



Home Office

NON-TECHNICAL SUMMARY

Studying cognitive function in animal models of brain disorders

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
- (c) Development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feedstuffs or any other substances or products, with one of the following aims mentioned in paragraph (b)

Key words

Memory, Animal behaviour, Brain disorders, Schizophrenia, Negative symptoms

Animal types

Rats

Life stages

adult

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?

To identify and assess the effects of drugs and other treatment interventions (e.g. exercise and environmental enrichment) in preventing or rescuing memory and other behavioural deficits in validated rat models for symptoms of brain disorders.

To determine how pharmacological agents and non-pharmacological treatments work.

To develop new tests and new models for mimicking the symptoms of brain disorders.

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?

It is important to undertake this work to address the unmet clinical need of memory and behavioural dysfunction in a number of brain disorders. Currently there is no licensed medication for the treatment of memory problems and negative symptoms in schizophrenia. Also the medication available to treat the symptoms in other brain disorders do not work very well.

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

Scientific publications - developing new information around the causes of memory impairment and new targets for people working to develop better tests and treatments.

Testing new treatment plans in this project could lead to new medicines for clinical trials in people with brain disorders.

New tests and models for mimicking the symptoms of brain disorders.

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

The scientific community and general public, through furthering knowledge, and improving understanding. The pharmaceutical industry, and drug discovery groups, as we will assist in providing new knowledge around new treatment targets. We have close links with the pharmaceutical industry and will inform their drug discovery plans through these links and via publication of our findings. Patients, carers and the NHS as ultimately this work will lead to new improved medicines for patients.

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

We are committed to the publication of negative and positive results. We regularly present our findings at national and international conferences and publish in high ranking scientific journals. Further to this we have a strong background in public engagement, regularly presenting at SciBar events and taking part in events for the public. Some of the work carried out is in collaboration with the pharmaceutical industry and experts from academia. We routinely use tissue for other complementary studies (e.g. electrophysiological studies that utilise techniques to look at how brain regions talk to each other) and post-mortem analysis (looking at relevant brain markers) ensuring we are always developing our knowledge of the model and its relationship with human findings.

Species and numbers of animals expected to be used

- Rats: A maximum total of 9500

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.

Much is already known about brain anatomy and chemistry, memory and how the brain works to control complex behaviours in adult rats. We have many years of experience in studying complex behaviour in rats, all our current tests are validated for rats and our tissue analysis techniques and methods are validated using rats. Many of our tests e.g. for complex memory and mood are fully validated for adult rats and not for other rodents.

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

Rats may be given a drug treatment by injection, or an environmental treatment such as voluntary exercise in running wheels. This may be carried out before or after the administration of compounds that induce memory changes and changes to brain circuits, e.g., phencyclidine (PCP), a psychotomimetic drug that mimics some of the symptoms of schizophrenia in both rats and man, such as hyperactivity, issues with memory, decreased motivation and also not wanting to interact with others.

A small blood sample may be taken from the tail vein at specified times to measure drug levels and/or biomarkers.

Some rats may be mildly food deprived and trained in food motivated tasks, the effect of treatments as described above will be measured to determine their effects on cognition and other behaviours such as activity.

Alternatively, some groups of untreated rats will be assessed in tests of memory and behaviour using long delays between trials to measure forgetting, or task manipulation to make the task more difficult, resulting in an increased demand on the brain systems.

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

The administration of phencyclidine (PCP) and other drugs may produce mild short-term pain from the injection site and also cause mild short-lived changes in behaviour such as an increase/decrease in activity.

Behavioural techniques are generally not stressful and can, in certain cases, be considered as enrichment.

Some animals will be placed on mild food restriction during testing and lose up to 10% of their free feeding bodyweight.

Some rats will have blood samples taken which may cause mild short-term stress from restraint and pain from the needle insertion.

At the end of the study, or as part of the experimental procedure rats will be killed humanely.

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)?

The expected maximum severity for the three protocols in this license is moderate. Approximately 80% of the rats used will reach moderate severity and 20% will reach mild severity.

