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# Critique of Pure Marmoset

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**Abstract**
The common marmoset, a New World (platyrrhine) monkey, is currently being fast-tracked as a non-human primate model species, especially for genetic modification but also as a general-purpose model for research on the brain and behavior bearing on the human condition. Compared to the currently dominant primate model, the catarrhine macaque monkey, marmosets are notable for certain evolutionary specializations, including their propensity for twin births, their very small size (a result of phyletic dwarfism), and features related to their small size (rapid development and relatively short lifespan), which result in these animals yielding experimental results more rapidly and at lower cost. Macaques, however, have their own advantages. Importantly, macaques are more closely related to humans (which are also catarrhine primates) than are marmosets, sharing approximately 20 million more years of common descent, and are demonstrably more similar to humans in a variety of genomic, molecular, and neurobiological characteristics. Furthermore, the very specializations of marmosets that make them attractive as experimental subjects, such as their rapid development and short lifespan, are ways in which marmosets differ from humans and in which macaques more closely resemble humans. These facts warrant careful consideration of the trade-offs between convenience and cost, on the one hand, and biological realism, on the other, in choosing between non-human primate models of human biology. Notwithstanding the advantages marmosets offer as models, prudence requires continued commitment to research on macaques and other primate species.



## Why Primates?

Historically, the most popular mammalian species for experimental neuroscientific research have been members of the rodent order, including rats (especially *Rattus norwegicus*) and mice (*Mus musculus*) [Manger et al., 2008], the latter being increasingly favored in this era of translational research owing to its tractability for genetic manipulation. Rodents have also been favored because of their convenience, being easy to breed and maintain in captivity, and by the belief that the important features of mammalian biology (including neurobiology) are shared widely, if not universally, among mammals [Logan, 2001, 2002].

Notwithstanding the convenience of rodents as research animals, there is increasing evidence of the inadequacy of rodents in translational research, at least for certain disorders [Kolata, 2013; Check Hayden, 2014]. Currently available genetically modified mouse models of human neurological disorders, especially age-related diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease,

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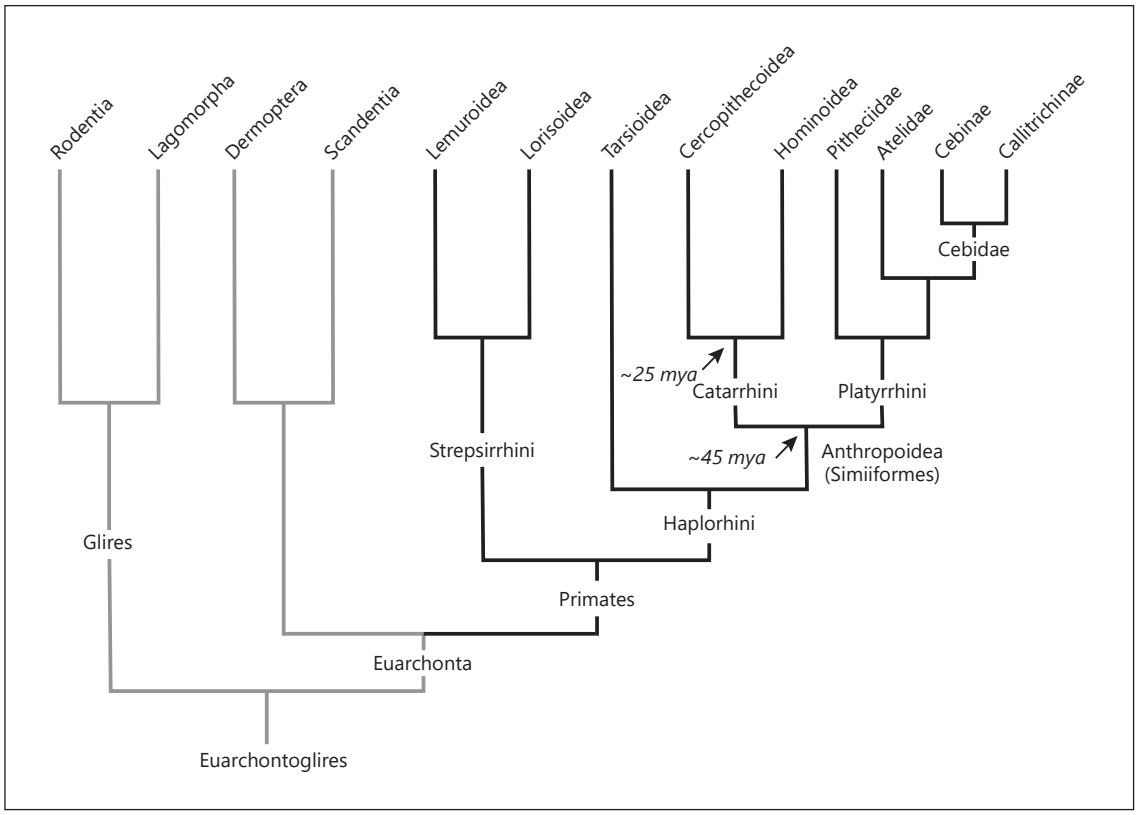


