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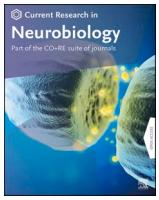

BioSimia, France CNRS network for nonhuman primate biomedical research in infectiology, immunology, and neuroscience

Emmanuel Procyk [a,*], Martine Meunier [b]

[a] University of Lyon 1, Inserm, Stem Cell and Brain Research Institute U1208, 69500 Bron, France
[b] University of Lyon 1, Integrative Multisensory Perception Action and Cognition Team (ImpAct), INSERM U1028, CNRS UMR5292, Lyon Neuroscience Research Center (CRNL), Lyon, France

A B S T R A C T

Research and developments based on nonhuman primate models have a specific place in biomedical sciences, and nonhuman primate species also have a specific place in the public opinion on the use of animal in research. While nonhuman primates are used in very limited number compared to other animal models, they are rightly the focus of deep ethical concerns. The importance of nonhuman primates in neuroscientific fundamental and preclinical discoveries together with the targeting of such research by activist groups well illustrate this fact. Nonhuman primates also highly contribute to other biomedical fields including immunology, virology, or metabolic and respiratory physiology. In all these fields, researchers, engineers and technicians face similar matters and share the same needs for optimal animal welfare, handling, and veterinary care, the same quest for first-rate research infrastructure and funding, and the same yearning for more public understanding and support. In this article, we give an overview of the evolution of human-animal relationships and public attitudes to animal research in France, and we recount the creation of BioSimia, France network for nonhuman primate biomedical research which now links all academic laboratories nationwide in all the domains for which nonhuman primates remain essential. We explain the principles as well as the outcomes of networking across disciplines. As a perspective, we outline the potential benefits of extending such network to a European scale.

1. The evolving French context of human-animal relationship

In 1761, when Claude Bourgelat, an expert horseman, founded the world first veterinary school in Lyon, France, he was mandated by King Louis XV to teach "*the principles and methods involved in curing livestock diseases*". For early veterinarians, the challenge was indeed to improve the health of horses and cattle on which both the military and agriculture depended (Degueurce, 2012). Today, livestock attracts only a minority (19%) of the veterinarians trained at the school founded by Bourgelat; the vast majority of them (73%) dedicate their career to the care of house pets (http://www.vetagro-sup.fr/formations/veterinaire/debouches/accessed on January 24, 2022). Veterinary medicine in France thus mirrors the evolution of human-animal relationships. As in other Western countries, animals are more and more kept only for companionship rather than used for work or food, and their owners often consider them as full-fledged family members (Amiot et al., 2016). The stunning images of civilians carrying their pets, no matter how old or sick, as they flee war-torn Ukraine on foot are a dramatic illustration of the strength of this bond today (https://theconversation.com/the-war-in-ukraine-is-powerfully-magnifying-our-love-for-animals-178867 accessed on April 5, 2022). In 2020, France counted no less than 62 million pets for about 67 million inhabitants and 30 million households. France ranks 4th among EU countries for the number of dogs and has the highest number of cats of the EU, 15 million, sharing the 1st rank with Germany which counts more households (41 million), and outranking the UK, which counts half as many cats for a similar number of households (28 million) (https://www.statista.com/statistics/515410/cat-population-european-union-eu-by-country accessed on March 18, 2022).

"Who would you save? Your dog or a stranger?" "Would you kill one person to save five?" Cognitive psychologists use our responses to such hypothetical dilemmas to explore our moral principles. They have long established that one of our major moral rule is to privilege human life over the lives of non-human animals (Petrinovich et al., 1993). In other words, human moral sense is inherently speciesist. There exists, however, a notable exception to this deep-seated speciesism: pet owners. Substantial proportions of them, 30% of the men and 45% of the women in Topolski et al., 's 2013 US study, prefer to spare their nonhuman companion rather than an unknown human, sacrificing their pet only to save a friend or family member (Topolski et al., 2013). The recent "Moral Machine" experiment (https://www.moralmachine.net/accessed on February 26, 2022), which compared how citizens would want

* Corresponding author.
E-mail address: emmanuel.procyk@inserm.fr (E. Procyk).

