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HUMAN HEALTH
Published: 11 October 2022
doi: 10.3389/frym.2022.953662

REDUCING THE NUMBER OF RESEARCH ANIMALS: HOW IMAGING TECHNOLOGIES CAN HELP

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Even when no other alternatives are available for scientific experiments, the use of research animals is still a difficult decision. To promote more ethical animal research, scientists must follow the 3Rs principle. Reduction is one of the 3Rs—it involves keeping the number of animals used to a minimum, by obtaining information from fewer animals or obtaining more information from the same number of animals. Imaging technologies allow scientists to see inside of the bodies of live animals without harming them, so that the animals do not need to be killed for scientists to study their organs. Using imaging techniques, scientists can study illness and responses to treatments. Animals can be imaged multiple times in long-term studies, so imaging techniques protect animal welfare by reducing the number of animals used in research.

Thanks to the endeavors of the Swiss 3RCC, these articles have been translated into the three main Swiss languages of German, French, and Italian.

RESEARCH IS NECESSARY

Our world continues to be challenged by devastating diseases, as illustrated only too well by the health emergencies brought on by the Covid-19 pandemic. Understanding how the bodies of humans and animals work is very important, because it helps scientists discover new treatments for animal and human diseases. The use of animals in research has been vital in supporting major medical breakthroughs, such as the discovery of vaccines and antibiotics that can prevent and treat dangerous infections. Research animals have also advanced our understanding of genetics and our knowledge of how the body's cells regenerate [1][1].

[1] https://www.animalresearch.info/en/medical-advances/medical-discovery-timeline/

3RS

Scientific principles that replace, reduce, and refine the use of animal in scientific experiments, to ensure humane and caring animal research.

However, animals are living, feeling beings that can suffer pain and distress, so using them for research is a difficult decision and must always be completely necessary and ethically justifiable. Most national and international laws protect the care and welfare of research animals, both for the wellbeing of the animals and as a way to support the highest-quality science. More than 60 years ago, two English biologists, Russel and Burch, set up the **3Rs principle** for performing humane animal research [2]. The 3Rs principle includes replacement of animals by alternative methods when possible, reduction of the number of animals used in research studies, and refinement of experimental methods and housing conditions to minimize the suffering of laboratory animals.

WHY DO WE STILL USE ANIMALS IN RESEARCH?

Despite great progress in the use of non-animal alternatives (for example using human samples or computer models), there are circumstances when animal studies are unavoidable—such as when studying a disease or testing a new medicine. Testing new drugs on humans is not ethically possible and, so far, there are no alternatives to animals that can replicate the complex, interacting parts of a living body (for example the effects of the heart beating and blood circulating under the control of the brain). Researchers have a legal and ethical responsibility to ensure that the treatments they are studying are safe to be used in humans or in the animals those treatments are designed for. There is still an urgent need for better medicines and vaccines to treat life-threatening conditions like cancer, brain disorders, or pandemics like Covid-19.

Mice are the most-used animals in research. Although much smaller than humans, mice have very similar body functions and share 95% of their genes with humans. This means that the way a mouse body functions and responds to medicines is often very similar to what is seen in humans, so using mice in research can be a very informative way for scientists to understand a disease and how it might respond to treatment. More recently, scientists are increasingly using fish, flies,

or worms to study body functions and new drug treatments, but the anatomy and the body-function differences between these animals and humans can be much greater, so there are limits to what these experiments can tell us.

LET US TALK ABOUT THE 3RS: WHY REDUCTION IS NEEDED

The 3Rs guide all research that uses animals, promoting the best animal care to support the highest-quality science. As scientists become better at understanding human diseases by looking at patients and working with alternative tests, these approaches will help to replace the use of animals in research. But in other cases, possibly during the final stages of testing the safety of new medicines in complex diseases like cancer or brain disorders, scientists may still need to use animals. When doing studies that require the use of animals, scientists must follow the reduction and refinement principles, to reduce the number of animals used and to ensure that they avoid or at least minimize any harm to the animals.

