Received: 26 November 2020 | Revised: 30 August 2021 | Accepted: 2 November 2021

DOI: 10.1002/ame2.12190

ORIGINAL ARTICLE

A novel mind-set in primate experimentation: Implications for primate welfare

Antonella Tramacere[1,2] | Atsushi Iriki[3]

[1]Department of Linguistic and Cultural Evolution, Max Planck Institute for the Science of Human History, Jena, Germany

[2]Department of Philosophy and Communication Studies, University of Bologna, Bologna, Italy

[3]Laboratory of Symbolic Cognitive Development, Riken Brain Science Institute, Tokyo, Japan

Correspondence
Antonella Tramacere, Department of Philosophy and Communication Studies, University of Bologna, Bologna, Italy.
Email: a.tramacere@gmail.com

Funding information
No funding for this research.

Abstract

We emphasize the importance of studying the primate brain in cognitive neuroscience and suggest a new mind-set in primate experimentation within the boundaries of animal welfare regulations. Specifically, we list the advantages of investigating both genes and neural mechanisms and processes in the emergence of behavioral and cognitive functions, and propose the establishment of an open field of primate research. The latter may be conducted by implementing and harmonizing experimental practices with ethical guidelines that regulate (1) management of natural parks with free-moving populations of target nonhuman primates, (2) establishment of indoor-outdoor labs for both system genetics and neuroscience investigations, and (3) hotel space and technologies which remotely collect and dislocate information regarding primates geographically located elsewhere.

KEYWORDS
animal models, cognitive neuroscience, natural parks, neuropsychiatry, primate experimentation, primate welfare, Research Domain Criteria

1 | INTRODUCTION

Efforts in cognitive neuroscience have begun to address mechanisms and processes of cognitive functions and psychiatric disorders. Cognitive functions are supported by complex and distributed brain processes. Psychiatric disorders, i.e. personality disorders or developmental syndromes (e.g. depression, schizophrenia, autism, Alzheimer, fragile X, etc.), comprise any impairment of the brain that disrupts to some extent neural connectivity underlying cognitive functions, irrespective of the nature of the mechanisms that have brought about this impairment. The study of cognitive functions and psychiatric disorders is mutually informative, because by understanding the functional correlates of specific cerebral impairments, it is possible to highlight the neurodevelopmental underpinnings of the human mind.[1] In addition, basic research in cognitive neuroscience informs investigations about mechanisms involved in neuropsychiatric disorders.

Human studies alone are not yet sufficient to achieve precise information about the mechanisms and functioning of the brain, and experimentation with nonhuman animals remains an important cornerstone of both neuroscience and neuropsychiatry. Humans belong to the primate order and share with other nonhuman primates (NHPs) several cognitive abilities sub-served by a homologous brain architecture. Therefore, since the dawn of cognitive neuroscience the NHP brain has been investigated via a number of perceptual and cognitive tasks, with monkeys typically been considered optimal candidates for inquiring about core processes and mechanisms of the human mind.

The assumption of evolutionary relatedness, by a homologous brain architecture, has guided the conjoint investigation of mental functions and dysfunctions in human and NHPs. The core idea is that by uncovering the cerebral underpinnings of primate psychological functions, we can acquire a more complete picture of the processes and mechanisms of human cognition and psychiatric disorders. To

date, a detailed map of the human brain has benefited from findings achieved during neurophysiological experiments with primates.

The evolutionary relatedness between human and NHPs has made primate experimentation pivotal for cognitive neuroscience research. At the same time, their phylogenetic closeness has been one reason for questioning primate experimentation in its current ethical form. The line of reasoning is that, since the NHP brain and body are like our own, they also suffer like us, and therefore they deserve increased welfare compared to other species. Consequently, new regulations have produced restrictions in the use of NHP in laboratory research [see Box 1].

One consequence of the new restrictions has been a progressive increase in rodent experimentation. To date, a great deal of experimental research in cognitive neuroscience is conducted in rodent species. Rodents have become among the most common animal models in cognitive neuroscience; many behavioral studies are also conducted with rodents, leading to an increase in the range of cognitive functions attributed to these mammals. Rodents are now known to possess astonishingly complex capacities, such as flexible behavior, spatial navigation, and episodic-like memory.

However, as we argue in this paper, if not combined with primate experimentation, cognitive neuroscience in rodents is limited. If the goal is to identify the neural correlates of the human mind, a knowledge of the specific neurobiological mechanisms that can inform generalizations about associated human cognitive functions is required. We contend that, if performed in parallel with human and rodent experimentation, NHP research has significant benefits, because it allows us to reach an understanding of human brain mechanisms through the study of a model brain more similar to human beings than that of rodents.