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autonomous vehicles to solve moral dilemmas in case of unavoidable accidents across 233 countries, revealed some noteworthy French peculiarities. France shares with the rest of the world three universal moral principles, namely, spare more lives over fewer lives, the young over the old, and people over animals. It stands out, however, from other Western countries (including UK, US, and Canada) by a much stronger preference for sparing the young and women, and a much weaker preference for sparing humans over pets (Awad et al., 2018). The French thus include pets among the vulnerable beings to be spared in priority more than other Westerners.

As the emotional, psychological, and physical connections people have with animals deepened, France has toughened the laws providing legal protection to animals, and has tightened the control of animal welfare. This is true for home animals, as well as for farm and laboratory animals. Domestic animals had been legally protected since 1850, when General Jacques Delmas de Grammont, another horse amateur, convinced the French parliament to vote a law making anyone "*guilty of publicly maltreating animals*" risk a fine of up to 15 francs and a prison sentence of up to 5 days (Pierre, 2007). In 2021, a quasi-unanimous Parliament passed a new law, backed with the same rare French unanimity by 9 out of 10 citizens, raising the maximum penalty for domestic or wild animal abuse to 5 years in prison and a fine of 75,000 euros, and banning or phasing-out a long list of animal uses including farming minks for fur, selling kittens and puppies in pet shops or online, displaying them in shop windows, and making wild animals perform in circuses, aquarium shows, television shows, nightclubs or private parties (https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000044387560 accessed on January 29, 2022).

Farm animals are under the watch of the French Ministry of Agriculture and Food, which has created in 2017 the French Reference Center for Animal Welfare (FRCAW; https://www.cnr-bea.fr/) to overlook their well-being. Farm animals have also found an influential advocate over the last decade with Association L214 (https://www.l214.com), France leading proponent of veganism since 2008. Association L214 has not persuaded many French to forsake their cassoulet, boeuf bourguignon, steak tartare, and other iconic meat dishes of French cooking: in 2020 only 2.2% of them declared following meat-free diets (https://www.franceagrimer.fr/Actualite/Etablissement/2021/VEGETARIENS -ET-FLEXITARIENS-EN-FRANCE-EN-2020accessed on March 8, 2022). The association succeeded, however, to raise meat eaters' awareness of the conditions in intensive animal farming units, live animal transportation, and abattoirs. As a result, France will be the first country in the world, along with Germany, to ban the controversial killing of millions of male chicks in laying hen farms, and implement ovo-sexing by the end of 2022 (https://agriculture.gouv.fr/la-france-sera-le-premier-pays-au-monde-avec-lallemagne-mettre-fin-lelimination-des-poussins-malesaccessed on March 9, 2022).

As for laboratory animals, they are, since January 2013, protected by European Directive (2010)/63/EU, the world strictest regulation of the scientific use of animals (Mitchell et al., 2021). In the French implementation of the EU Directive, every animal facility dedicated to research is licensed and regularly inspected (often unexpectedly and at least once a year for nonhuman primates) by the Ministry of Agriculture and Food, and each scientific project is authorized by the French Ministry of Higher Education, Research, and Innovation, which supervises the 131 French ethics committees dedicated to animal research. Since 1992, the GIRCOR *(Groupe Interprofessionnel de Réflexion et de Communication sur la Recherche*), a nonprofit association founded, as the UK Understanding Animal Research (https://www.understandinganimalresearch.org.uk/accessed on March 16, 2022), by public and private research institutions and pharmaceutical companies, is in charge of informing the French medias and general public about animal research (https://www.gircor.fr/accessed on June 13, 2022). In 2021, the major French public research operators founded the French Center for the Replacement, Refinement, and Reduction of animals in research (FC3Rs) which, like the UK NC3Rs created in 2004 (https://www.nc3rs.org.uk/accessed on March 30, 2022), will be dedicated to the promotion of the Replacement, Reduction, and Refinement approaches in biomedical research. General public attitudes towards animal research in France are evaluated by GIRCOR/IPSOS periodical polls, such as those by IPSOS-Mori in the UK or the Pew Research Center in the US. The latest survey was conducted in September 2021 on 1000 persons aged 16 or older (https://www.gircor.fr/wp-content/uploads/2022/04/ipsos_gircor_les_francais_et_le_recours_aux_animaux_a_des_fins_scientifiques_rapport.pdf.