REDUCTION

One of the 3Rs principles that promotes the use of the smallest number of animals possible, while still obtaining valuable research information.

Reduction aims to use the smallest number of animals possible, by obtaining information from fewer animals or by obtaining a greater amount of information from the same number of animals. When planning a research study to test a new medicine, scientists should plan how many animals will be needed. This number includes those animals that will be used to test the new medicine and a group of animals that will experience the same living conditions but do not receive the medicine, called the control group. Scientists must also think about how many times the animals must be tested or investigated. For example, animals may receive a medicine that changes their heart function, so a scientist might need to check the animals' heart rates every so many hours, days, or weeks, to study the medicine's effects. But the scientist might also need to examine the heart directly, which can only be done after the animal is humanely killed. This means that, if the scientist wants to study animals at multiple time points, many animals would need to be killed. To avoid killing the animals, it would be ideal to be able to visualize internal tissues and organs in a living animal, without causing it harm. Visualizing the internal structures of a living animal would allow scientists to study how the animal's tissues are affected during a disease and whether any tissue damage improves with new medicines. **Imaging technologies** is a technique that allows scientists to do precisely this—to look inside an animal's body while it is alive, without causing it any harm, to study the animal's organs and functions (Figure 1).

IMAGING TECHNOLOGIES

Creating pictures of the inside of a living body for analysis. These include techniques such as X-rays and ultrasound.

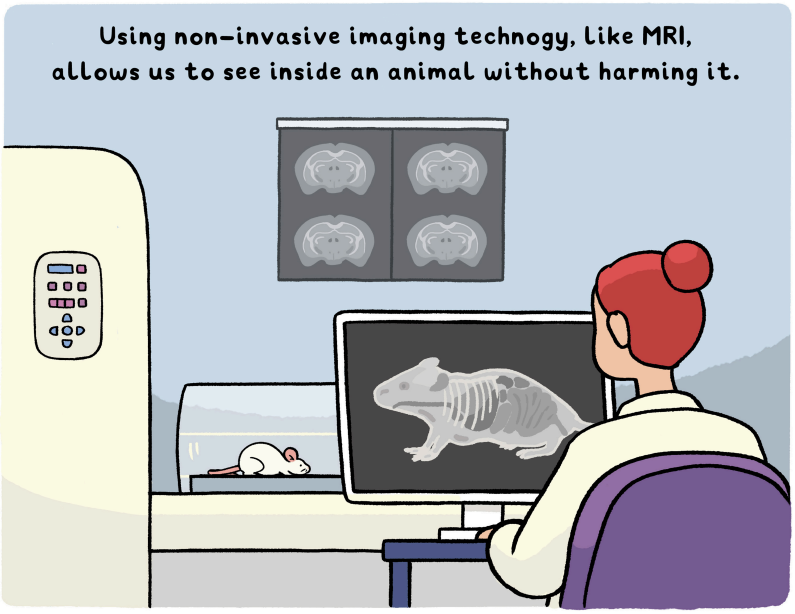

Figure 1

During imaging, the animal is anesthetized so that it does not move and does not feel distress. Imaging technologies help us to look directly inside an animal's body—at its skeleton or internal organs like the heart—without causing any harm. Once the animal has been imaged, it is monitored closely while it recovers from the anesthesia, and then it is transferred back to its housing with the other animals. Most imaging sessions take 15–30 min and animals recover well after a short anesthesia.

IMAGING TO REDUCE USE OF LABORATORY ANIMALS

Non-harmful imaging technologies, such x-rays or ultrasound, allow scientists to visualize the skeletons of live animals, to see their hearts beating, or to observe their brain function. Thus, imaging technologies help scientists to study how animals' bodies are affected by illnesses and how they respond to treatments in real time, without the need to harm or kill them [3].

Imaging is used extensively in animal research, using equipment similar to that used for humans but adapted to the smaller size of mice, rats, or fish. Unlike humans, animals will generally be put to sleep using **anesthesia**, so that they do not move around or panic when they are placed in an unfamiliar environment to be imaged. Imaging technologies allow scientists to look at the size and shape of an animal's organs, to detect tumor growth or a bone fracture, for example. Imaging also allows scientists to study how organs function, for example to study an animal's heart beating or blood moving through the blood vessels to carry oxygen around the body. Importantly, scientists can also see how an animal's cells and tissues respond to inflammation or injury by measuring how much oxygen or energy these cells or tissue use.