Our argument comes with concrete proposals for primate welfare. We claim that NHP experimentation in cognitive neuroscience can be conducted within a new mind-set that harmonizes the use of novel technologies with scientific practices promoting primate welfare. Specifically, we envisage a system of remote technologies and a combination of indoor-outdoor laboratory structures that are compatible with increased ethical standards for primate research. After describing a series of tools and labs technologies that may fit the scope, we make a series of observations on the epistemic and economic benefits that our proposal may bring.

We start by reviewing the use of both rodents and primate models in cognitive neurobiological research (Section 2). In Section 3, we emphasize the importance of studying NHP by discussing recent research guidelines (i.e. Research Domain Criteria) launched by the National Institute of Health. In Section 4, we present the core of the proposal for studying NHP while improving welfare measures for NHP. We then review the potential benefits of studying NHPs in Section 5 and discuss more general costs and benefits trade-offs in Section 6.

BOX 1 Changes in NHP experimentation

In parallel with the study of primate cognition and the discovery of their genetic, neural and behavioral similarity with human beings, the status of NHP in research has generated much debate. While the similarity has scientific advantages, it poses ethical problems because of a likelihood that primate experience pain and suffering in ways that are similar to humans.[2] This argument has accompanied several initiatives aiming at protecting NHPs. In 1993, the Great Ape Project (GAP) took birth, endorsing that great apes hold the right to life, individual liberty, and freedom from torture. In 2008, Spain was the first to acquired GAP in its legislation, followed by Austria, New Zealand, Netherland, Sweden, and UK. The ban in Sweden, however, does not extend to non-invasive behavioral studies, and research on great ape cognition continues to be carried out on zoo gorillas. Sweden's legislation also bans invasive experiments on gibbons. In Europe, primate research is regulated by the Directive 2010/63/EU, who banned most studies on great apes (European Parliament 2010: Article 8). Further, the Directive 2010/63/EU permits research on monkeys only if it is provided the work could not be carried out in any other species (European Parliament 2010: Article 8). Many protests against monkey experimentation have led to legal disputes in many countries, such as Australia and United States. Some institutions are no longer using primates, such as the Harvard Medical School, which closed its affiliated primate facility in 2015. Others are reviewing their primate use: for instance, the US National Institutes of Health announced recently that it would review all NIH research that it funds. A completely opposite trend is happening in China and some African countries (Kenya, South Africa and Ethiopia), where due to different approach to primate experimentation, the number of NHPs used in research is increasing.

2 | ANIMAL MODELS IN NEUROBIOLOGY

In the past few decades, research with rodents has become prominent in various sub-fields of cognitive neuroscience, and progress has been made through rodent experimentation. Mechanistic features and functions of key neural circuits common to the mammalian order, such as reward and emotional systems, have been deeply investigated through brain research in mice and rats. Further, new techniques, such as deep brain stimulation and optogenetics, have been mostly tested in the rodent models, allowing generalizations of brain mechanisms to the human brain.

These achievements, however, should not lead us to forget the differences between the human and rodent brains, which matter for translation of rodent findings to human beings. For example, the size and cortical organization of the prefrontal cortex, von Enconomo neurons, neurotransmitters and neuromodulatory pathways[3] are different in rodents and primates. As a consequence, the neural mechanisms and processes underlying cognitive traits in the

two taxa can be very different, although the observed behavior is analogous.

Consider attention as an example. Critical differences do exist between rodent and primate mechanisms and processes of attention. In humans and NHPs the allocation of attention is determined by a frontoparietal neural network.[4] This includes parts of the oculomotor system aligning the fovea with objects of interest, and provides spatially selective feedback signals to extrastriate visual cortex that cause attention-dependent changes in gain.[5,6]

Although rodents can and do move their eyes, they lack a fovea, and lack the prefrontal oculomotor infrastructure that serves to deploy spatial attention in primates.[7] Consequently, brain research in rodents can be informative to the extent that it highlights coarse-grained factors affecting the capacity to allocate attention in human. However, it tends to be limited when the goal is uncovering how human cortical connectivity is affected by top-down neural processing in the ability to deploy attention. As consequence, experimentation with rodents may restrict successful development of therapies for psychiatric disorders in which attention processes are affected.