**Fig. 1.** The ordinal and supraordinal phylogeny of the primates. The primates (black lines) are a monophyletic group, the closest relatives of which are the Scandentia (tree shrews) and Dermoptera (colugos or flying lemurs). Together, these clades constitute the Euarchonta. The sister group of the euarchontans is Glires, comprised of the order Rodentia and order Glires (rabbits and pikas). Collectively, these groups constitute the Euarchontoglires. The primate phylogeny is from Fleagle [2013]. The phylogeny of Euarchontoglires is from Murphy et al. [2001].

have failed to reproduce important features of the human disease phenotype [Levine et al., 2004; Li and Li, 2012; Perrin, 2014; Burns et al., 2015; Onos et al., 2016]. Furthermore, drugs developed in rodents frequently do not produce comparable effects in humans [Rittirsch et al., 2007; Hyman, 2012; Perlman, 2016; van Dyck, 2018]. Sometimes, much higher drug doses in rodents are necessary to yield effects seen at lower doses in non-human primates and humans, as for example with the adrenergic α-2A agonist guanfacine [Arnsten, pers. commun.], which has proven useful for treatment of ADHD [Arnsten, 2010] and PTSD [Arnsten et al., 2015]. In addition to the deficiencies of mouse models of neurological diseases, mouse models of human immunology, inflammation, and sepsis have also been found wanting (see Mestas and Hughes [2004], and citations therein), and the genetics of development in rodents and humans differ in important respects [e.g., Liao and Zhang, 2008].

In retrospect, it is not difficult to understand why rodent models of the human brain have important limitations: rather than sharing a common brain organization, comparative studies have revealed that mammals are remarkably diverse. For example, rodents and primates differ in the numbers of cortical areas, the fiber systems that link them, the numbers of neurons in a cortical column, the morphologies of pyramidal and non-pyramidal cells, the pattern of peptide expression by cortical neurons, the regional and laminar distribution of neurotransmitters and receptors, and the embryology of the cortex [for reviews, see Preuss, 2001, 2007, 2010; Hof and Sherwood, 2007; Molnár and Clowry, 2012; Kaas, 2013] – and that is just the anatomy of the cortex! Differences in neuroanatomy and other aspects of brain biology are only to be expected, given the substantial phylogenetic distance between primates and rodents (Fig. 1).

Common marmosets
- Small (~400 g)
- Short gestation (~4.5 months)
- Twin births common
- Rapid development (~1.5 years to adulthood)
- Old-age reached early (~8 years)
- Short-lived (~14–16 years in captivity)
- Small, unconvoluted brains

Rhesus macaques
- Larger (~6.5 kg)
- Longer gestation (6 months)
- Single births
- Slower development (3–5 years to sexual maturity)
- Longer-lived (median = 25+ years; maximun = 40 years)
- Larger, convoluted brains
- Potentially dangerous (herpes B virus), requiring major commitment to engineering and administrative controls, personal protective equipment

**Fig. 2.** Some characteristics of marmosets and macaques relevant to their utility as models of human neurobiology. The marmoset photograph is courtesy of Texas Biomedical Research Institute and Kathy West Studios. The macaque photograph is courtesy of the Yerkes National Primate Research Center, Emory University.