The proportion of supporters of animal research in France, as estimated by the GIRCOR/IPSOS poll unconditional question "*Are you in favor of or opposed to the use of animals for scientific purposes?*", dwindled from 51% in 2015 to 38% in 2021. Support is much weaker in women (29%) than in men (49%) in keeping with the greater concern for animal welfare characterizing women irrespective of their culture (Randler et al., 2021). Today, approval of the majority of the French population is marshaled only when the "why" and "how" of animal research are duly specified. Support soared to 75%, for example, in the 2021 poll, for the conditional question "*Do you agree that animal use should be allowed for research advancement in the health domain and the development of new medical treatments?*". Even the use of nonhuman primates, frowned upon by many, especially women (48% compared to 24% of men), is deemed acceptable by 63% of the population if there is no alternative and the goal is to advance research on life-threatening diseases. These major increases in public acceptance (+37% in the first example, +27% in the second one) when much-needed contextual information is provided reveals a large "moveable middle" of uncertain people, akin to that recently highlighted in the US (https://speakingofresearch.com/2021/06/16/unveiled-the-moveable-middle-on-animal-research-is- larger-than-we-thought/accessed on April 21, 2022), for which explanations about animal research are necessary. It is therefore up to us, life scientists, to provide context to the public, share our findings and our beliefs in their importance, and explicit what our work can add to the knowledge, health or well-being of our contemporaries and all their family members, including the furry ones.

Informing the "movable middle" is direly needed in France where most (70–80%) people admit to knowing very little about the terms and conditions of the use of animals for scientific purposes. Based upon the GIRCOR/IPSOS 2021 poll, 85–95% of the French have not heard of, or know very little about the regulations and regulatory bodies governing animal research, and 86–90% mistakenly believe that apes are used in research (the EU banned their use in 2013), while fish are not (fish are the 2nd most used animal model after mice in the EU). This amalgam of missing information and misperceptions fuels suspicion and wariness. In 2021, only half of the French trusted scientists to do their most to ensure the well-being of their animals (50%) (https://www.gircor.fr/wp-content/uploads/2022/04/ipsos_gircor_les_francais_et_le_recours_aux_animaux_a_des_fins_scientifiques_rapport.pdf accessed on June 13, 2022). Improving this poor score is an attainable challenge. Farmers, who are the target of anti-speciesism activists as much as scientists (Pistollato et al., 2016; Ceccato et al., 2021), nevertheless enjoy a good image in the eyes of the public. In 2021, the majority of French people trusted farmers (79%) and believed (72%) them to be concerned by animal welfare (https://www.ifop.com/publication/les-francais-leurs-agriculteurs-et-leur-alimentation/accessed on March 16, 2022). Unlike agriculture, whose products we eat or wear everyday, science rarely has an immediate impact on daily life. Discoveries generally take time to find useful applications, e.g. the initial discovery making today's GPS possible dates back to the 19th-century (Ahmadpoor and Jones, 2017). Today's scientists therefore need to find ways to explain their work in the simplest form and link it to everyday life to make it more relevant and appealing to the general public.

Researchers in France are becoming more aware of the necessity to inform the public about the goals and conditions of animal research. A change towards the openness and transparency pioneered by UK

researchers, who have established their positive influence on public support (Mendez et al., 2022), is under way. French scientists are strongly encouraged to provide the general public with a more accurate representation of their work. This was illustrated, on February 22, 2021, by the signature of the "French transparency charter on the use of animals for scientific and regulatory purposes" by many universities, research institutions and biomedical companies. France is thus the fifth country in Europe - after the United Kingdom, Spain, Portugal and Belgium - to sign a national agreement committing its life-science community to speaking openly to policy makers, the media and the general public about the use of animals in biomedical studies.