This is just an example, but striking differences between rodents and primates also include communication based on mobility of facial expression,[8] capacity for mentalization,[9] and the use of both motor and sensory tools, and enhanced tactile specialization,[10] among others. In each of these cases, cognitive functions seem to depend on primate-specific brain specializations, which in turn may affect the way cognitive dysfunctions arise.

It is worth of emphasizing that we do not aim to dismiss the importance of rodent models in neuroscience. At the same time, we do not contend that NHP experimentation alone is sufficient for uncovering the biological bases of human cognition. Animal experimentation depends on being able to select the right model for addressing the right questions. The choice of the species to be used depends on many factors that are not only methodological in nature, but also ethical.

In line with this general maxim, experiments with mice and rats are important, not only to uncover brain mechanisms and processes which are common to rodents and humans, as described above in the case of attention. The rodent model is also important for inquiring into the genetic variability associated with atypical brain function, and increased vulnerability to diseases. Neurobiological experiments in rodents have proved useful to investigations of the effect size of specific sets of genes in neurocognitive functions that are common to human beings and rodents. For instance, screening for loss or gain of gene functions in mice has helped to highlight the mechanisms of action of specific molecules, and to determine neuromolecular pathways affecting aspects of sensorimotor control. To date, we already know of several molecular and neural circuitries associated with typical and atypical sensorimotor capacities in human beings that have guided mechanist studies in rodents.

Although rodents are optimal animal models for inquiring into neurobiological functions that are common to human beings and rodents, they are of limited use in uncovering the neurobiological bases of cognitive capacities that are specific to NHPs. Thus, addressing these questions in rodent species in order to formulate general mechanisms that also apply to humans is a gamble, which is already producing results that suffer from limitations.[3,11]

Experimentation with NHPs is more appropriate for studying the biological bases of human cognition for a number of reasons. There are more consistent similarities between two primate species than between two different taxa, at the genetic, neural, and socio-behavioral levels.[12] Given the close biological similarities between NHPs and humans, NHP research could significantly reduce the uncertainty associated with translation of findings to humans and be instrumental in producing more realistic mechanist models of human cognitive functions.

Further, the phylogenetic proximity of humans and NHPs makes more likely that they will share many of the specific neural mechanisms involved in brain physiology, behavior, and susceptibility to disease. Gene maps of NHPs and humans are highly conserved and therefore NHPs will more closely model the complex gene-gene and gene-environment interactions that control human neurophysiological processes.[12]

Further, beyond the phylogenetic (and thus genetic) closeness, there are anatomical similarities. Primate brains follow similar rules of cerebral changes, which do not apply to rodents. In rodents, variations in brain size outpace variations in the number of brain neurons. Rodent brains vary in mass as a power function of the number of brain neurons, whereas in primates, brain size increases linearly as a function of the number of neurons.[13] This makes the rodent brain structurally dissimilar, in terms of number of neurons, layer structures and connectivity, to the primate brain and thus suitable as a model for studies targeting primate-specific cognitive functions.

We are aware that no animal models will ever fully recapitulate human cognition, which is the result of species-specific environmental and cultural influences, but NHP experimentation can still provide important information for identifying brain mechanisms implicated in the emergence of human cognitive functions. Human experimentation and alternative methods are not yet a mature branch of research. Until we can develop non-invasive, but nonetheless efficient experimental tools for investigating the fine-grained functional-mechanistic aspects of human cognition, to compare evidence obtained during investigations in humans with research on neurobiological mechanisms in animals closely related to us.

3 | THE RESEARCH DOMAIN CRITERIA APPROACH TO NEUROPSYCHIATRY

In 2010, the National Institute of Mental Health promulgated the Research Domain Criteria (RDoC), a long-term framework for research in psychiatry based on progress in genetics, neurobiology, and clinical observation, with the goal of understanding the mechanisms underlying normal and abnormal human behavior. RDoC involves the combination of the systems genetics approach, plus the technologies related to disease modeling, and developmental and social neuroscience, informed by clinical investigations.[14]

Systems genetics is a growing field of genetics that inquires into the interactions of biological information underlying complex traits, by using a range of experimental and statistical methods to quantitate phenotypes.[15] Among these methods, Genome-Wide Association Studies have identified thousands of genetic loci that contribute to several cognitive traits, including psychiatric diseases. Further, recent technological developments (such as micro-arrays, high-throughput CHIP-seq, RNA-seq, etc.) are now allowing us to quantitatively survey hundreds or thousands of biological molecules, from DNA sequence variations to epigenetic marks to levels of transcripts, proteins and metabolites that are associated with the development of specific functional and dysfunctional traits.[16]

Meanwhile, cognitive neuroscience is advancing in the use of technologies for the investigation of neural activity, highlighting the neurodevelopmental underpinnings of specific cognitive functions and dysfunctions. These include neuroimaging, electroencephalography, magnetoencephalography, transcranial magnetic stimulation, and positron emission tomography. Other techniques, which can be used in human beings exclusively under specific clinical conditions, include electrode recording of single or multilevel populations of neurons.

