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NON-TECHNICAL SUMMARY

Understanding visual processing in freely moving animals

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

Vision, Neuroscience, Movements, Behaviour, Vestibular System

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

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?

Human and other animals have the extraordinary ability of using vision to control balance, perform complex movements, manipulate objects and navigate their natural environments – we call this ability visual-motor integration. The aim of the project is to understand the cellular basis of visual-motor integration under natural conditions.

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?

Vision is one of our most valued senses and large parts of our brains are dedicated to interpreting the signals from our eyes to enable us to “see” and perform the actions required by our daily life. We have a good understanding of how nerve cells in the eye respond to light, but we know comparatively little about how these responses are combined with internal information about our own movements. Filling this gap is key to advance our understanding of how the brain controls behaviour – a fundamental question in neuroscience and psychology.

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

This project will advance our understanding on how the brain controls behaviour. These advances will be communicated to the scientific community via scientific publications in international open access journals. To engage with the general public our science will be presented in accessible format at science festivals. The new material produced (new source codes to analyse data, new set-ups and assays for studying animal behaviour) will be uploaded on public repositories for the wider scientific community and anyone interested in using it.

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

In the short term the international scientific community interested in vision and behaviour. Since we are developing new techniques to study vision and behaviour in freely moving animals, such techniques will also have the potential to reduce suffering and stress compared with traditional approaches in which animals are physically constrained (thereby advancing 3R's Refinement). In the longer term some of our discoveries could provide benefits to the wider community by finding translational applications for vision restoration and movement disorders.

The outcomes of this project will also provide better understanding of how the brain integrates information from visual and vestibular systems. This is particularly relevant for patients affected by vestibular disorders such as Meniere's Disease (MD) and Persistent Postural Perceptual Dizziness (PPPD). We know that MD and PPPD affect our ability to see and maintain steady balance, especially during eye and body movements, but it is unclear how such deficits in balance and visual perception arise. This poses a challenge in developing effective rehabilitation therapies. Our project, by providing an improved understanding of the cellular basis of visual-vestibular integration, will lead the way to developing more effective rehabilitation strategies.

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

Dissemination of knowledge will be maximised via scientific publications in international open access journals, talks at scientific conferences and public engagement activities. Data and software we develop for our project will be made freely available on public repositories to maximise uptake and data re-usage. Unsuccessful approaches will also be documented in publications and public repositories.

Species and numbers of animals expected to be used

- Mice: 931

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.

We are interested in how the visual system functions and how it controls behaviours.

Although non-mammalian vertebrates have retinas that are rather similar to those of humans, their visual and motor systems differ from our own in other key respects. Firstly, they have a wide variety of light sensitive cells outside of the eye. Secondly, the functional and anatomical organisation of their cortical regions, the brain regions that changed the most during mammalian evolution and that contain fundamental stations for integrating visual and behavioural information, is substantially different from mammals and humans. For these reasons, we have no other alternative but to work with mammals.

We use laboratory mice because we can build upon a wealth of existing information about the visual system in this species, and because we have access to animals carrying naturally occurring mutations or engineered genetic modifications that are very useful for our objectives.

We use adult animals since vision and behaviours develop at this life stage.

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

The most common experiment will consist in presenting an animal with visual stimuli and recording eye/head/body movements and changes in electrical activity in the brain. To do that animals need to previously undergo recovery surgery to implant brain recording electrodes and a small attachment piece to secure miniaturised cameras used for eye tracking.

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

Surgery will cause pain during the recovery period. This will be treated with pain killers, and we do not expect it to last for more than a few hours. There will also be transient stress associated with handling and with being placed in open behavioural arenas.

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)?

We are using mice for all protocols. Expected proportions of severities are:

Moderate: 47%

Mild: 32%

Non-recovery: 21%

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?

Vision and behaviours are emergent properties of the retina and the brain and, as such, can only be studied using humans or animals. We can measure movements in humans, but the range of techniques suitable for measuring and manipulating brain activity is far smaller in humans than laboratory animals. Thus, to access electrical brain activity from single and multiple nerve cells we can only use animals.