### Why Marmosets?

It is evident that rodent models of the human brain and human neurological diseases have shortcomings that, for many purposes, outweigh the benefits of convenience. The case for models more closely related to humans – non-human primate models, that is – has received new impetus. But in what non-human primate should effort and resources be concentrated? The most intensively studied non-human primates are species of the genus *Macaca*, most commonly *M. mulatta*, the rhesus macaque. Macaques have many advantages: we have had captive colonies for many decades, and know much about their rearing, housing needs, behavior, and neurobiology. Macaques, however, have liabilities as well: they are relatively large, mature slowly, and have a low reproductive rate (compared to smaller primates), are quite aggressive (especially *M. mulatta*), and their saliva and other body fluids and tissues can harbor a virus (macacine herpes virus, also known as herpes B virus) that is potentially lethal to humans [Wisely et al., 2018], necessitating specialized engineering and administrative controls. Collectively, these factors make macaque colonies expensive to establish and maintain, with the result that the number of macaque facilities available to researchers is limited. Moreover, the diversity of primate species available for neuroscientific research has been markedly reduced in recent years.

Recently, support has been growing for increased use of the common marmoset, *Callithrix jacchus*, as a non-human primate model. In this role, marmosets have been placed at the center of the Japanese national brain initiative, the Brain/MINDS project [Cyranoski, 2014; Okano et al., 2016], and the importance of marmosets has been highlighted in recent special issues of *Neuroscience Research* (2015) and *Developmental Neurobiology* (2017) [see especially the essays by Burkart and Finkenwirth, 2015; Mitchell and Leopold, 2015; Miller, 2017]. Interest

in marmosets as research animals is not new: there is, in fact, a long history of research on marmosets, particularly (although not exclusively) in the neurosciences, where the small size of the brain facilitates cortical mapping studies [Miller, 2017]. What is different today is that marmosets have come to be seen as having important advantages compared to macaques. Among the favorable features are their small size, rapid development, rapid reproduction, and a lifespan that is longer than that of mice but shorter than that of macaques [Okano et al., 2012; Sasaki, 2015; Tokuno et al., 2015; Salmon, 2016] (Fig. 2). In addition, marmosets are safer to work with, as they do not carry macacine herpes virus. These factors make them less expensive to rear and maintain than macaques, and the rapid development and short lifespan of marmosets means that studies of brain development and aging can be completed more quickly in marmosets than in macaques. Marmosets also possess features of prosocial behavior that, due to convergent evolution, mirror those of humans, including female-male bonding and aspects of cooperative breeding, such as infant carrying and food sharing by adult males, the infants' siblings, and even non-kin [Fernandez-Duque et al., 2009; Burkart and Finkenwirth, 2015; Erb and Porter, 2017; Schiel and Souto, 2017]. Marmosets are also sometimes said to be monogamous, although they have been observed in the wild to form monogamous, polygynous, and polyandrous groupings [reviewed by Schiel and Souto, 2017].

Marmosets, then, are increasingly being viewed as a general non-human primate model with which to address issues of human behavioral and cognitive neuroscience across the lifespan. Nevertheless, there is no question that the greatest impetus for the current interest in marmosets stems from the opportunity they provide to apply techniques for genetic modification that have been developed in mice to a non-human primate, including the powerful CRISPR/Cas9 techniques [Okano et al., 2012; Kishi et al., 2014; Sasaki, 2015; see also Ledford, 2016]. Compared to macaques, the high rate of reproduction and rapid maturation exhibited by marmosets could accelerate the process of creating and evaluating genetically modified models. American researchers, perceiving the need for marmosets to fill this role, have decried their present lack of availability in the USA [Servick, 2018].

The question I want to address here is whether marmosets are really the best choice as a non-human primate stand-in for humans, paying particular attention to the advantages and disadvantages of marmosets compared to the currently dominant macaque model. My purpose is not to discourage research on one species or the other. In fact, I hold the view that our understanding of the fundamental principles underlying nervous system structure and function benefits from studying a diverse array of species [Preuss, 2000; Preuss and Robert, 2014; Striedter et al., 2014], as does the reconstruction of brain evolution. That said, the variety of primate species available for study by neuroscientists has shrunk dramatically over the past several decades. For this reason, and because of the concentration of resources that must be achieved to develop genetically modified animals, for practical purposes, we have been nearly reduced to having to choose between marmosets and macaques, or some combination of the two. While the choice of marmosets over macaques will seem to many to be an obvious one, given their many practical advantages, I think the case is less clear. To understand why, it is necessary to delve into the phylogeny and comparative biology of primates.

