

Roger Lemon outlines the many benefits and also the controls in place to protect monkeys used in research

overnment figures show that each year around 2,500 monkeys are used in biomedical research and testing in the UK. The number of monkeys used is relatively small compared with numbers of rodents and other experimental animals: over 1.9 million animals were used in experimental procedures during 2016, the great majority being rats and mice.

Of the primates that were used in research, over 80% (mostly marmosets and macaques) were involved in safety testing of new drugs and vaccines. There is a legal requirement for these to be tested in animals before they can be used in human patients, and in some cases the monkey is the best model for these tests.

The remaining monkeys (about 20%) were used in either basic research, which yields fundamental biological knowledge, or in applied research, which helps to understand and develop treatments for disease. UK legislation that regulates experiments using animals states that monkeys can only be used when it is essential to carry out the tests or procedures on a primate, and when the research question cannot be addressed using a 'lower' species, such as a rat, mouse or fish.

Bearing these restrictions in mind, the main basic and applied research areas in which monkeys are used are:

- research into infectious diseases such as Ebola, Zika, HIV and tuberculosis
- neuroscience.

Neuroscience research with monkeys

Monkeys are used in neuroscience research, including psychological research, because they exhibit a number of complex behaviours

that are unique to primates, including humans. Examples of such behaviours are in advanced cognitive processes (such as memory, learning and decision making), in sophisticated visual perception and recognition, and also in research on skilled hand movements for tool manufacture and use. Understanding these complex behaviours, and their underlying brain processes, is crucial to meeting the growing challenge of long-term neurological conditions that underlie a wide variety of mental health and neuropsychiatric disorders.

Mirror neurons discovered in monkeys

One topical example is that of the 'mirror neuron system'. Mirror neurons were discovered through work with macaque monkeys in the 1990s. It was found that certain neurons

Signposts



neuroscience, mirror neurons, dopamine reward system, gambling addiction, plasticity, ethics, 3Rs MONKEYS EXHIBIT A NUMBER OF COMPLEX BEHAVIOURS THAT ARE UNIQUE TO PRIMATES, INCLUDING HUMANS

responded when the monkey's own grasping movements matched a similar grasping movement being performed by a human. These neurons are thought to comprise a rapid system for identifying the nature and purpose of actions carried out by others, using one's own actions as a reference. More broadly, these 'mirror neurons' have been suggested as playing a role in 'social neuroscience' — the brain mechanism underlying our capacity to identify the actions, feelings and thoughts of others. Such a system may play a role in many of our social interactions.

So monkey research opened up a new line of thinking about social neuroscience. The experiments in which these exciting neurons were first discovered entailed direct recording of neurons in the cortex of awake behaving monkeys. Although there is accumulating evidence for a similar set of mirror neurons in humans, it is unlikely that they would have been discovered in humans. Such recordings cannot be carried out in humans (the procedure is invasive), although some are now being performed in clinical patients as part of their treatment.

Understanding dopamine and reward

Another recent example of neuroscience research involving animals concerns the role of dopamine in reward. In 2017, three scientists working the UK — Wolfram Schultz, Peter Dayan and Ray Dolan — were awarded the Brain Prize for discoveries resulting from the observation that a particular group of brain cells release the neurotransmitter dopamine when a monkey makes a decision that yields a reward. This system is particularly good at rewarding actions that give rise to unexpected rewards — an important learning and survival mechanism.

Further insights were reached by combining the recordings in monkeys with computational modelling of the decision-reward system in humans. The research also helped to explain how this system can go wildly wrong, such as in excess gambling.

Why does understanding these brain mechanisms matter?