2. BioSimia network goals and science

About 400 academic laboratories are concerned by animal research in France according to the GIRCOR. They are affiliated to multiple national and governmental institutions like the National Center for Scientific Research (CNRS), the National Institute for Health and Medical Research (Inserm), the health and living science labs of the French Alternative Energies and Atomic Energy Commission (CEA), Institut Pasteur, Ecole Normale Supérieure (ENS) and universities nationwide. In 2020, France used.

1.65 million animals for research, 3996 of them (0.24%) being nonhuman primates, monkeys or prosimians. Compared to the number of animals used for food, these numbers are modest. To provide the average of 84.5 kg of meat eaten by each person every year, the country consumes 500 million chickens per year and keep 47 million laying hens, 13.7 million pigs, 6.6 million sheep and goats, and 5.9 million bovines throughout its territory (https://www.insee.fr/fr/statistiques/2012795 accessed on February 02, 2022).

Among the French government research institutes, the CNRS offers funds to support collaborative national networks, called Groups Of Research (Groupe De Recherche, or GDR), federating academic teams sharing a specific scientific interest (e.g. memory). In 2016, we proposed to the CNRS's life-science institute to create a network (BioSimia) federating all French academic teams whose research in neuroscience, immunology, infectiology, virology, or metabolic and respiratory physiology involves nonhuman primates. BioSimia filled a gap. The existing national networks involving nonhuman primates concerned either all of Primatology, or all animal models, or all private and public users and suppliers of nonhuman primates. No network specifically federated researchers from public laboratories involved in biomedical fields. As in several countries in Europe, French teams working with nonhuman primates were rather isolated, with only usual scientific or personal interactions to share expertise, techniques, issues, and practices. The need for a specific network to build a community and share experiences and practice was obvious.

The CNRS granted BioSimia a 5-year contract starting in January 2017. The objectives were to promote the scientific advances resulting from biomedical primate research, to disseminate methodological innovations and help sharing the know-hows (imaging, pharmacology, chemogenetics, behaviour …), to support scientific and technological developments that replace, reduce, refine (the 3Rs) the use of nonhuman primates in research or improve animal welfare, to stimulate continuous and dynamical interactions within the nonhuman primates research community in France and abroad, and to nurture exchanges with national research agencies and other stakeholders (breeding stations, platforms …).

Nonhuman primate models are at the heart of current international scientific and strategic issues because they open up very directly to clinical applications, overcoming some problems with species jumps imposed by other animal models (Phillips et al., 2014; Roelfsema and Treue, 2014; Friedman et al., 2017). Nonhuman primates in France represent only 0.24% of animals used for scientific purposes, and the species concerned are mainly *Macaca fascicularis* (80%), Rhesus macaques (*Macaca mulatta*), Marmosets (*Callithrix jacchus*), baboons (*Papio papio, Papio anubis*), saïmiris (*Saimiri sciureus*), vervet monkeys (*Chlorocebus sabaeus*) and microcebus (*Microcebus murinus*). By the very nature of the primate models, this research is difficult, but has extraordinary potential both at the fundamental level, to enrich our knowledge, and at the preclinical level, for the development of new therapies. In France, although many of BioSimia's research teams are in the field of neuroscience, the community also includes laboratories and large infrastructures for infectiology and immunology, two other fields for which nonhuman primate models are central.

