Science Bulletin 66 (2021) 1499–1501

Contents lists available at ScienceDirect

Science Bulletin

journal homepage: www.elsevier.com/locate/scib

Commentary

# Gaining a better understanding of nonhuman primate research

Ji Dai [a,b]

[a] CAS Key Laboratory of Brain Connectome and Manipulation, The Brain Cognition and Brain Disease Institute, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences; Shenzhen-Hong Kong Institute of Brain Science, Shenzhen 518055, China
[b] University of Chinese Academy of Sciences, Beijing 100049, China

The use of animals in research has long been debated. In particular, the use of nonhuman primates (NHPs) in either basic or applied research is controversial [1,2]. The concerns mainly arise from an ethical perspective given the great similarity between NHPs and humans. While this similarity has scientific advantages, it has also raised concerns that experimental primates may experience pain and suffering in ways similar to humans. Therefore, people who believe that experimental animals are being mistreated in laboratories have established many organizations to protect animal rights, which has led to many animal rights movements in places around the world. On the one hand, these movements have reminded researchers to treat their experimental animals more appropriately and to promote the evolution of animal policies. On the other hand, some of the movements have turned violent. In addition to attacking animal facilities and making great damage to targeted institutions, activists from some animal rights groups have threatened researchers and their families, or have even engaged personally in violence (e.g., placing a bomb in a researcher's house or car). Scientists doing primate research are the most likely to become the target of such crimes [3] (also see https://www.uclahealth.org/u-magazine/three-who-stood-up; https://www.sciencemag.org/news/2014/03/animal-rights-extremists-increasingly-targeting-individuals). Some famous researchers have even had to abandon their studies because of threats or attacks. For example, in 2015, Professor Nikos Logothetis, a director at the Max Planck Institute for Biological Cybernetics in Tübingen and a leading neuroscientist in the world studying the brain using monkeys, announced he would no longer work with macaques in Germany after being targeted by animal rights activists and receiving death threats, which caused enormous shock in the science community.

Therefore, people from the scientific community have also united to defend their work and explain why animals are used in medical and scientific research. They are attempting to increase the transparency of scientific research and keep the public from being misled. One important claim from the scientific community is that animal rights is a pseudo-concept because rights are related to obligation and people cannot claim rights for animals as they cannot be responsible for animals' behavior (i.e., we cannot claim survival rights for gazelles or cheetahs when we watch the latter chasing after the former). Some organizations (i.e., Research Defence Society and Understanding Animal Research) have been formed to achieve a broad understanding of the humane use of animals in medical, veterinary, scientific, and environmental research. In fact, researchers are required to follow the "3Rs" (Replacement, Reduction, and Refinement) when using experimental animals. Some official academic organizations, including the National Association for Biomedical Research and the Society for Neuroscience, also post detailed guidelines regarding animal research on their websites as well as rational explanations to answer frequently asked questions. All institutions have an ethics committee to supervise animal research, and stricter policies are being enacted every day.

NHPs, which are the main focus of the debate, actually account for a minuscule proportion of all animal research (i.e., less than 0.5% in the UK, https://speakingofresearch.com/facts/animal-research-regulations-in-the-uk/). Most primate subjects are purposely bred macaques, and research on great apes (e.g., chimpanzees and gorillas) has been banned in the UK and other countries. Nevertheless, NHP research has resulted in life-changing medical advances for many public health challenges. As an important example, to combat the global outbreak of coronavirus disease 2019 (COVID-19) [4], vaccines are the best way to protect people and stop it from spreading, but effective vaccines would not be possible without studies and tests on NHPs [5]. Research on monkeys has also helped to create new vaccines and treatments (e.g., for Parkinson's disease (PD) [6], Ebola [7], Zika [8], and acquired immune deficiency syndrome (AIDS) [9]), develop new strategies to treat heart disease [10], and develop animal models for mental illness (e.g., depression and autism) [11].