As we have seen, primate research increases our knowledge about how the brain works

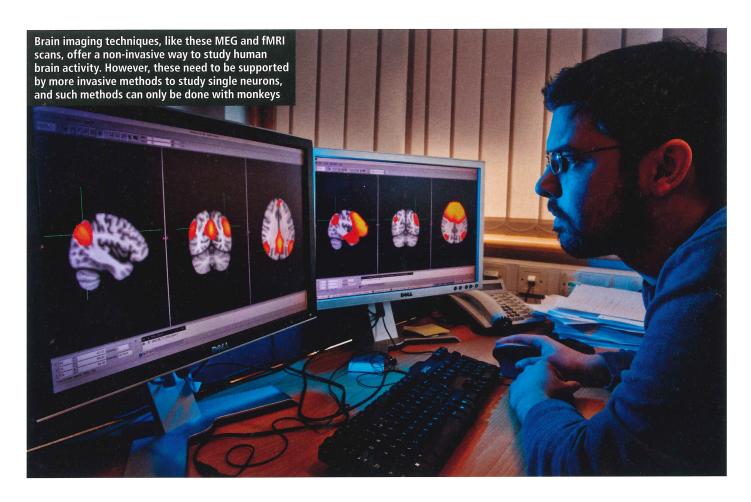
and is particularly relevant for understanding the human brain. Achieving fundamental knowledge has always been a central objective of scientific research. But it goes much further than this.

Treating Parkinson's disease

Parkinson's disease is a degenerative disorder of the nervous system that severely affects motor coordination. There have been recent advances in treatment using deep brain stimulation of a structure called the *subthalamic nucleus*. Electrodes are surgically implanted in this structure and a stimulator delivers small electric currents through these electrodes, with the stimulation adjusted to overcome the motor symptoms of Parkinson's.

This treatment is based on experiments in monkeys carried out in the UK and USA in the early 1990s. There was then a rapid translation into the clinic, with the first Parkinson's patients being treated in 1993. Over 200,000 patients have benefitted from this treatment. (See the article on Parkinson's disease and deep brain stimulation in PSYCHOLOGY REVIEW Vol. 20, No. 2.)





Recovery from stroke

Again in the early 1990s, other research in monkeys demonstrated that after a stroke, intensive physiotherapy could radically alter the motor circuits in the brain. The effects of this 'plasticity' in motor function were further shown to have a beneficial impact on the degree of recovery of arm and hand movement in stroke patients. This plasticity is still being routinely exploited by physiotherapists and neurologists today, since recovery of hand movements is crucial for the quality of life for stroke patients, allowing them to feed and clean themselves, for example.

Brain-machine interfaces

Another area of research that has attracted a great deal of attention is the development of 'brain-machine interfaces'. These devices are becomingly increasingly important for returning voluntary movement and even sensation to patients permanently paralysed by disorders such as spinal injury or motor neurone disease.

The approach uses activity recorded from the patient's brain while they 'imagine' making the required movement. This activity is then processed by a computer and used to control a robot or a cursor on a computer screen, allowing the patient to communicate and to control movements again. Importantly, the techniques that are now being used to record activity from the human brain were all developed in the monkey.

Could brain imaging in humans be used instead?

Could monkey neuroscience be replaced by brain imaging in human volunteers? Non-invasive approaches to human brain function, such as brain imaging, have made major advances over the past two decades. These methods, which can be used to monitor the gross activity in different brain networks, have helped to define which networks are active during complex behaviours.

However, to understand the neuronal mechanisms that operate within these networks it is necessary to complement these human studies with invasive methods to record the activity of single neurons. Psychological and neuroscience research in monkeys involves training monkeys to perform complex motor and cognitive tasks and then monitoring the spikes of single neurons during task performance. Complex

behaviours involve activity in many thousands of individual neurons in distributed networks in the brain and spinal cord.

These invasive recordings have allowed us to improve the accuracy with which the brain imaging results can be interpreted, and to provide the essential link between measures of activity in single cells versus networks. As pointed out above, these recordings cannot be used in humans, and that is why animal models are essential. Importantly, both monkey *and* human research are needed to ensure progress.

Could non-primates be used instead of monkeys?

Many advanced behaviours are shared by monkeys and humans, but are not found in rodents and other non-primate species. Similarly, there are brain regions and pathways which are far better developed in humans and monkeys than in other animals. For example, the prefrontal cortex constitutes a large part of the primate cortex, and is known to be important for decision-making, working memory and the planning of actions. By contrast, it is a relatively minor structure in the rodent brain.