## What Is a Marmoset? A Very Short Course in Primate Phylogeny and Brain Evolution

### *Primate Diversity and Taxonomy*

It is tempting to think of non-human primates as a homogenous entity – "the primate" or "the monkey." Yet primates are a diverse group of mammals consisting of no fewer than 200 species in several major subgroups, varying markedly in ecology, behavior, and social organization [Fleagle, 2013]. With a few exceptions, the composition and relationships among these major subgroups are now largely agreed upon, and in any event the areas of controversy do not affect the following presentation. The platyrrhine primates, which include the marmosets, have historically been one of those exceptions, but there is now broad consensus about the relationships of marmosets and their close relatives, the tamarins and Goeldi's monkey, which collectively constitute the callitrichine subfamily of primates [Schneider and Sampaio, 2015]. For the purposes of this paper, I base the taxonomic terms, phylogenies, and divergence dates mainly on the authoritative treatment of Fleagle [2013]. Additional valuable sources about primate evolution and anatomy include Ankel-Simons [2007], Gebo and Severson [2014], Martin [1990], Ravosa and Dagosto [2007], and Ross and Kay [2004], while Baum and Smith [2012] provide an excellent introduction to modern phylogenetic concepts and methods. Note, however, that while there is now considerable (if not universal) agreement about who is related to whom among primates – that is, the branching order of the primate tree – the same tree can be accommodated

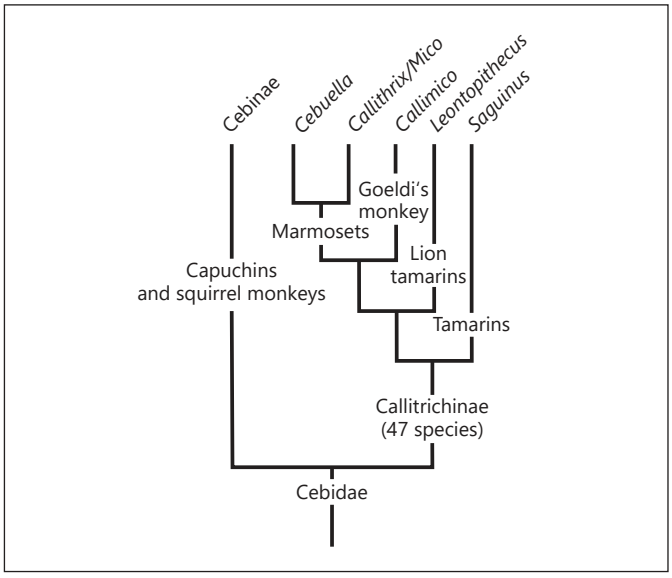


**Fig. 3.** Relationships of the Callitrichinae, a subfamily of the platyrrhine family Cebidae. Based on Fleagle [2013].

within different systems of taxonomic nomenclature. So, for example, the marmosets and their close relatives are classified by some workers as a subfamily (Callitrichinae) and by others as a family (Callitrichidae). Fleagle [2013] treats them as a subfamily and I have adopted that usage. To complicate matters further, while most authorities prefer their taxonomies to consist only of monophyletic groups, others retain older, non-monophyletic taxonomies even when they accept modern interpretations of relationships. So, while most authors accept that tarsiers are more closely related to anthropoid primates than they are to the lemurs and lorises, and so prefer a main division of the primates into Strepsirrhini and Haplorhini, others prefer a more traditional taxonomy, grouping tarsiers with lemurs and lorises in the Prosimii, as distinct from the Anthropoidea (also known as the Simiiformes). Finally, I make little distinction in this paper between common marmosets and other marmoset species, or between rhesus macaques and other macaque species.

*Primate Phylogenetics and Evolutionary Specializations*

Groups of animals are defined by common ancestry; a natural group of animals (a "clade" in phyletic parlance) is the complete set of species descended from a single ancestral species, also known as a "monophyletic" group. The features (character states) of the last common ancestor (LCA) that distinguish a species or a clade from its close relatives (its outgroups) are referred to as its shared derived traits (informally: "specializations"). While comparative molecular data are increasingly used to identify clades and reconstruct their relationships, reconstructing the anatomy of ancestral species typically requires comparative anatomical data from living species, with additional data provided by fossils, when available.