In the field of fundamental or translational neurosciences, French teams work on aspects very specific to primates such as motor skills of the upper limbs (pointing, prehension, etc.), eye movements, general motor control and basal ganglia, development and anatomy of the cortex (Markov et al., 2013; Dehay et al., 2015; Dehay and Kennedy, 2020), sensory, multi-sensory and attentional processes (Astrand et al., 2016; Perez et al., 2022), memory and executive functions (Stoll et al., 2016; Wirth et al., 2017; Baraduc et al., 2019), and social cognition. Many of these teams work with nonhuman primate models in direct connection with the study of the human brain, for fundamental knowledge, for the development of new therapies and neuroprosthetics, and using models of pathologies and imaging for anatomical studies, cerebral metabolism and the search for peripheral biomarkers. French neuroscientists have also contributed to several recent breakthroughs made possible by nonhuman primate research. New brain-machine interfaces dedicated to locomotion to restore walking to hemiplegic patients have been developed in macaque monkeys (Capogrosso et al., 2016, 2018), work that has led to awesome human applications (Rowald et al., 2022). The development of neuroprostheses, genetic or cellular therapies to preserve sight (Ben M'Barek et al., 2020; Yu-Wai-Man et al., 2020) or to restore vision in patients with total or partial blindness, are based on developments in nonhuman primate models (Blaize et al., 2020; Prévot et al., 2020; Sahel et al., 2021). Primates are the only animal models to possess a macula for high-acuity central vision, hence the importance of the nonhuman primate models for the development of therapies, particularly for age-related macular degeneration (Picaud et al., 2019). Gene and cell therapies in primates open up major avenues for therapeutic innovation in neurology through the use of vectors targeted and functioning on primates. Approaches studied in nonhuman primate models for Parkinson's disease or Huntington's disease have been applied to patients (Jarraya et al., 2009; Palfi et al., 2014, 2018; Aron Badin et al., 2019; Badin et al., 2019). Among the various actors, dedicated infrastructures are precisely intended to accelerate the transformation of discoveries resulting from fundamental research into medical innovations for the treatment of diseases of the nervous system. Primate models have also made it possible to better characterize the principles of transmission and propagation of prion diseases (Gary et al., 2019; Mikol et al., 2021).

Infectiology and immunology are two other major fields in France for which primates are essential. Several teams work on the development of innovative therapies against infectious diseases, on viral infections and autoimmune diseases, on transplantation techniques and on the immunogenicity of grafts or on graft interactions (van der Wiel et al., 2018; Serguera et al., 2019; Mai et al., 2020). Indeed, the cellular effectors, in particular of the immune system, of nonhuman primates are identical or very close to those encountered in humans, thus ensuring the same use of research tools, and a more direct extrapolation of the results obtained in humans. Monkeys are therefore a model of choice for studying host-pathogen relationships and validating candidate vaccines and other innovative therapies such as antibodies. The validation of therapies such as antivirals or vaccines inevitably involves testing on nonhuman primate models. This is currently the case for the COVID-19/SARS-Cov2 crisis, triggering, in fact, a market competition and an international shortage of nonhuman primate models. French institutes play a significant role in the description and pursuit of therapies for COVID 19 (Maisonnasse et al., 2020; Gonçalves et al., 2021; Naninck et al., 2022; Sulbaran et al., 2022) and in the validation of respiratory disease models

(Lemaitre et al., 2021).

3. BioSimia network achievements

The first mission of the GDR was to build a list of the research teams working with nonhuman primates throughout the national territory. Over the years, BioSimia identified over 60 teams working in neuroscience, infectiology, immunology, or physiology laboratories affiliated to universities or national research institutions. From 2017 to 2021, BioSimia forged cross-disciplinary scientific and technical exchanges that did not exist until then, thus building an unprecedented union of the nonhuman primate academic biomedical community. To the best of our knowledge, all nonhuman primate laboratories hosted by government scientific research institutes or by universities in France now adhere to BioSimia. In 2022, this community counts about 470 technicians and scientists who are all committed to the French transparency agreement signed by BioSimia in 2021 and all share the procedures recommended by the consortium (the first national guidelines concerned fluid regulation in neuroscience studies). Every year, the consortium holds a meeting "Les Journées BioSimia" which, thanks to the pandemic, have now a hybrid online and in person attendance (https://biosimia2021.sciencesconf.org/data/BioSimia_Programme_2021.pdf accessed 1 July 2022). In addition to scientific and technical subjects, the meeting includes presentations and round tables on breeding, welfare and its measures, refinements, and reflections on animal and alternative models. In addition, BioSimia sponsored the Marmobrain Workshop an international conference organized in Marseille in 2021, and supported two collaborations between primatologists and biomedical scientists aimed at improving laboratory macaques' welfare through automated testing devices installed in their living quarters. Finally, two websites were created, a collaborative one to host information shared by all its members, and an informative one to provide the general public with facts about nonhuman primate research (https://gdr-biosimia.com/).

