Brains, Genes, and Primates: The future of higher research on the planet of the apes

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Caeser, from Planet of the Apes. Credit: peta.org

(Phys.org)—'Brains, Genes, and Primates' is the title of a curious perspective article recently published in the journal *Neuron*. In it, a who's who of dignitaries and luminaries from the field of neuroscience

toss out a life raft to the now ailing vocation that has operated under the umbrella of 'primate neurophysiology'. Beginning with an eclectic mix of primate-exclusive features and skillsets, the authors make the case for the continued necessity of nonhuman primates as essential models for studying the human brain. That salvation comes via the extension to the primate realm of the ability to manipulate the genome and subsequent evo-development of rodents with godlike prowess.

What we are referring to here is gene editing. The question is no longer if and when nonhuman primates should serve as platforms to evaluate these new transgenic techniques, but which species to do it in. Unfortunately for this budding new field, the timing couldn't be worse. Enlightened minds have long demonstrated for more considerate treatment of our monkey brethren, but recent events now suggest that the beginning of the end of that moral battle is already here. Emblematic of the perceived rampant disregard for animal welfare was the dispassionate disaster that ensued in the wake of Hurricane Katrina, where many monkeys perished in their first-floor battery cages at medical research facilities in New Orleans.

More recently, high-profile places like Harvard have moved to wind down their own operations at primate research centers. The coup de grâce, at least for the most egregious kinds primate experiments, was the recent announcement by the head of the Max Planck Institute for Biological Cybernetics in Tübingen, that all macaque experiments would be shuttered 'as quickly as possible' and the lab would switch to rodents. The director, Nikos Logothetis, was and is a neurophysiologist extraordinaire. His work in the mid-nineties included such research classics as 'What is rivalling during binocular rivalry?' Although this kind of work really gets at the core of how brains and minds operate in a way few studies ever will, it demands a lot from its animal subjects in terms of their training regimen and what they must endure as room and board.

It's these kinds things that activists like those at PETA employ to great effect when they picket the entrances at sunny neurosciences conferences. Images of exposed or bleeding craniums of animals bolted into restraints is enough to make even career-hardened neuroscientists question which side of good they are really on. For anyone daring to bring a child along to any of these events, there is simply is justifiable accounting for the truths they would witness, and therefore the conclusions they would draw about the chosen livelihood of their own parents.

At the rodent level, there are several obvious shortcomings the authors point to as far as making advances in our understanding of the brain. For example, the rodent eye lacks a fovea, and as such does not have the oculomotor infrastructure for focusing attention on the world in the way primates do. Rodents do make eye movements, but they are generally reflexive kinetic and vestibular adjustments of a more predictable nature. Similarly, rodents lack much of the same finer provisioning for control of fingers and vocal apparatus. These are the fine instruments for which primates evolved the elaborate outer mantle of their brains.

By a somewhat contorted flow, the authors of the perspective introduce primate gene editing techniques. These include things like zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPRs). The authors note that as it exists now, programmable editing of preimplantation embryos suffers from various inefficiencies including off-target and mosaically-patterned gene modifications. Some of these limitations can be met through various related embryonic stem technologies—cloning by somatic cell nuclear transfer, or with haploid stem cells, for example. One might also creatively pursue the generation of primate primordial germ cells (precursors of both oocytes and spermatozoa), or directly make primate spermatogonial stem cells. The latter persist as a small population in the testis having the unique ability to self-renew and produce 'daughter' spermatids through meiosis throughout adult life.

The obvious need for continued primate testing for things like emergency Ebola vaccines aside, it is far from clear that gene editing and stem cell studies can save the now beleaguered primate research barrack. If not, then what might rescue primate research? The answer may be more obvious than we might we might first casually think. What we need is a win-win both for ape and man, something that is humane, yet capable of producing useful results. One thing to realize is that as higher monkeys, and great apes in particular, grow old and infirm, they suffer from many of the same ailments we do.

Not least of these concerns might be nervous system degeneration—in short, a general loss of brainpower. If researchers take an animal and deafen it to test hearing devices, or give it a gene for a debilitating

demyelinating disease, many folks are going to cry foul. But take an animal that loses their hearing in the ripeness of age and give it a cochlear implant, or one no longer having the will to hunt a deep brain stimulator, and you have flipped the ethics of game back on the aggressor. Yes, it would be prohibitive if those in the animal husbandry business had to wait until their animals died of natural causes before serving them up, but research is more a subtle game.

The real insult to animals both on the farm or in the lab is not how humane the final seconds were as it was sacrificed. Rather, it is the conditions under which they lived their entire lives. The real 'Planet of the Apes' does in fact exist. It is a tiny island in the middle of the Farmington River in Liberia. The sixty or so chimps that make a living there on 'Monkey Island' are survivors of a nearby research facility where they were used in the study of viruses like hepatitis. A local caretaker brings them some fruit each day to help them survive. Although these animals are no longer are used for research, if there was a will and a way, the potential for a win-win collaboration between wild and civil ape clearly exists at places like this.

Several of the specious covenants made between researcher and funder for several huge neuroscience projects around the world are now beginning to come due. As these bonds now mature, and the debtors to the fantastic promises of the Human Eurobrain projects or BRAINI initiatives invariably default, a vacuum is left wanting to be filled. Powerful but incompletely imagined tools, like molecular tickertapes and barcodes to read and store neural connections and activity have now largely fallen by the wayside. Simply bringing any one small part of the research efforts would undoubtedly require extensive cooperation from neurally-accessorized primates.

In the days of yore when Artificial Intelligence researchers talked as much of AI as they did of IA—Intelligence Amplification—research on

the higher primates was a given. Such IA is now the topic of several Darpa initiatives to build so-called RAM implants for augmented memory, 'cortical modems', or other devices that interact with the brain at the level of consciousness. However, the NIH-style labs that gave rise in a bygone era to visions of Altered States are no longer viable today. Instead, its more humane successor, a Monkey Island where willing primate participantes play both neurophysiologial and genetic games may be what is needed for progress.

But before any of that happens, there will need to be equal cooperation between groups like PETA, and groups representing researchers like the Society for Neuroscience (SNS). While there are now nearly as many outreach programs within the SNS as there are meeting subdivisions, there seems to be none for activists. That's because like gun rights proponents, all know that any ground given can unleash an avalanche that buries any liberties enjoyed. On the flip side, those arguing for animal rights have demonstrated zero signs of higher primate behavior in their failure to discriminate the finer points of despair between great ape or worm.

In other words, they generally reserve the same ire for those who would probe a worm as they reserve for those who would keep primates in barren cages, starve and water deprive during training, and bolt into chairs by their heads where they forced them to perform for juice—all the while being the willing reaper of the benefits gained, in both drug or device, from that research.

More information: Brains, Genes, and Primates, *Neuron*, dx.doi.org/10.1016/j.neuron.2015.03.021