What, then, were the shared, derived traits present in the LCA of the primates? Answering this question requires an examination of the living primate groups, and comparison to their close relatives. The closest relatives of the order Primates are the orders Scandentia (tree shrews) and Dermoptera (flying lemurs or colugos), followed by Glires (the rodent-rabbit group; Fig. 1). The features primates share that distinguish them from these non-primate groups include, among other things, close-set, forward-facing eyes (orbital approximation and convergence, respectively) surrounded by complete bony rings, and grasping extremities with opposable first digits and broad terminal digits tipped with nails rather than claws [Cartmill, 1974, 1992; Martin, 1968; Sussman and Kinzey, 1984] (Fig. 3). The behavioral reconstructions presented in the papers cited above suggest that the primate LCA was nocturnally active and foraged for flowers, fruit, and insects in the terminal branches of trees (the "fine-branch niche") using their nail-tipped digits to grasp branches too fine to be effectively gripped with claws.

We can conduct the same kind of analysis for each of the different primate subgroups. Today, the order Primates is usually considered to consist of two infraorders, Strepsirrhini and Haplorhini. The former consists of two main groups, the lemurs of Madagascar and the loris-galago (bushbaby) group from Africa and Asia. The strepsirrhines are important for comparative analysis because they are in certain respects more conservative evolutionarily than the haplorhines, retaining such ancestral mammalian characteristics as a dog-like wet, hairless nose (rhinarium), and a groove connecting the rhinarium to the vomeronasal organ (VNO), a chemosensory receptor epithelium that in turn sends neural projections to the accessory olfactory bulb (AOB). Moreover, many of the living strepsirrhines are nocturnal, consistent with reconstructions of the primate LCA, and strepsirrhines retain a number of ancestral features of the visual system (to be discussed below).

While strepsirrhines are the "wet-nosed" primates, haplorhines are the "dry-nosed" primates: they lack a wet rhinarium and associated median groove and typically have a shorter snout than the strepsirrhines. The eye is

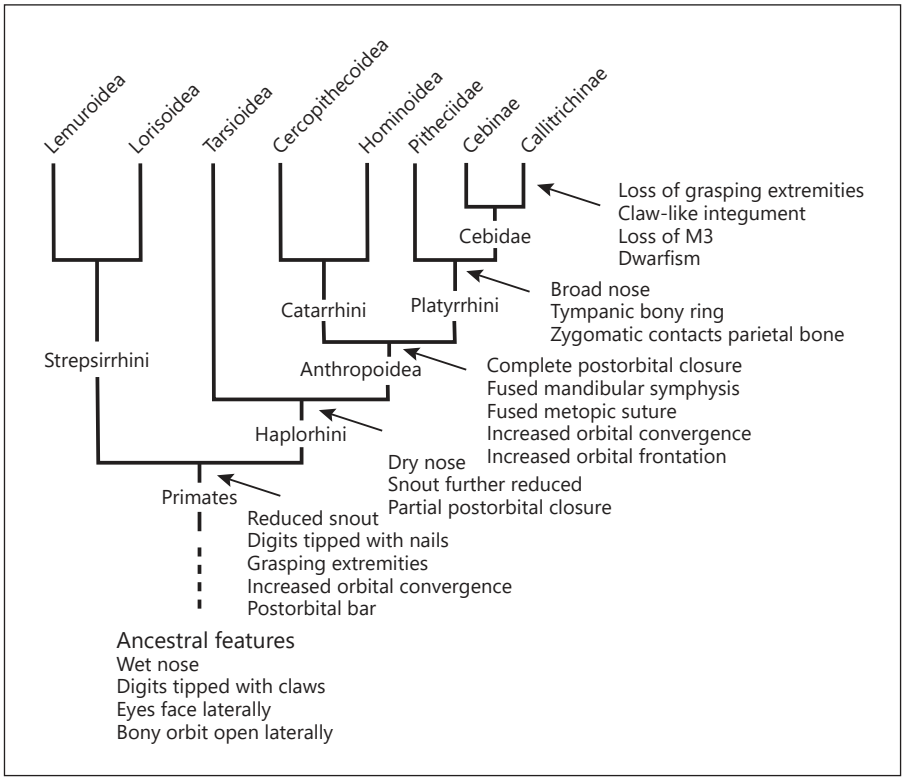


**Fig. 4.** The evolutionary history of the anatomical characteristics of the callitrichines. See the text for citations.

enclosed partially (tarsiers) or virtually completely (anthropoids) posteriorly by a bony plate, and the orbits are set even more closely together than in strepsirrhines [Ross, 1996; Fleagle, 2013]. The haplorhines include the tiny, but huge-eyed, tarsiers and the anthropoids. The species-rich anthropoid group includes the platyrrhines and catarrhines – the New World and Old World anthropoids, respectively. The catarrhines consist of the hominoids (apes and humans) and the cercopithecoids (the Old World "monkeys"). The platyrrhines are usually referred to as the New World "monkeys." Features of the visual system suggest that the haplorhine LCA was diurnal, with nocturnality evolving secondarily in tarsiers and in the platyrrhine owl monkeys.

