



Home Office

NON-TECHNICAL SUMMARY

Neurobehavioural Mechanisms of Mental Health

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.

Key words

mental health, psychiatric disorders, cognition, behaviour

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?

Our research aims to understand how and why mental health disorders occur, and to develop new treatments for people suffering from these disorders. Our work focuses on the psychological processes (e.g. attention, memory, compulsion) that are dysfunctional in a number of different mental health disorders, meaning that our work goes beyond individual disorders (i.e. it is “transdiagnostic”). Some aspects of our work, however, have greatest relevance to specific mental health disorders, including drug addiction, obsessive-compulsive disorder, schizophrenia and post-traumatic stress disorder. We use animal models that allow us to investigate dysfunctional psychological processing – developing new models if necessary – to understand the causes and consequences of mental health disorders in the brain. Building on our previous work, our research aims to identify new drug targets and new forms of behavioural therapy that could treat mental health disorders. Some of our previous work is now beginning to be translated to humans.

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?

Mental health problems cost the UK an estimated £105 billion per year, with 50% of these costs reflecting decreased quality of life for those affected. Thus, mental health disorders place a considerable burden on not only the affected individual, but also social and economic burdens on society. The case for new treatments is strong, as currently available therapies are not effective for all patients; for example, only 50% of those with post-traumatic stress disorder show a reduction in fear with cue exposure therapy. Our research aims to understand the bases of these disorders, and develop new treatments for them. We aim to develop new rodent models for mental health disorders that give us a better understanding into why certain behavioural or drug therapies work, to investigate why certain subpopulations are vulnerable to mental health disorders, and why they respond differently to treatment. We also aim to use these models to develop new and better treatments for mental health disorders.

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?

We use the minimum numbers of animals possible to achieve biologically and statistically meaningful data. We anticipate that we will use approximately 8700 rats in 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?

The specific research questions that each experiment aims to address will determine the types of procedures that are experienced by the animals. Many of our research questions can be addressed by testing animals' memory and decision-making in sophisticated behavioural tasks rewarded with palatable food. Where we are attempting to modulate the psychological processes we are studying, we may give injections of specific types of drugs that affect activity in the brain; sometimes, we will give multiple injections, either with different doses of the same drug, or with drugs having different effects on the same chemical system (e.g. increasing or decreasing activity in that system). We only give multiple injections to the same animal where we need to be able to compare an individual animal's behaviour across these different conditions.

Some of our research questions investigate the parts of the brain that are involved in these psychological processes. We target the parts of the brain that constitute its motivational circuitry. For these experiments, we have to manipulate the brain directly by intracranial surgery (by e.g. surgically damaging specific parts or implanting recording devices). For our research into drug addiction, we have to implant the animals with intravenous catheters so that they can later self-administer drugs of abuse. This is critical for our experiments, as our addiction research studies the psychological processes that allows drug use to become compulsive (rather than dependence, which could be induced by experimenter-delivered injections of drugs). We need animals to be able to initiate their drug use in order to address our scientific questions, and to produce translational models that will be of maximum benefit to addicted patients. Whenever our animals undergo surgical procedures, they receive appropriate anaesthetics and painkillers around the time of the operation, and are very carefully monitored at the time of surgery and throughout the experiments for any signs of pain or distress. If the animals show signs of suffering and we are not able to reduce these in consultation with the Named Veterinary Surgeon, then we humanely kill the animal. Fortunately, such instances are very rare.

Some aspects of our research address disorders in which aversive learning plays a major role (e.g. phobia, or post-traumatic stress disorder). These disorders can only be studied by exposing animals to inescapable (uncontrollable) stressors, and in our experiments we use mild electric shocks as the aversive outcome. Many of our animals experience no more than three mild inescapable electric shocks in their lifetimes, and this is sufficient to allow us to study the psychological processes that underlie learning about stressful events. Electric shock is the most useful aversive outcome for our scientific purposes, because it allows us to precisely control the timing of cues predictive of an aversive outcome and the outcome itself (unlike more general stressors, such as exposure to the scent of predators) and because it engages the same brain circuitry as the mental health disorders that we are studying (unlike, for example, air puffs to the eye, which engages reflexive circuitry with has little relevance to our scientific questions). Animals that experience these inescapable stress conditions do not show changes in behaviour outside the environment in which the shock is delivered (e.g. changes in body weight or interaction with other animals).