Considering that molecular and neuroscientific technologies are now enabling pathway-based, systems-level approaches that have the potential to delineate the neurobiological context in which genetic variations exert their effects, one of the next scientific steps may involve providing a road map between set of genes and mental functions by connecting a sufficient amount of data about neural systems underlying cognitive and behavioral phenomena.

The recommendation of the NIH is to take into account not only observations at the behavioral level, but also to integrate knowledge related to the neurobiological bases of human mental phenomena. With the promotion of RDoC, the scientific community further acknowledges that in research about mental phenomena.

Nevertheless, there are still limitations to the types of research that can be conducted in human beings. It is not yet possible to perform investigations at the level of populations of neurons or molecular screening of human neural tissues. In addition, there are also several difficulties related to the ethics of possible interventions. Because of the intrinsic limitations of systematic investigations of biology and behavior of healthy and diseased humans, RDoC includes animal experimentation as an integral part of its research practices.[17]

As previously explained, research conducted with the most common animal models in neurobiology, i.e. rodents, is limited. The brain differences between rodent models (rats and mice) and human beings are such that the cognitive dysfunctions under investigation may be generated by primate specific biological features or specie-specific functions. Consequently, to study the neurobiological bases of psychiatric disorders through different levels of analysis, we need to conduct research in animal models that are closer to the human cerebral and molecular phenotypes.

Basing on these assumptions, we think that one possible way to proceed, among others, is the application of the RDoC guidelines to primate experimentation, to implement a research agenda that involves investigations of multilevel information in target species of monkeys. The research agenda would include the study of NHP brain, behavior and genetics. More specifically, systems genetics and cognitive neuroscience investigations in NHPs could be instrumental in collecting data in NHP subjects that allows analysis of multilevel information (from genetic profiles, to molecules, to neuronal circuitry), through large-scale investigation of behavior.

In this context, rodent research would still be fundamental. The rodent model would be important for disease modeling, to inquiring into the genetic variability associated with atypical brain functioning, and increased vulnerability to diseases. In parallel with rodent research, experimentation on NHPs would provide complementary information, with a set of brain and molecular high-resolution techniques being instrumental in inquiring into target brain functions in monkeys.

It is not the goal of this paper to delineate the exact combination of techniques and experimental methods that could be utilized in such an enterprise. A few examples, to be developed in future work, illustrate how NHP experimentation could include the systems genetics[16] tools that we have listed above. Through these tools, it will be possible to proceed to large genetic GWAS analysis, and molecular screening of central and peripheral tissues.

Furthermore, molecular imaging techniques could be used to detect fine-scale, diffuse, and slow activities of complex network structures.[18,19] More detailed brain investigations could also benefit from newly emerging wireless implantable neural recording.[20] Finally, high throughput supercomputers and computer simulation techniques would be required to deal with huge amounts of data (i.e., Big Data),[21] collected at multiple levels of analysis. Big data supercomputers are utilized to detect patterns of significance in various types of input data. We will provide additional considerations on the use of these techniques in the next section, showing how they could enable systematic investigations of molecular, cellular and circuit-level landscapes of the primate brain across typical and atypical development.[22,23]

The focus of the remaining part of this article relates to the practical and ethical aspects of primate experimentation. Monitoring the emergence of cognitive functions in NHPs requires both practical and ethical changes in primate experimentation. Novel housing structures and technologies are needed for scientists to perform, over the developmental lifespan of primates, large-scale genetic, epigenetic and metabolite screens, to interrogate complex circuit-level dynamics, assess basic cognitive abilities, measure neurodevelopmental processes, track the behavior of the target individuals and of the social niche that surrounds them and that they interact with. These changes could have interesting implications for primate welfare. In the next sections, we make concrete proposals on how these desiderata could be implemented.

4 | THE OPEN NICHE OF PRIMATE EXPERIMENTATION

The investigation of molecules, neural circuitry and behavior in NHP populations would need novel structures and technologies for

primate experimentation. Crucially, these structures must be in line with new standards for primate welfare. The scientific community and the general public are determined to provide improved conditions for NHP individuals participating in cognitive neuroscience research. We think that these desiderata can be satisfied both at the methodological and ethical level.