Anthropoid primates are distinguished from other primates by a variety of modifications of the teeth and skull, as shown in Figure 4. Also, they are generally larger than other primates, and display a wide range of morphologies, social organizations, and behaviors. Among anthropoids, the platyrrhine and catarrhine groups are distinguished by the breadth of the external nose, differences in the sutural patterns of the skull, in the structure of the middle ear, and in the number of teeth in the dental rows (Fig. 4).

*"Monkey" – An Aside*

I have put "monkey" is scare quotes above because the term is problematic, for at least two reasons. For one, it suggests that New World monkeys (platyrrhines) and Old World monkeys (catarrhines; cercopithecoids) are, collectively, a natural group, more closely related to each other than either is to apes and humans. In fact, Old World monkeys are more closely related to apes and humans than they are to New World monkeys (Fig. 1). From a phylogenetic perspective, "monkey" is not a monophyletic group and therefore does not represent a valid biological category [Baum and Smith, 2012].

The problem is amplified by the central place of "monkey" in an older, but highly influential, view of primate evolution, exemplified in the work of the pioneering primate anatomist W.E. Le Gros Clark, whose influential synthesis of primatology, *The Antecedents of Man* [Le Gros Clark, 1959] went through multiple editions. Like most scientists working before the modern era of phylogenetics, Le Gros Clark viewed the primate order as approximating an ascending scale, with tree shrew, lemur, tarsier, monkey, and ape stages, each representing an adaptive grade that increasingly approximates the highest stage, namely humans (Fig. 5). This view of primate evo-

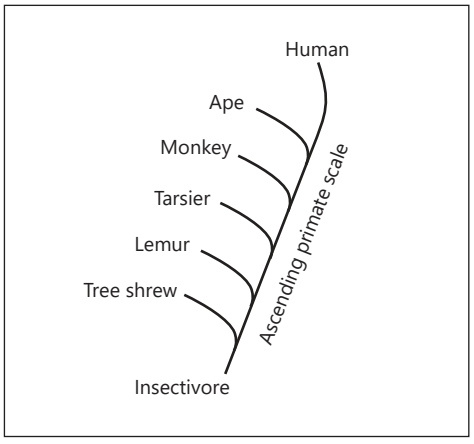


**Fig. 5.** Le Gros Clark's conception of primate evolution as a series of grades, including a monkey grade, culminating in humans [based on Le Gros Clark, 1959]. This older view stands in contrast to the modern conception of primate evolution as being tree-like, and in which Old World monkeys (cercopithecoids) are understood to be more closely related to humans than are New World monkeys (platyrrhines). Note that tree shrews are no longer considered primates (although they are close relatives), and that none of the living insectivore species are considered close relatives of primates.

lution has been rejected by modern evolutionary biologists, who understand evolution in terms of diversification rather than ascent, a view better represented by the metaphor of a tree than by a scale [Baum and Smith, 2012; Preuss and Robert, 2014]. In primatology, this change has come about with the accumulation of knowledge about the differences and similarities displayed by the various primate clades. The idea that the New World platyrrhines and Old World cercopithecoids collectively represent a coherent monkey stage of primate evolution cannot be sustained today, nor can the idea that the living primates form a progressive series from simpler to more complex forms.

*The Marmoset Anatomical Mosaic*

The branching nature of the evolutionary tree implies that any natural group of animals can be understood as displaying a mosaic of features: some shared with its relatives, by virtue of common ancestry, and some distinctive of that group – its derived or specialized features. It is instructive to consider a few of the morphological features that make up the marmoset mosaic (Fig. 4). These include character states inherited from the common ancestor of the primate order, including relatively forward-facing, closely spaced bony orbits. As anthropoids, however, marmosets exhibit even greater convergence of the bony orbits and their eyes are enclosed within a bony cup. As platyrrhines, and in contrast to catarrhines, marmosets have widely spaced nasal apertures and a ring-like tympanic bone to which the tympanic membrane is attached (in contrast to catarrhines, in which the tympanic bone extends laterally to form a tube), and they retain three premolars from their haplorhine ancestors.