In addition to benefiting public health, NHP research has uncovered many basic mechanisms underlying cognitive functions. One notable example is the groundbreaking work of Hubel and Wiesel, who started the systematic study of neural information coding in the visual cortex of cats and macaques [12], leading to their Nobel Prize in 1981. Of all the animal models used in neuroscience, the monkey brain is the most similar to the human brain. Thus, researchers could take the advantage of the macaque brain to reveal the mechanisms underlying many cognitive functions, including perception, attention, learning and memory, decision-making, motor control, and the processing of reward and

*E-mail address:* ji.dai@siat.ac.cn

https://doi.org/10.1016/j.scib.2021.02.021

punishment. These studies serve as the neural basis to further inspire the development of artificial intelligence (AI). In particular, NHP research on sensory and motor systems has led to the new field of neuroprosthetics, which can restore the severe loss of sensory abilities or movement capabilities in paralyzed patients. Moreover, the development of brain–machine interfaces (BMI) has benefited greatly from neurophysiological experiments in NHPs showing that it is possible to use natural-brain cortical-neural activity to operate computers, robots, and artificial limbs, restore volitional control of movement for paralyzed limbs, or compensate for perceptual deficits [13,14].

Advocacy groups that seek to ban animal research often suggest that researchers are not appropriately aiming to replace animals with other alternatives. There are, indeed, many alternatives to animal research available, like *in vitro* cell culture, organs-on-chips, and computer simulation. These alternatives may replace part of the animal research, but none of these methods can fully replace animal research because they were created to mimic only part of the complex living system. Rather than working independently, all parts of the system connect and influence each other. As biomedical techniques continue to evolve, there may come a time when we can eliminate the need for animals; however, we are not there yet.

As recommended by a working-group report chaired by Sir David Weatherall in 2006, "There is a strong scientific case for the carefully regulated use of nonhuman primates where there are no other means to address clearly defined questions of particular biological or medical importance" (https://mrc.ukri.org/documents/pdf/the-use-of-non-human-primates-in-research/). This opinion was echoed by the Scientific Committee on Health and Environmental Risks (SCHER) of the European Commission, which published a report in 2009 concluding, "SCHER sees no valid scientific reasons to support a discontinuation of the use of primates in basic and applied research, or in the development and testing of new drugs" (http://ec.europa.eu/environment/chemicals/lab_animals/pdf/scher_o_110.pdf). Later in 2017, SCHEER (former SCHER) updated their opinion and restated that "appropriate use of NHPs remains essential in some areas of biomedical and biological research and for the safety assessment of pharmaceuticals" (https://ec.europa.eu/environment/chemicals/lab_animals/pdf/Scheer_may2017.pdf). We have gained copious knowledge from rodent research, yet only a minor portion of such results directly benefit human health. For example, billions of dollars have been thrown at the investigation of Alzheimer's disease (AD) in the past few decades (https://www.forbes.com/sites/robinseatonjefferson/2018/11/29/top-biopharmaceutical-research-companies-publish-update-on-the-state-of-alzheimers-research-in-us/?sh=257885944e77), and most studies used rodent models. Although scientists could create so-called "AD mice" and treat AD mice in the laboratory using many approaches, treating patients with AD is still a major challenge globally. One of the major reasons is that the mouse brain is significantly different from the human brain. Furthermore, rodent PD models are unable to recapitulate the selective and overt neurodegeneration seen in patients, whereas monkey models replicate such important pathological features well [15]. Scientists even found a naturally occurring PD monkey but none has been reported in rodents, suggesting that NHP shares similar pathogenesis of PD with humans and is the ideal candidate to develop genuine "animal versions of PD" [16]. This evidence strongly supports that NHP is irreplaceable in the foreseeable future, at least for the investigation of neurodegenerative diseases.

As discussed previously, NHP will continue to play an essential role in biomedical research. Therefore, banning NHP research or even restricting the transportation of experimental primates could severely hinder the advance of cognitive science, cures, and vaccines for many serious illnesses. However, scientists conducting NHP research from all over the world are still facing great pressure from animal rights groups. A better understanding of NHP study is needed in the public, and a better policy for NHP study should be achieved by policymakers and scientists to ensure the continuous progress of NHP study (Fig. 1). SCHEER suggested that "when communicating about NHP use with the public, the scientific community should provide an accurate description of the benefits, harms to animals, and limitations of such research, and be realistic about the potential outputs and impacts" (https://ec.europa.eu/environment/chemicals/lab_animals/pdf/Scheer_may2017.pdf). It is crucial to understand the questions of the public and obtain their trust. In the meantime, scientists and the public must continue to monitor NHP research to ensure that all animals are treated ethically and all practices are strictly following the "3Rs". Global collaboration should be strengthened to fully use current NHP resources, disregard repetitive projects, and focus on addressing the big questions.