We think that it is possible to establish wild-like environments for target populations of NHPs that allow free movement. In turn these conditions could allow scientists to inquire into cognitive phenomena and neurobiological correlates which are common to the primate order. In other words, the investigation of cognitive functions through collection of data at different levels of analyses in free-moving primate groups may serve both scientific and ethical purposes.

With the objective of maximizing the feasibility and the potential benefits of conducting brain research through the RDoC guidelines in NHPs, our proposal is to construct a niche allowing non-invasive or minimally invasive experimentation on target species of monkeys. This niche for primate experimentation could make use of primate natural parks with a combination of indoor and outdoor spaces. We briefly describe the infrastructures and technologies underlie this proposal below.

4.1 | Primate natural parks

Primate natural parks are park-like enclosed spaces for hosting target species of NHPs. NHP populations hosted in these parks could mimic natural populations living in the wild, while allowing scientists to conduct multi-level investigations, from an ecological and longitudinal perspective. These spaces would contain both indoor and outdoor research infrastructures. The indoor enclosure would be fitted with neuroimaging and neural recording technologies, system genetics instrumentation and other tools adapted for cognitive-behavioral experiments.

The natural parks would also contain appropriated lab spaces, furnished with sets of novel technologies, chosen in line with the research questions and ethical considerations. For example, recording of neuronal activity in these labs can be conducted through brain imaging techniques, or with chronic electrode implants, which have completely different impacts on primate well-being.[24] Detailed discussions at the scientific and ethical levels are required to assess what research strategies and types of technologies can be combined for conducting primate mental research in an efficient way and with appropriate welfare conditions.

The outdoor space would be adapted to the hosted species of NHPs and adjusted to the ecological needs of the target natural-like populations of primates. There are already examples of natural parks. Some examples of nature labs for NHPs can be found in the indoor-outdoor environment of the National Primate Research Center of Thailand. This is a zoo where visitors can see and interact with different species of primates. These infrastructures also house indoor research stations, where different types of experiments are conducted. The outdoor spaces are further endowed with cameras to record behavioral variables of the groups of primates hosted.

NHP living in naturalistic settings may further offer the possibility of inquiring into the range of naturally occurring dysfunctions in NHPs. Specifically, through focus observations and testing of NHP socio-cognitive behaviors, it may be possible to detect interindividual variability that is potentially predictive or reminiscent of human disease vulnerability (for a concrete example see Ref. [25]). The neurobiological mechanisms behind interindividual behavioral variability would constitute a valuable source of information for neuropsychiatric research.[26,27]

Another advantage of primate natural parks is that primates do not have to be transported for long distances, housed in facilities (e.g. where they live in restricted spaces, isolated cages, and artificial environments), and subjected to laboratory conditions. This reverses the logic of classical lab experimentation. Currently, most brain research is conducted in the lab, where animals are generally housed in cages and live in socially isolated spaces, in order to provide controlled conditions in which experiments and measurements can be performed. In contrast, in research in natural labs, it is the scientists, and not animals, that move.

4.2 | Hotel space and remote technologies

The establishment of natural parks would require what has been called 'hotel space'. These are housing structures, where visiting researchers can spend time while carrying out experiments with primate individuals housed in the indoor-outdoor spaces of natural parks.

The hotel space would need to utilize telecommuting approaches to storing the data collected during animal experimentation, to analyze, and in some cases share data collected on site.[3] The hotel space would need to be endowed with *remote technologies*, such as the Internet of Things (i.e. a new paradigm in modern wireless telecommunication), that would allow the storage and transfer of information in real time,[28] IT based knowledge management (i.e. an information technology system to enhance and organize knowledge),[29] and cloud-based big data processing for allowing cost-efficient exploration for voluminous data sets.[22]

For countries that are far from NHP natural habitats establishing primate natural parks may be difficult, but the existence of hotel spaces close to these parks could potentially offer unlimited possibilities for studying NHPs on site. The benefits deriving from these structures could thus be shared through different partners.

Establishing hotel spaces would be necessary for scientists who want to work with NHPs but are at an institute that lacks the resources (Landmann quoted by Vivien Marx, 2016; http://blogs.nature.com/methagora/). In addition, the new technologies, such as Internet of Things and Remote Lab, could also allow data monitoring and data processing in research centers that are geographically far from the place where primates are located. Obviously, this also means that agreements about cross-border collaboration,

data sharing, data security and intellectual property must be put in place (Iriki quoted by Vivien Marx, 2016; http://blogs.nature.com/methagora/).