Marmosets also possess distinctive specializations. Marmosets and other callitrichines are remarkable for having lost the grasping hands and feet that characterize most primates, and for having transformed the digital nails into claw-like forms. These changes permit callitrichines to cling to tree trunks in order to exploit saps and gums as food sources. As callitrichines, marmosets also exhibit the loss of the most distal molar in the upper and lower tooth rows, which is retained in other platyrrhines and in catarrhines. This may be a consequence of the very small size of callitrichines, compared to other anthropoids. The *C. jacchus* adult body size averages approximately 320 g, which is in the mid-range for callitrichines (approximately 110–620 g), and as a group the callitrichines show no overlap with the size range of other anthropoid primates [Martin, 1992]. The very small size of callitrichines is evidently the result of phyletic dwarfism, a dramatic evolutionary reduction of size from ancestors that were larger [Ford, 1980; Rosenberger, 1984; Sussman and Kinzey, 1984; Martin, 1992; Montgomery and Mundy, 2013].

Whereas callitrichines were once considered primitive anthropoids, recognition of the extensive and remarkable anatomical and behavioral specializations of callitrichines has led to their being characterized as the most specialized of all the platyrrhine primates. As Sussman and Kinsey [1984] put it, "[Callitrichines] have a suite of highly derived morphological features, and they can no longer be regarded as morphologically primitive New World primates." Similarly, Fleagle [2013, p. 109] has concluded, "Callitrichines are the smallest and most morphologically derived New World anthropoids."

*The Marmoset Neuroanatomical Mosaic*

One can carry out a similar exercise with callitrichine and marmoset neurobiological features (Fig. 6). A disproportionate number of these features involve the visual system, likely reflecting the fact that this is the part of the nervous system that has received the most comparative study in primates. For example, callitrichines possess a pair of retinal cone photopigments, namely the short-wavelength sensitive (S) and medium-to-long wavelength sensitive (M/L) opsins [Jacobs, 2008], which they inher-