ANESTHESIA

The use of medicines to ensure that an animal is unconscious and free of pain during a medical procedure like imaging.

The ability to take a picture of the structure and function of internal organs helps scientists get more detailed information from a single animal, which improves the quality of their research studies. Imaging also helps scientists understand animal bodies, which helps them detect any signs of discomfort so they can act quickly to provide

animals with better-quality care. This helps to improve animal welfare (Figure 2).

Figure 2

Imaging helps scientists see how internal organs change as an animal grows or when it is treated with a drug. For example, if animals have a high body temperature that causes inflammation in the brain, scientists can use imaging to see whether brain inflammation could be treated by various medicines. Imaging a living animal can provide a lot of information, which helps reduce the number of animals needed for research studies.

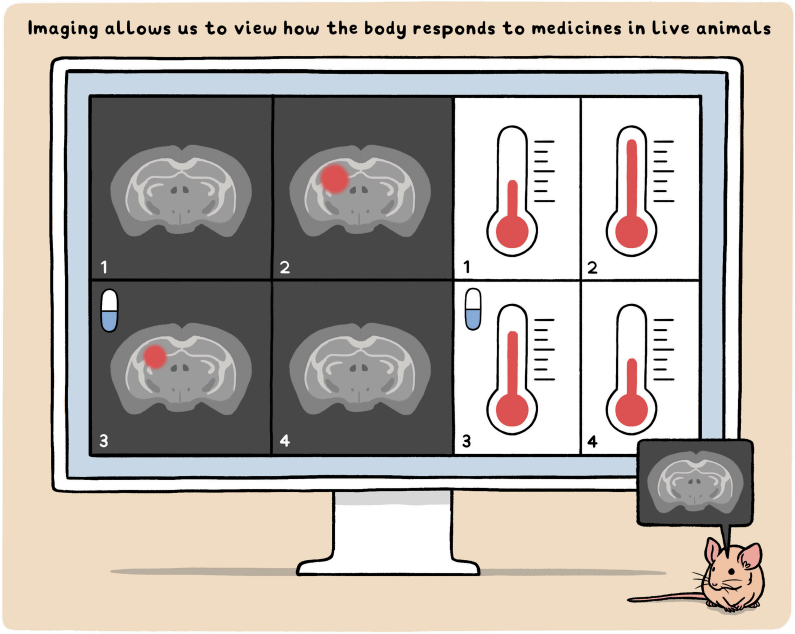

Figure 2

HOW IMAGING WORKS

There are several imaging techniques commonly used for laboratory animals (Figure 3) [3, 4].

One of the most-used methods is called computed tomography (CT) scans. CT produces 3D, x-ray-based images of solid tissues like bones, allowing scientists to study the structure of bone tissue. This method is very useful for studying bone fractures or changes in the skeleton.

Magnetic resonance imaging (MRI) maps water molecules in the tissues to create pictures of soft internal organs such as the heart, brain, liver, or digestive system. This technique is most often used to analyse the nervous system, especially the brain and spinal cord.

Nuclear imaging detects radiation emitted by small radioactive tracer molecules injected into the body, to analyse the functions of internal organs. Typically, tracers are molecules chemically similar to glucose, the body's main energy source. We can image whether these tracers are rapidly taken up by cancer cells and/or inflamed cells inside the animal's body. This allows scientists to map where these diseased cells are located.