The rational of the hotel space and remote lab is also appealing for investigating the number of NHP populations living wild or semi-wild in countries such as Japan, Singapore or anywhere close to the primates' natural habitat. In Japan, for example, several monkey parks are spread throughout the territory and are open to visitors. In Singapore, although not specifically for primates, there are many safari parks where animals live in wild-like environments and are managed by caretakers under international standards of animal welfare. These animals could constitute a further source for studying inter-individual variability at the behavioral level, and analyzing various biological samples (e.g. from the feces to the blood or the buccal mucosa).

5 | COST AND BENEFITS TRADE-OFFS OF PRIMATE EXPERIMENTATION

Conducting primate experimentation through the establishment of natural parks, remote technologies and hotel spaces for scientists working on site is clearly an ambitious and visionary enterprise. However, it could give short- and long-term benefits, by minimizing both ethical and scientific concerns, and could probably achieve balanced financial funding.

Firstly, the methodological integration described above could have advantages for primate welfare. NHPs living in a naturalistic environment would benefit from conditions that are normally associated with animals living in the wild, in terms of space to move about freely and availability of social interactions. Thus, from a strict primate welfare perspective, housing NHPs in natural parks would alleviate the conditions that primate research subjects currently experience during neurobiological research, such as being confined alone in cages.

Although this proposal would be suitable only for cognitive ethology and cognitive neurobiology research, which utilizes about the 19% of the total of NHPs used in research,[30] its potential benefits should not be underestimated. In fact, according to the latest report available, a consistent number of primates are held by facilities but not used in any experimental protocols.[31] Our proposal would avoid NHPs being housed in facilities for behavioral and neurobiological research, thereby enduring artificial and socially isolated living conditions without contributing to scientific discovery.

We also mention, but do not argue for, another aspect. Large-scale molecular and behavioral investigations of populations through the establishment of hotel spaces close to primate populations living wild or semi-wild could also be useful for tracking the danger of extinction in primate species, their levels of distress and other indicators of wellness.

Sudden aberrations in ecosystem are well documented, as a result of which wild populations of NHPs become increasingly susceptible to stochastic genetic, demographic changes, new infectious diseases and destructive infestations of invasive insects. Monitoring these changes may have positive influences on the enterprises associated with wildlife conservation and protection against extinction risks. Further, it may help to track changes that might in turn endanger humans through processes of zoonosis.[32]

It is also worth noting that this proposal is in accordance with current ethical frameworks, i.e. the '3Rs', which promote the search for alternatives and serve as the cornerstone for ethical guidelines in animal research. The 3Rs' set out three goals for experimenters: replacement of animals by alternative methods; reduction of their numbers by means of statistical techniques; and refinement of the experiment so as to cause less suffering.[33] More specifically, this proposal is in line with the goal of refinement, which not only aims to avoid or minimize pain or adverse effects, but also to maximize well-being, through the implementation of environmental enrichment and the promotion of positive elements of welfare, such as comfort and security.[34]

Natural parks for primate experimentation may also be associated with economic and practical advantages. Besides being subjected to protests from animal activists, some traditional primate facilities have high running costs due to the expense of animal management and employing qualified personnel. In contrast, natural parks could balance the economic costs by generating income from research centers worldwide (which aim to send researchers to study and collect data on NHPs) by providing zoo/safari type experiences for visitors and through educational programs.

Countries endowed with natural habitats for NHPs, such as Japan, India, Sri Lanka or Singapore, have witnessed increasing degrees of conflict between humans and feral monkeys over the last several decades.[35] NHPs become pests when they seek to obtain food and water near human habitation. Artificial feeding leads to changes in monkey behavior, and in population ecology by causing overpopulation of relatively aggressive monkeys. The solutions that some countries have adopted, such as killing, sterilizing or translocating monkeys, are mostly unfeasible for ethical, practical and economic reasons. On the one hand, killing a large number of animals is considered unethical according to the welfare regulation of several countries, while on the other hand sterilization and translocation practices are expensive and very laborious, because they require specialized personnel and long-term commitment.[35]

To sum up, natural parks for primate experimentation may be beneficial from both a methodological and ethical perspective and in particular may (1) enhance scientific validity, by providing a more suitable animal model for the study of mental functions and psychiatric disorders that can be translated into effective therapies, (2) provide naturalistic wild-like environments for NHPs, and avoid their translocation to different countries, and (3) allow data collection that can benefit primate conservation, and help control of risks from human-animal interactions.