As a consequence of the animal rights movement, NHP research is getting more difficult in Europe (E.U.) and the United States (U.S.). However, China is making policies to promote biomedical research in both basic and translational studies involving NHPs. Several primate research centers are being established in the country, including the International Center for Primate Brain Research in Shanghai and the Brain Science Infrastructure in Shenzhen. These research centers have high-quality primate facilities that are run following E.U./U.S. guidelines. Some facilities have obtained certifications from the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC), which means that all aspects of these facilities, including animal quality, welfare, biosafety, veterinary care, management, and equipment, have reached the same level as that in the E.U./U.S. Many scientists working in these research centers are recruited from the E.U./U.S., where they gained experience in both research and management. Further, all the research is regulated and supervised by Institutional Animal Care and Use Committee and the local government (e.g., the Laboratory Animal Monitoring Department and the Public Security Department). China is rich in NHP resources, making the cost of NHP study much lower than that in Western countries. More importantly, China is leading the development of genetically modified NHP models, including gene-edited monkeys and clones [11,17]. Taking all these together, China is attracting more scientists to work with their Chinese collaborators or even move to China. As an important example, earlier in 2020, Professor Logothetis announced that he would move to Shanghai with his team members, where he would be easier to pursue his work on macaques.

To continue leading the global NHP research in the future, the Chinese government could consider establishing a national NHP repository as a national bank to ensure a sufficient supply of experimental NHPs and balance the market. The outbreak of COVID-19 dramatically increased the demand for NHPs and caused a short supply in 2020. The Chinese government may also consider importing NHPs from Southeast Asia to overcome the temporary shortage. Special funds should be invested in this field to support experimental animal enterprises and research institutions. The Chinese media should also work closely with scientists and other international media to efficiently share scientific advances with the public globally. Chinese scientists should communicate with other scientific communities in the world to remain at the forefront of animal welfare and ethics. Close global collaboration is essential to obtain a better understanding of NHP research and ensure its continuous progress.