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

- Killed
- Kept alive

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?

It is not possible to measure the control of the brain on behaviour in cell systems. Much is already known about memory and how the brain controls complex behaviours in rats, so studies using live animals are essential to obtain a greater understanding of normal and abnormal states and to test the effectiveness of new treatments. Currently, this work must involve the use of whole animals as studying the effects on behaviour is a central feature of the project and as to date, there is no suitable alternative to using rodents for these types of studies.

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

Where possible we perform studies using in-vitro cell models to aid our understanding of how cells in the brain work.

We also undertake a number of studies using human post-mortem brain tissue to help work out similarities and differences with our animal studies.

However, studying behaviour and how memory, mood and social impairment is related to brain disorders is extremely complex and cannot be fully studied using in-vitro preparations or computational approaches.

This work therefore must require the use of animals as behaviour and testing new treatments is the most important part of the project.

We only test new compounds that have been carefully selected using in-vitro screens to ensure only the most promising drugs go into our animals.

Furthermore, we first conduct pilot studies with each new compound, starting at the lowest dose to check for any potential side effects prior to larger studies.

Why were they not suitable?

Currently there is no suitable alternative to the use of animals for behavioural research.

It is necessary to use animals to model the complex memory and social deficits seen in brain disorders such as schizophrenia.

In-vitro preparations or computational tests cannot be used as they lack the required complexity due to insufficient biological data.

We will carry out in-depth analysis on tissue samples from animals as we are searching for biological and behavioural changes induced by our model and treatments.

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?

We have 20 years' experience in developing and refining this model and behavioural tests so that the fewest numbers of animals are used. Estimations are based on the numbers of rats used in studies in previous years. In 2020 we increase the estimated number of rats used as study numbers had risen due to demand from pharmaceutical company clients.

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

We have taken advice from an external, approved statistical expert, who has assessed our power analysis calculations to ensure that we have minimum number of animals for the maximum statistical power.

We have lots of experience of analysis of these datasets from our previous work and in consultation with other external statistical experts and colleagues within the Pharmaceutical Industry and at this University. We have a member of the team who works with the NC3Rs Experimental Design Assistant to help us to design robust animal experiments.

Where appropriate we minimise the overall numbers of animals used by re-using the same animal in different behavioural tests, and where appropriate, testing more than one drug in the same animal. Numbers will be further reduced by using repeated measures designs where possible. Re-using the same animals is only carried out following veterinary examinations "fit to remain" immediately following a treatment/procedure and a second veterinary examination prior to re-use "fit to be re-used".

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

We will use the literature and pilot studies in small numbers of animals to guide us when setting up new behavioural tests, ensure animal stress is kept to a minimum, ensure animals are used to the testing arenas before studies begin and we also provide our researchers with excellent training.

We will monitor the reliability of our studies closely and upon generation of new data we can alter group sizes as appropriate and in consultation with statistical experts.

We are working closely with colleagues to develop behavioural tests that improve data yield to reduce animal numbers further by minimising the potential negative effect of animal handling in our studies.

We have a number of behavioural tests that require minimum training so where appropriate we minimise the overall numbers of animals used by re-using the same animal in different behavioural tests, and where appropriate testing more than one drug in the same animals.

We routinely collect blood and brain post-mortem tissue and share tissue from our animals with other research groups, which optimises the numbers of animals used and will maximise data output from every experiment.

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.**Animal Models.**

We use rats as we have detailed knowledge of their behaviour and brain organisation, which shows remarkable similarity to humans. Our rat models of human diseases show symptoms such as memory loss and subtle brain changes that are very similar to human patients. All our current tests are fully validated in rats and our tissue analysis systems are validated using rat brain.

We will use a sub-chronic (7 day) dosing schedule of psychotomimetics (e.g. phencyclidine) to produce long-lasting behavioural deficits in rats, which can only be seen when their memory and social behaviour is challenged, the effects are very specific to memory deficits with low impact to the welfare of the animals. We also use longer time-delays between experimental trials in some of our tests which allows the animals to naturally forget what they had previously learnt.