Over the years, BioSimia has represented France nonhuman primate academic biomedical community with national bodies such as the regional veterinary services, the National Commission for the Protection of Animals Used for Scientific Purposes (CNEA), and the National committee for ethical reflection on animal experimentation (CNREEA) (drafting of recommendations for good practice on scientific protocols), the GIRCOR, the Ministry of Higher Education, Research and Innovation (working group on the retirement of laboratory monkeys), or at national meetings of the French association for sciences and techniques of laboratory animals. BioSimia also represented the French scientific community at the European level during the public hearings of the EU SCHEER committee in charge of the 2017 re-assessment of European Directive (2010)/63/EU for the European Commission. BioSimia has become an interlocutor to whom the governmental institutions or the scientific community turn to obtain information on the research, training, or any other subject related to nonhuman primates, the interaction within the community leading to the production of recommendations, and standards useable by all laboratory personnel. BioSimia also conducted in 2020 a national survey of its members' unfulfilled scientific objectives due to the COVID pandemic and China's interruption of nonhuman primates exportation, and is currently leading the efforts to manage the current worldwide shortage of laboratory monkeys.

BioSimia concluded its 1st five-year term by writing a White Paper in October 2020 on the present: and future of nonhuman primate research in France, a report made available to the entire community and supervisory authorities.

4. Perspectives

The development of the BioSimia network in the first 5 years has been quite positive and the CNRS has granted the group a 2nd five-year term from 2022 to 2026. Several challenges await BioSimia during its 2nd term. They include 1) stimulating mutual aid around the principles of 3Rs in coordination with the FC3Rs, 2) promoting communication and transparency on nonhuman primate research in accordance with the 2021 National Charter, 3) keeping a sustained activity within the consortium and a constant flow of information between BioSimia and institutional bodies, and BioSimia and the general public, 4) fostering exchanges between academic actors and private actors of nonhuman primate biomedical research, such as pharmaceutical companies and CROs, around common critical issues such as the future of breeding monkeys for research in Europe.

The 2020 pandemic has dramatically highlighted the importance of nonhuman primate biomedical research and development, in this specific case, to understand the coronavirus infection process and to develop and test vaccines or therapeutic strategies. At the same time, the crisis has led to restrictions and ban of international transportations of monkeys in particular from China (one of the main providers of monkeys to the rest of the world). The consequence is massive for European laboratories, further amplified by intense market pressure for access to monkeys with other providers and intense competition with the United States in particular who is massively re-investing in national breeding centres.

As emphasized above, nonhuman primates are central to major domains of research including cancer, vaccine development, infectious disease and brain research. But while infectious, mental and brain diseases lead to multi-billion yearly spending in Europe, and despite health research being one of the major axes of European investments, nonhuman primate research is subject of intense political and societal debates. Important parts of debates are ill-informed being fueled by well-organized activist lobbies. Scientists are not as organized nor as audible and a well-informed debate in society and with political representatives requires scientists to contribute to the debates.

In view of the impacts of the 2020 health crisis on European science and health sectors, BioSimia community observes that the functioning and successes of scientific networking around nonhuman primate models, as in France, might be of interest at the European scale. European biomedical research is currently facing several challenges in terms of scientific sovereignty, development and ethics. A fully functioning scientific network can develop and promote excellence in training researchers and personnel involved with animal research, in promoting high standards of research facilities and animal welfare across European countries, in contributing to the reflexion on animal resources within Europe, in being able to provide help, counselling and sharing of expertise. The scope of such a network would cover all fields of science involving nonhuman primates, hence forming a unique multidisciplinary European consortium.

CRediT authorship contribution statement

Emmanuel Procyk: Conceptualization, Writing – review & editing. **Martine Meunier:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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