MONKEY RESEARCH ADHERES TO PRINCIPLES OF THE '3RS' (REDUCTION, REFINEMENT AND REPLACEMENT)

Another example is provided by the areas of the visual cortex related to colour and three-dimensional vision that are only found in primates. In addition, those motor pathways considered to be critical for manual skill are found only in dexterous primates, including humans, but are not present in rodents.

Welfare of monkeys used in research

Because monkeys are highly sentient and valuable animals, any research involving them carries serious ethical and welfare concerns. The general public is rightly concerned about the ongoing debate about the continued need to use monkeys in biomedical research. To regulate that research the UK has some of the most stringent animal protection laws in the world.

These laws govern the circumstances in which monkeys may be used in research: only monkeys specifically bred for research

may be used, and there has been a long-term ban on wild-caught primates and use of great apes. The laws also set down the conditions under which monkeys are housed and how scientific procedures are carried out. Primates can only be used when absolutely necessary.

The regulations seek to ensure that the benefits of the research outweigh any harm experienced by the animals during the research, and that harm is kept to the absolute minimum. For example, monkeys are very social animals and research establishments are now required to provide social housing (pairs or groups of monkeys housed together) for all captive monkeys.

The '3Rs'

There is a considerable effort to ensure that monkey research adheres to principles of the '3Rs' (Reduction, Refinement and Replacement). Researchers therefore aim to find new models that can either reduce the number of monkeys used, or replace their use altogether, or at least to ameliorate the effects of the research procedures on the physical and mental wellbeing of the monkeys needed for research. The UK has a National Centre for the 3Rs (www.nc3rs.org.uk) and research establishments are required to follow their guidelines on primate accommodation, care

and use. Another key area is training staff for care of monkeys used in research.

All establishments that use monkeys in research have signed a 'Concordat on Openness' (concordatopenness.org.uk) to make it easier for the public to find out what sort of research they do and under what conditions. Some institutions, such as Oxford University, offer a 'virtual tour' of their monkey facilities.

To finish...

Biomedical research involving monkeys remains important for understanding the complex brain and behaviour of primates, including ourselves. Research in monkeys complements many other approaches, including computational modelling, and non-invasive methods in human volunteers and patients. It remains a vital part of the research effort. It will certainly help to unravel more mysteries of psychology and neuroscience in the future.

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challenge yourself

1 Roger Lemon states the case for the use of monkeys in neuroscience, including 80% for testing new drugs and vaccines and the rest for basic or applied research (for example, developing new treatments for human diseases). In addition, UK law states that there is a legal requirement for certain drugs to be first tested in animals before their use with human patients. Why do you think that the majority (i.e. 80%) of this research is for testing new drugs as opposed to developing new treatments? Can you suggest some practical and ethical issues in using monkeys that also need to be considered here but are not covered in the article?

2 The author goes on to describe the close relationship between humans and other primates in terms of their complex behaviours (for example, memory, learning, decision making). This helps us to better

Complete these activities to check and extend your understanding of the use of monkeys in neuroscience research

understand long-term neurological conditions in humans. Can you list two or three of these conditions and briefly describe how these impairments affect individuals with these conditions?

3 Mirror neurons are the neurons activated in response to observing another's behaviour. Research has looked at the brains of macaque monkeys. To what extent can we extrapolate the findings of these mirror neurons to understanding *human* social interaction and perspective-taking (for example, Theory of Mind)? Justify your answer with an example(s).

Researching with monkeys has also helped researchers treat Parkinson's disease, assist recovery from stroke and even use brain imagination techniques (for example, mind techniques to bypass paralysed regions of the body) to help return voluntary movement to previously paralysed people. What further innovations might you predict for the next two decades in psychology?

S Visit the 'Concordat on Openness' website at concordantopenness. org.uk to see what research is currently undertaken (and what is not) with monkeys. Take the virtual tour of monkey facilities at Oxford University via the same site. Why do



you think such openness and transparency is important in this area (for example, social sensitivity of research, ethical issues, animal research versus animal experimentation etc.)?

Anthony Curtis