Methods and monitoring.

Welfare is very important for successful experiments and we continually aim to refine our techniques and practices. Our behavioural tests, which we often use to longitudinally assess our rats in a number of behavioural tasks, are not stressful to the animals, and could be considered as enrichment. We aim where possible to refine animal welfare for our laboratory rats.

In our recent experiments we started to investigate the use of playpens for cages of animals as a method of improving welfare in animals used in long term behavioural studies. These studies are ongoing and in collaboration with colleagues in academia. Making sure the playpen system works effectively could lead to a method that can be incorporated in to other animal facilities housing rodents and provide additional environmental and social enrichment.

We use a validated monitoring system to assess animals for adverse effects for any new treatment, which greatly reduces the number of animals that could experience a potential adverse effect. For animals that do receive a new treatment in this way, careful continual monitoring ensures termination is rapid if an endpoint is reached. This procedure ensures rapid decision making and actions that minimise any potential suffering to that animal. Before we test a new drug for a pharmaceutical company in one of our behavioural tasks, information is shared to prove that the compound has previously been checked for safety and the dose ranges we aim to use do not produce adverse side effects, thus ensuring that adverse effects in our studies are further minimised.

None of the models that we will use are expected to experience severe side effects; however, if seen in any animal it will be humanely killed.

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

An adult rat is superior for our studies compared to a less sentient species or a more immature life stage because the physiological systems involved in learning and memory have been so extensively studied and widely published in this adult animal.

We are unable to measure complex behaviour patterns in immature life stages, less sentient species or in a terminally anaesthetised animal. We have selected adult rats as their social structure enables detailed analysis of social behaviour. Furthermore, this work must entail the use of the whole animal as behaviour is a central feature of the project. If any relevant, non-animal alternatives become available during the course of this project, we will aim to implement them in our studies.

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

We have started to study the effects of time spent in playpens on rat behaviour with the aim of possibly introducing this to our experimental animals and highlighting the effects of this enrichment to other researchers and colleagues. We have also conducted a pilot study to assess the effects of playful handling of rats, which shares some similarities to the rat tickling technique, on behavioural outputs. Our ongoing studies are comparing the positive effects of exercise on memory in the form of voluntary wheel running in rats.

Refinements include habituating rats to new behavioural test arenas in home cage groups to reduce any potential stress when habituated singly.

Animals undergoing dosing procedures are removed from the main holding room into a separate room to prevent the induction of stress to stock animals and other experimental animals due to vocalisations.

In our longer-term studies such as reversal learning, rats are placed onto soft paper bedding instead of standard wood-based bedding to prevent the risk of developing hock sores.

Further refinements include reducing the maximum total number of injections of pharmacological compounds from 28 to 21 days and also reduced the frequency of injections over the 21 day period to once per day instead of twice per day (after day 7).

Recently we employed an expert in rodent handling and procedures to provide a training/refresher course in animal restraint and oral gavage dosing for our research technicians. This expert training ensures improved handling, reduced restraint and improved dosing techniques resulting in reduced stress to the animals and improved animal welfare.

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

We consult with other leaders in the field of behavioural research to implement any improvements in animal welfare and care. We have access to the extensive library of NC3Rs resources which includes guidelines, practical information, links to themed hubs and publications, other online resources, and video training materials. We routinely attend appropriate events organised by the NC3Rs and our local animal facility. We follow the PREPARE (Planning Research and Experimental Procedures on Animals: Recommendations for Excellence) and the ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments) for guidance on how to plan and report animal experiments.

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

We attend, and encourage other members of the team to register for the regular 3Rs symposiums and webinars organised by the NC3Rs. We have taken advice from our local NC3Rs manager, on implementing environmental enrichment using play pens and we are currently collaborating with researchers at others Universities, with the aim to apply for an NC3Rs project grant to study the effects of play pen enrichment on rat welfare and behaviour.