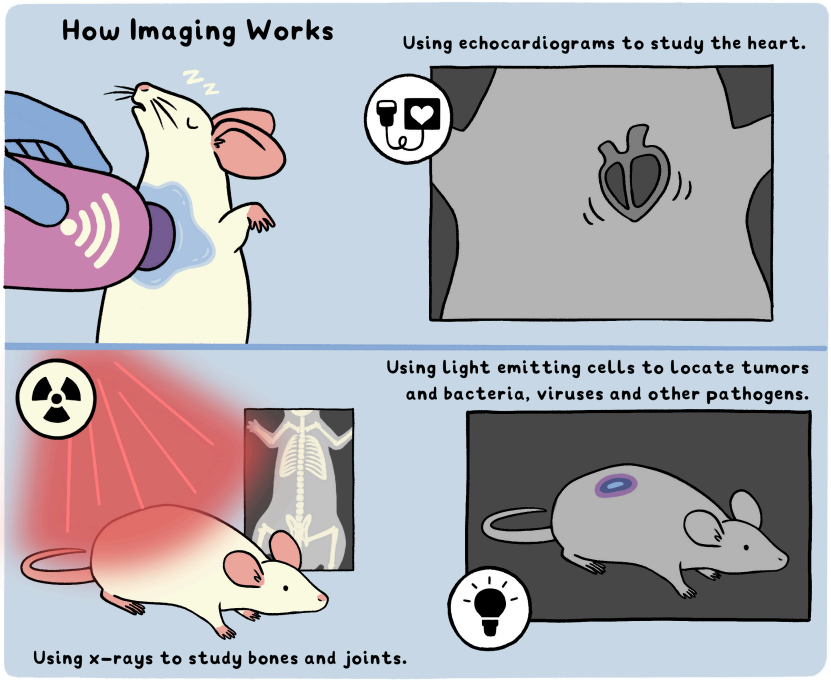

Figure 3

Animals are imaged with technologies similar to those used to image humans. Non-harmful physical and chemical techniques such X-rays, the detection of light-emitting cells, or ultrasound **(echocardiograms)** are used to look at the skeleton, examine cell growth, or assess blood flow through the heart, for example. Viewing cell/tissue structure and function in real time is very important for studying diseases and for finding effective treatments, without harming or killing animals.

ECHOCARDIOGRAM

Imaging the heart function using ultrasound.

Optical imaging is used to detect cells inside animals' bodies that can emit light. This technique is based on the ability of organisms like fireflies to make light in their abdomens by a controlled chemical reaction. Using the same chemical reaction, animal cells can be modified to emit visible light, which helps scientists to identify their locations inside the animal's body. Detecting these glowing cells is useful for studying cell growth and energy use in cancer cells, for example.

Ultrasound uses high-frequency sound waves produced by the movement of organs, like the sound waves produced by the heart beating. These sound waves travel across the animal's body, are collected, and turned into a moving image. This imaging technique is commonly used for studying heart function.

Before an imaging study, researchers must confirm the total number of number of times that an animal will be imaged and anesthetised. Only a limited number of imaging sessions is allowed per animal (generally one to three sessions), and researchers must monitor the health and wellbeing of the animals during the entire study.

CONCLUSION

Imaging has dramatically improved animal studies, enabling scientists to monitor disease progression in real time and to study the responses of animals to medicines without causing them harm [4]. Imaging

allows scientists to get detailed information on the anatomy and functions of animals' bodies without the need to kill them to access their internal organs. This is an important step for reducing the number of animals used in research. Importantly, imaging helps scientists to better understand an animal's body functions and how they may be affected by experimental procedures. This allows scientists to detect early signs of illness or suffering that could cause further distress in the animals. Identifying such effects early helps scientists to take immediate actions to improve animal care and welfare and to prevent or minimize suffering (for example by giving painkillers or more nutritious food). Overall, imaging directly benefits animal welfare and improves scientific research through reducing the number of research animals used—a key component of the 3Rs principle.

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SUBMITTED: 26 May 2022; **ACCEPTED:** 05 September 2022;
PUBLISHED ONLINE: 11 October 2022.

EDITOR: Robert T. Knight, University of California, Berkeley, United States

SCIENCE MENTOR: Christopher R. Cederroth

CITATION: Tremoleda JL (2022) Reducing the Number of Research Animals: How Imaging Technologies Can Help. Front. Young Minds 10:953662. doi: 10.3389/frym.2022.953662

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