For some of our research addressing post-traumatic stress disorder, the animals are required to experience stronger stressors, and in these experiments they are exposed to up to 15 mild inescapable (uncontrollable) electric shocks in a single training session, which models uncontrollable trauma. This procedure leads to changes in the brains of animals that are relevant to post-traumatic stress disorder, and are necessary for us to understand changes in psychological processing that are relevant to the development of the disorder, and to developing new treatments. This procedure is also not effective for all animals (approximately 13% do not show changes in behaviour or brain changes), which allows us to study this 'resilient' population with the hope of identifying why they are effectively protected against

post-traumatic stress disorder following stressful conditions. This is a well-established model of post-traumatic stress disorder and represents a refinement over some other models, but we will investigate further refinements to this procedure in parallel with our behavioural studies.

Animals may experience more than one of these broad types of procedure in the course of an experiment, depending on the specific question that the research is addressing. Where we are specifically investigating vulnerability to mental health disorders, animals may undergo early life stressors (e.g. repeated separation of pups from their mother, or older animals from other animals) in addition to the procedures listed above. For questions relating to comorbidity (having more than one) of mental health disorders (e.g. between post-traumatic stress and addiction, for which comorbidity is estimated to be as high as 60% of patients) animals may undergo the more stressful aversive conditioning and later be implanted with intravenous catheters (implants allowing us to link a sterile injection line to the animal's jugular vein) so that they can self-administer drugs of abuse. Thus, although animals may experience more than one type of procedure, for each animal we perform the minimum number of procedures that will allow us to address the specific scientific question we are investigating with that experiment.

At the end of experiments, all animals are humanely killed, and wherever possible and appropriate we collect brain tissue for further analysis of the tissue using molecular biological techniques.

Replacement

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

This research is only possible with the use of animals. Human studies (e.g. brain imaging studies) are useful, but can only show that changes in brain region activity correlate with mental health disorders, not that they cause them. Furthermore, it is not ethically possible to study the genetic and/or environmental factors that underlie predisposition to, and the development of, neuropsychiatric disorders in humans. Similarly, it would not be possible to develop new treatments for brain disorders without testing them in animal models first. In vitro models (e.g. brain slice preparations) or computer simulations cannot be used because the modelling of behaviour in these systems is not yet sufficiently advanced.

Reduction

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

We are fully committed to using the minimum number of animals required to obtain data that are statistically and biologically meaningful. We carefully design our experiments to maximise the behavioural data collected from each animal, and to minimise distress. We take replicability of our data very seriously, and routinely calculate effect sizes from pilot studies or previous literature to determine the minimum number of animals required for reliable data. We randomly allocate rats to experimental groups wherever possible, though sometimes rats are 'pseudorandomly' allocated (e.g. if we testing the effects of a particular treatment on a specific behaviour, rats are assigned to groups to ensure that their

pre-treatment behaviour is the same). We also make use of automated software to collect behavioural data wherever possible, and where this is not the case (e.g. when behaviour has to be quantified by a person) we take great care to ensure that the person scoring is unaware of the experimental group allocations. We design our statistical analyses of the data in advance, and have extensive experience of this; additionally, when we are designing new studies that might require new analysis methods, we can refer to experts within our establishment to advise on this.

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 use rats because they are the least sentient (able to perceive and feel things) species that can model neuropsychiatric disorders. The brain circuitry implicated in many mental health disorders is very similar between rodents and humans, and the behavioural tasks that we use are widely recognised as modelling specific aspects of these disorders. (Some of these tasks can be used in both humans and animals.) As stated above, one aspect of our work involves developing animal models of mental health disorders, and this includes refinement work where necessary. We continuously monitor developments in the scientific literature for refined techniques and adapt our methods to incorporate these where possible. For example, in our amendment of June 2020 we added the technique of fibre photometry to the licence. This technique allows us to collect and measure the activity of individual brain cells in real-time, giving us more data from a single animal and so allowing us to reduce the numbers of animals we use.

We also check that our experimental techniques are working as they should in unconscious animals where necessary and possible. We take the welfare of the animals very seriously. Most of our animals are trained to perform sophisticated behavioural tasks, and any type of illness or pain would compromise their behaviour. Thus, we have scientific as well as ethical reasons to ensure high standards of welfare. When an experiment requires that animals undergo surgery, we conduct surgery to surgically sterile standards and provide pain relief during and after surgery. Animals are monitored frequently (often undergoing daily testing) and any adverse effects are observed by scientific and animal care staff, recorded and discussed with the Named Veterinary Surgeon. If these cannot be quickly reduced then animals are humanely killed to prevent suffering. We have extensive experience of working with rats and we are well-trained in the clinical signs that mean an animal is unwell. If any animals show any signs consistent with brain damage following surgery, they are immediately killed to avoid suffering. If animals show other clinical signs such as subdued behaviour, piloerection or hunching, they are monitored closely and the Named Veterinary Surgeon will be consulted. If no improvement was shown within 24 hours, then the animal would be humanely killed.