6 | CONCLUDING REMARKS

In this paper, we have proposed that research on free-moving populations of primates (conducted in parallel with human and rodent

experimentation) can provide key mechanistic information that can be generalized to explain and understand human cognitive functions. Recent advances in neural and molecular tools can be combined to investigate primate behavior and psychology, and their neurobiological underpinnings. These tools might include system genetics tools, experimental and statistical methods to quantitate phenotypes, and techniques for neuroimaging, electrophysiology and wireless neural recordings.

We have given examples of infrastructures (i.e. natural parks and hotel spaces) and technologies (e.g. remote labs, Internet of Things, cloud-based Big Data processing) that could be used to conduct primate experimentation in a way that can enrich primate welfare. We have proposed natural parks that allow target populations of some primate species to live in a more ecological setting with free movement and socially enriched spaces. Our proposal can be interpreted as offering a new mind-set for primate neurocognitive research, constituting an interdisciplinary effort to understand the mechanisms systemically operating in the brain and body of primate models, which could have important implications for the way we use primates in the field of neuroscience and neuropsychiatry research.

The establishment of primate natural parks for primate cognitive experimentation is in accordance with current ethical frameworks (i.e. the '3Rs'). However, it also subtly incentivizes an enrichment of current understanding of animal ethics. That is, the open field of primate cognitive research can provide a new perspective on animal ethics: some animal species have the potential to live and/or interact collaboratively with humans, and this can affect the relationship we can establish with these animal species and the value we assign to them.[36] Thus, beyond the protection of primates according to their capacity to experience pain (in accordance with existing regulations), this research approach could be used to harmonize human and NHP interests.

To apply this new mind-set to primate mental research and implement connected investigative practices would require the establishment of updated ethical guidelines, which could lead on the one hand to developing new rules for NHP experimentation, and on the other hand to new guidelines for collaboration between research centers, laboratories and researchers. Although the aim of this manuscript is not to propose these guidelines, but to advance the general proposal, we hope that this perspective can constitute a starting point for future discussion.

ACKNOWLEDGEMENT

The authors do not have acknowledgment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Both authors contributed to the ideation and writing of the paper.

ORCID

Antonella Tramacere https://orcid.org/0000-0002-7522-4645

REFERENCES

1. Millan MJ, Agid Y, Brune M, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov*. 2012;11:141-168.
2. Hendriksen CFM. The ethics of research involving animals: a review of the Nuffield Council on Bioethics report from a three Rs perspective. *Altern Lab Anim*. 2005;33(6):659-662.
3. Jennings CG, Landman R, Zhou Y, et al. Opportunities and challenges in modeling human brain disorders in transgenic primates. *Nat Neurosci*. 2016;19:1123-1130.
4. Kastner S, Ungerleider LG. Mechanisms of visual attention in the human cortex. *Annu Rev Neurosci*. 2000;23:315-341.
5. Moore T, Armstrong KM, Fallah M. Visuomotor origins of covert spatial attention. *Neuron*. 2003;40:671-683.
6. Moore T, Fallah M. Microstimulation of the frontal eye field and its effects on covert spatial attention. *J Neurophysiol*. 2004;91:152-162.
7. Faulstich BM, Onori KA, du Lac S. Comparison of plasticity and development of mouse optokinetic and vestibulo-ocular reflexes suggests differential gain control mechanisms. *Vision Res*. 2004;44:3419-3427.
8. Tramacere A, Ferrari PF. Faces in the mirror, from the neuroscience of mimicry to the emergence of mentalizing. *J Anthropol Sci*. 2016;94:113-126.
9. Krupenye C, Kano F, Hirata S, Call J, Tomasello M. Great apes anticipate that other individuals will act according to false beliefs. *Science*. 2016;6308:110-114.
10. Yamazaki Y, Namba H, Iriki A. Acquisition of an externalized eye by Japanese monkeys. *Exp Brain Res*. 2009;194(1):131-142.
11. Kaiser T, Feng G. Modeling psychiatric disorders for developing effective treatments. *Nat Med*. 2015;21:979-988.
12. VandeBerg JL, Williams-Blangero S. Advantages and limitations of nonhuman primates as animal models in genetic research on complex diseases. *J Med Primatol*. 1997;26(3):113-119.
13. Herculano-Houzel S. The remarkable, yet not extraordinary, human brain as a scaled-up primate brain and its associated cost. *Proc Natl Acad Sci USA*. 2012;109(Supplement 1):10661-10668.
14. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167:748-751.
15. Civelek M, Lusis AJ. Systems genetics approaches to understand complex traits. *Nat Rev Genet*. 2014;15:34-48.
16. Gandal MJ, Leppa V, Won H, Parikshak NN, Geschwind DH. The road to precision psychiatry: translating genetics into disease mechanisms. *Nat Neurosci*. 2016;19:1397-1407.
17. Maestripieri D, Lilienfeld SO. Using the NIMH Research Domain Criteria (RDoC) in human and nonhuman primate research. *Psychophysiology*. 2016;53(3):367-371.
18. Filipek PA. Neuroimaging in the developmental disorders: the state of the science. *J Child Psychol Psychiatry*. 1999;40:113-128.
19. Tymofiyeva O, Hess CP, Xu D, Barkovich AJ. Structural MRI connectome in development: challenges of the changing brain. *Br J Radiol*. 2014;87:20140086.
20. Borton DA, Yin M, Aceros J, Nurmikko A. An implantable wireless neural interface for recording cortical circuit dynamics in moving primates. *J Neural Eng*. 2013;10(2):026010.
21. Merelli I, Perez-Sanchez H, Gesing S, D'Agostino D. Managing, analysing, and integrating big data in medical bioinformatics: open problems and future perspectives. *Biomed Res Int*. 2014;2014:134023.
22. Akbarian S. Epigenetic mechanisms in schizophrenia. *Dialogues Clin Neurosci*. 2014;16:405-417.
23. Kang HJ, Kawasawa YI, Cheng F, et al. Spatio-temporal transcriptome of the human brain. *Nature*. 2011;478:483-489.
24. Crist RE, Lebedev MA. Multielectrode recording in behaving monkeys. In: Nicolelis MAL, ed. *Methods for Neural Ensemble Recordings*. Taylor & Francis Group; 2008.