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

We have considered using computer simulations and experiments in humans to address our scientific purposes.

Why were they not suitable?

We are a long way from being able to recreate in-silico such complex systems as retina, multiple brain regions and body movements working together. Therefore, computer simulations cannot address our scientific objectives at this stage. Experiments in humans cannot provide invasive measurements of nerve cell activity that are required for our scientific objectives.

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 estimate is based on our yearly usage of animals in previous projects using a comparable approach.

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

Whenever possible we compare behavioural and neuronal responses to different experimental conditions (typically different visual stimuli) within each animal, thus removing inter-animal variability. Presentation of the experimental conditions is performed by using randomised block designs to further reduce the number of animals required for our statistical analyses. When performing new protocols small pilot experiments are used to optimise experimental conditions before running larger scale experiments. Whenever possible to exclude bias in the results, pilot data recorded under the same experimental conditions are included to further reduce animal numbers.

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

We use advanced 3D pose analysis - advanced methods developed in our group to obtain 3D reconstruction of animal head, body and eye positions. These methods provide automated and objective analysis of mouse behaviour, maximising the amount of information available from each experiment and avoiding the potential for observer bias in scoring behaviour. In the same spirit, we employ the highest throughput electrodes available that enable us to obtain high quality data from the largest number of nerve cells from individual animals.

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.

We use laboratory mice because we can build upon a wealth of existing information about the visual system in this species, and because we have access to animals carrying naturally occurring mutations or engineered genetic modifications that are very useful for our objectives.

We are interested in how vision controls behaviours. Whenever possible we will focus on innate behaviours (e.g. spontaneous exploration, threat avoidance). These do not require training that would typically involve water / food deprivation adding additional stress to the animals.

It is fundamental for our objectives to study awake behaving animals. Whenever possible we will rely on experiments in freely moving animals. Compared with awake head-fixed experiments, freely moving is a more natural approach, it is better tolerated by the animals and does not require additional experimental sessions to habituate the animal to head-fixation.

We will record brain activity by implanting brain electrodes. The size, weight and wiring of these implants will be optimised before implantation in awake animals to reduce burden to the animal.

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

We use laboratory mice because we can build upon a wealth of existing information about the visual system in this species, and because we have access to animals carrying naturally occurring mutations or engineered genetic modifications that are very useful for our objectives.

Rodent visual systems develop after birth, meaning that we cannot address our questions at a more immature life stage. The core aim of our project is to study the interactions between vision and behaviour - therefore these experiments can only be performed in awake behaving animals.

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

Surgery will cause transient pain however we will expect this not to last for more than few hours. Appropriate analgesics will be provided to the animal before and after the surgical procedure. During recovery from surgery animals will be monitored daily for signs of pain and distress. In the rare event in which animals will be found to approach humane endpoints (e.g. maximum weight loss, piloerection, eye/face expressions) they will be promptly and humanely killed according to best established practices.

We will use specialised cages to facilitate feeding and drinking in surgically operated mice. Animals will be gradually habituated to these new cages before the surgery to minimise post-surgical stress. We use advanced 3D pose analysis methods developed in the group to provide automated and objective analysis of mouse behaviour, maximising the amount of information available from each experiment and avoiding the potential for observer bias in scoring behaviour.

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

We consult protocols, training resources and guidelines on best practices in animal experiments available through the NC3Rs website (https://www.nc3rs.org.uk/3rs-resources) and will adhere to them whenever relevant. Topics covered include handling and restraint, euthanasia, humane endpoints, welfare assessment, anaesthesia, and analgesia.

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

We are actively engaged with NC3Rs events (www.ncrs3.org.uk). Having developed new refined methods for studying mouse behaviour over the last 5 years, we have regularly given talks to NC3Rs events. We keep ourselves updated with 3Rs innovations by regularly visiting the NC3Rs website and attending 3Rs related events. now receive regular 3Rs updates through the animal unit and our local 3Rs manager.