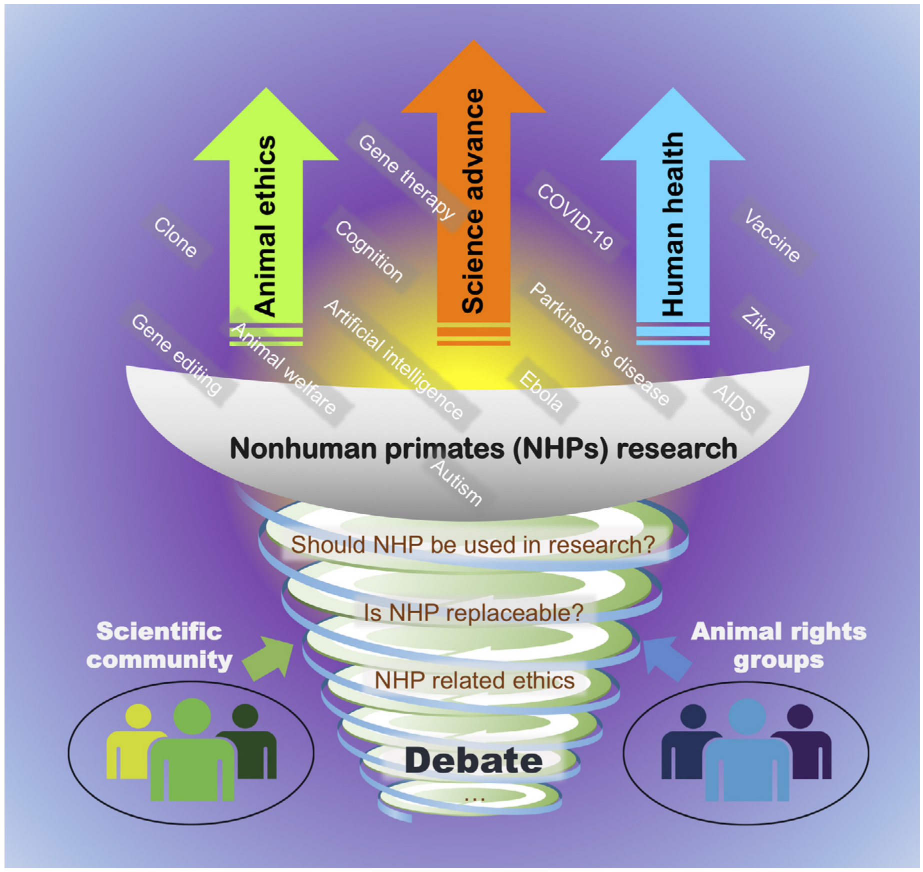


**Fig. 1.** The debate between the scientific community and animal rights groups promotes the development of animal ethics, and a better understanding of NHP experiments will advance science and benefit human health.

## Conflict of interest

The author declare that he has no conflict of interest.

## Acknowledgments

This work was supported by the National Natural Science Foundation of China (U20A2017), the Natural Science Foundation of Guangdong Province (2020A1515010785), the Youth Innovation Promotion Association of Chinese Academy of Sciences (CAS, 2017120), and the CAS International Partnership Program (172644KYSB20170004).

## Appendix A. Supplementary materials

Supplementary materials to this article can be found online at https://doi.org/10.1016/j.scib.2021.02.021.

## References

[1] Goodman S, Check E. The great primate debate. Nature 2002;417:684–7.
[2] Weatherall D, Munn H. Moving the primate debate forward. Science 2007;316:173.
[3] Schiermeier Q. Primate work faces German veto. Nature 2007;446:955.
[4] Shi Y. New virus, new challenge. Innovation 2020;1:100005.
[5] Corbett KS, Flynn B, Foulds KE, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. N Engl J Med 2020;383:1544–55.
[6] Blesa J, Trigo-Damas I, del Rey N-G, et al. The use of nonhuman primate models to understand processes in Parkinson's disease. J Neural Transm (Vienna) 2018;125:325–35.
[7] Bennett RS, Huzella LM, Jahrling PB, et al. Nonhuman primate models of Ebola virus disease. Curr Top Microbiol Immunol 2017;411:171–93.
[8] Osuna CE, Whitney JB. Nonhuman primate models of Zika virus infection, immunity, and therapeutic development. J Infect Dis 2017;216:S928–34.
[9] Evans DT, Silvestri G. Nonhuman primate models in AIDS research. Curr Opin HIV AIDS 2013;8:255–61.
[10] Shiba Y, Gomibuchi T, Seto T, et al. Allogeneic transplantation of iPS cell-derived cardiomyocytes regenerates primate hearts. Nature 2016;538:388–91.
[11] Zhou Y, Sharma J, Ke Q, et al. Atypical behaviour and connectivity in *SHANK3*-mutant macaques. Nature 2019;570:326–31.
[12] Wurtz RH. Recounting the impact of Hubel and Wiesel. J Physiol 2009;587:2817–23.
[13] Andersen RA, Aflalo T, Kellis S. From thought to action: the brain-machine interface in posterior parietal cortex. Proc Natl Acad Sci USA 2019;116:26274–9.
[14] O'Doherty JE, Shokur S, Medina LE, et al. Creating a neuroprosthesis for active tactile exploration of textures. Proc Natl Acad Sci USA 2019;116:21821–7.
[15] Yang W, Liu Y, Tu Z, et al. CRISPR/Cas9-mediated *PINK1* deletion leads to neurodegeneration in rhesus monkeys. Cell Res 2019;29:334–6.
[16] Li H, Su L, Yang L, et al. A cynomolgus monkey with naturally occurring Parkinson's disease. Natl Sci Rev 2020;8:nwaa292.
[17] Liu Z, Cai Y, Wang Y, et al. Cloning of macaque monkeys by somatic cell nuclear transfer. Cell 2018;172:881–7.

Ji Dai is a principal investigator (PI) at Shenzhen Institutes of Advanced Technology (SIAT), Chinese Academy of Sciences (CAS). He obtained his Ph.D. degree from the Institute of Biophysics, CAS, and completed the postdoc training at Brown University. He joined the Institute of Psychology in 2014 and then moved to SIAT as a PI in 2017. His research focuses on the neural mechanism underlying cognition and the modeling of brain disease using nonhuman primates.