimise harm to the animal by habituating the animal to the experimental room as well as to Experimenter. In order for the food reward experiments to be effective, animals have to be given a restricted amount of food during the experiment. The food restriction is always closely monitored and kept to a minimum. During the exploration experiments, we record the activity of brain cells in both the hippocampus and connected brain areas to determine how these cells interact and activate each other, and how this lets the animal navigate and perceive space. In some cases, these neurons are manipulated via lesion, drug, electrophysiological or optical methods to reveal what activates these cells and how. Also, in some cases, we use these methods to try and mimic the damage observed in hippocampus-related dementia such as Alzheimer’s disease.

Replacement

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

We inform our study design by describing brain activity using computers whenever possible. We use rats and mice because it is not possible to study the role of the hippocampus in real-world navigation without using behaving animals. Moreover, mice present one of the best animal models for studying the mechanism of Alzheimer’s disease. Namely, it is possible to genetically modify mice to express substances that we find produced in human brains with Alzheimer’s disease; this lets us investigate their effect on brain cells and an animal’s ability to use its GPS system and remember places.

Finally, we will share our data with other researchers to reduce the risk that experiments are repeated.

Reduction

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

We minimise the number of animals used in these experiments wherever possible. We used computer-based mathematical descriptions of brain activity to make specific predictions that require fewer animals to test. Furthermore, continual technical advances allow us to monitor more and more brain cells within each given animal, allowing us to use fewer animals overall. Almost all procedures involve long term experimentation with the same animals, which significantly reduces the number of animals needed to reach reliable conclusions.

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.

In these studies, we use rats and mice since they are very good at navigating in familiar environments and remembering what has happened to them there. We know a lot about the structure and basic working principles of their brains and, in particular, about the parts of the brain to be studied in this project.

Optimal results in behavioural experiments require that the animals are healthy, in good spirits, and motivated to perform well. For this reason, the majority of our behavioural tests involve positive reward rather than punishment, in order to encourage animals to navigate. Before animals are used in experiments, they will be acclimatised to their home cages as well as experimental environments, if this does not interfere with experimental design, e.g. when responses to novel environments are investigated.

We are also using the minimum level of food restriction required to make sure the animals perform adequately on each experimental task. Professional surgical procedures and pre- and post-surgical care including administration of pain relief drugs ensure a minimum of adverse effects and the minimum level of suffering caused by any surgical or other intervention.

All animals live in enriched environments with a lot of space and toys such as wooden balls, play tunnels and exercise wheels. Because both rats and mice are highly sociable animals, the animals are housed in groups in large home cages wherever possible.