25. Yoshida K, Go Y, Kushima I, et al. Single-neuron and genetic correlates of autistic behavior in macaque. *Sci Adv*. 2016;2:e1600558.
26. Alper J, Lida A; Institute for Laboratory Animal Research; Roundtable on Science and Welfare in Laboratory Animal Use; National Academies of Sciences Engineering and Medicine (U.S.). *Design, Implementation, Monitoring, and Sharing of Performance Standards for Laboratory Animal Use: Summary of a Workshop*; 2015.
27. Nass SJ, Gorby G; National Cancer Policy Forum (U.S.); National Academies of Sciences Engineering and Medicine (U.S.). *The Role of Clinical Studies for Pets with Naturally Occurring Tumors in Translational Cancer Research: Workshop Summary*; 2015.
28. Atzori L, Iera A, Morabito G. The internet of things: a survey. *Comput Netw*. 2010;54:2787-2805.
29. Alavi M, Leidner DE. Knowledge management and knowledge management systems: conceptual foundations and research issues. *MIS Quarterly*. 2001;25(1):107-136.
30. Carlsson HE, Schapiro SJ, Farah I, Hau J. Use of primates in research: a global overview. *Am J Primatol*. 2004;63:225-237.
31. United States Department of Agriculture. Annual Report Animal Usage by Fiscal Year (2014). United States Department of Agriculture, Animal and Plant Health Inspection Service; 2015.
32. Lappan S, Malaivijitnond S, Radhakrishna S, Riley EP, Ruppert N. The human–primate interface in the New Normal: challenges and opportunities for primatologists in the COVID-19 era and beyond. *Am J Primatol*. 2020;82(8):e23176.
33. Ferdowsian HR, Beck N. Ethical and scientific considerations regarding animal testing and research. *PLoS One*. 2011;6:e24059.
34. Buchanan-Smith HM, Rennie A, Vitale A, Pollo S, Prescott MJ, Morton DB. Harmonising the definition of refinement. *Anim Welf*. 2005;14(4):379-384.
35. Dittus W. An online forum for exchanging ideas for dealing with issues of pest monkeys. *J Primatol*. 2012;1:1-2.
36. Sunstein CR, Nussbaum MC. *Animal Rights: Current Debates and New Directions*. Oxford University Press; 2006.

How to cite this article: Tramacere A, Iriki A. A novel mind-set in primate experimentation: Implications for primate welfare. *Anim Models Exp Med*. 2021;00:1–8. doi:10.1002/ame2.12190