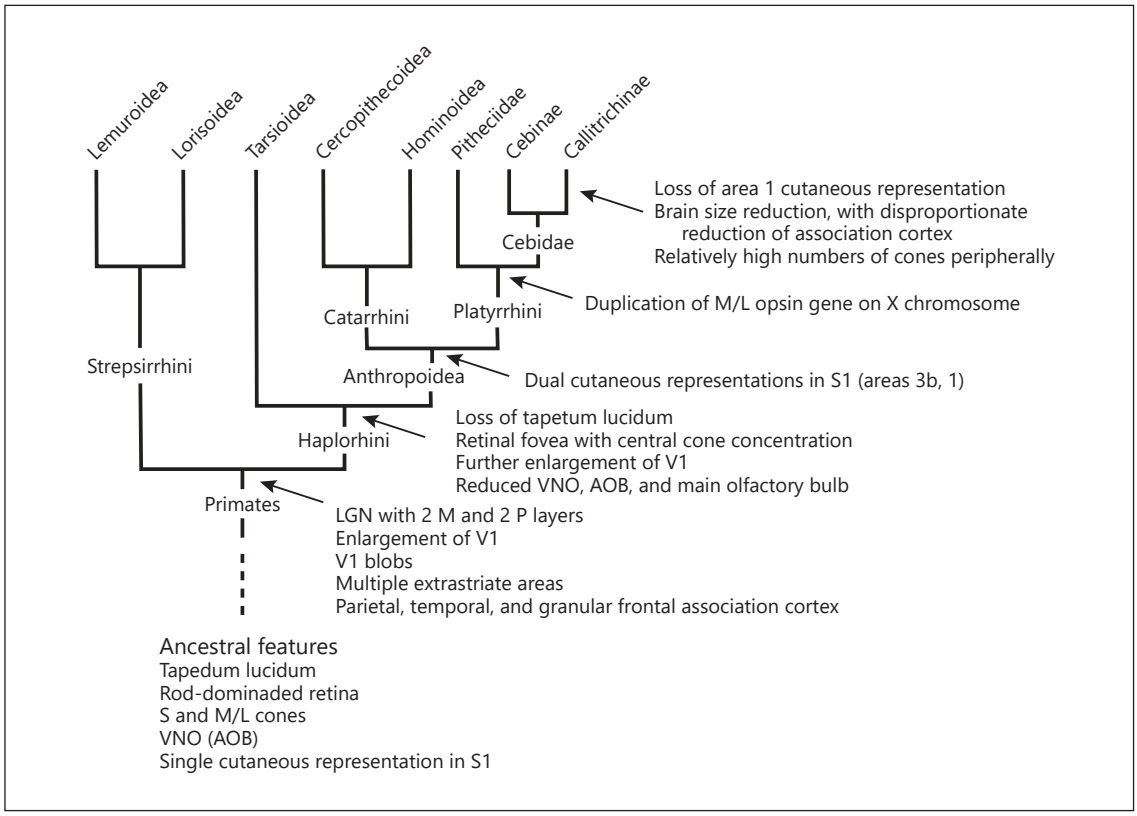


**Fig. 6.** The evolutionary history of the neuroanatomical characteristics of the callitrichines. See the text for citations.

ited from their mammalian ancestors. However, the X-linked M/L opsin gene is polymorphic in callitrichines, as in many other platyrrhines, so that some females are trichromats, whereas the males are dichromats [Jacobs, 2008].

Callitrichines also possess a host of features inherited from early primates that appear to be primate specializations. These include an enlarged primary visual area (area V1) [Stephan et al., 1981], and a lateral geniculate nucleus (LGN) that has four main layers, two magnocellular and two parvocellular [Le Gros Clark, 1941; Kaas et al., 1978; Solomon and Rosa, 2014]. In some other anthropoids, such as macaques and humans (but not all other platyrrhines and catarrhines), the parvocellular layers have split and interdigitated, creating the appearance of a six-layered LGN [Kaas et al., 1978]. Marmosets also possess cytochrome oxidase-rich "blobs" in the primary visual area [Solomon, 2002; Solomon and Rosa, 2014], which receive projections from the koniocellular cells of the LGN, cells that reside outside the magnocellular and parvocellular layers. This is a specialization of primate area V1 [Horton and Hubel, 1981; Horton, 1984; Preuss and Kaas, 1996], although similar features evolved convergently in carnivores [Murphy et al., 1995].

Callitrichines also share with haplorhines and with other anthropoids modifications of the visual system related to the change from ancestral primate nocturnality to diurnality [Ross, 1996] (Fig. 6). Among these are the loss of a reflecting tapetum lucidum, which enhances nocturnal visual sensitivity and is present in strepsirrhines and many other mammals [Martin, 1990, pp. 298–300; Ollivier et al., 2004; Peichl, 2005]. Also, like most haplorhines, but unlike most strepsirrhines [Ross, 1996; Collins et al., 2005], callitrichines possess a retinal fovea, with a concentration of cones in and around the fovea [Troilo et al., 1993; Finlay et al., 2008]. Additionally, whereas area V1 in the catarrhines that have been examined show clear segregation of projections from the LGN representing the left and right eyes [Horton, 1984; LeVay et al., 1985; Horton et al., 1990; Florence and Kaas, 1992; Cheng et al., 2001; Adams et al., 2007], in callitrichines and several other platyrrhine taxa, the degree of segrega-

tion may be more variable or reduced [Hendrickson et al., 1978; Livingstone, 1996; Sengpiel et al., 1996; Roe et al., 2005].

As in strepsirrhines and in other anthropoids that have been studied [Rosa and Tweedale, 2005; Lyon, 2006], marmosets possess a large number of extrastriate visual areas, divisible into dorsal and ventral systems, and including the higher-order outposts of the visual system in the posterior parietal cortex and inferotemporal cortex [Rosa and Krubitzer, 1999; Paxinos et al., 2012; Atapour et al., 2018]. Marmosets possess additional regions of primate-specific, higher-order territories: these include the granular areas of the dorsolateral prefrontal cortex [Burman et al., 2006; Burman et al., 2011], which are unique to primates [Preuss, 1995; Passingham and Wise, 2012]. Marmosets possess primate-specific limbic cortices [Preuss and Goldman-Rakic, 1991b; Vogt et al., 2013; Vogt and Paxinos, 2014], including posterior cingulate areas 23 and 31 [Armstrong, 1985; Zilles et al., 1986] and the posterior parahippocampal cortex [Palmer and Rosa, 2006]. Finally, marmosets, like other strepsirrhine and anthropoid primates, possess a dorsal pulvinar (also known as medial pulvinar) nucleus [Brysch et al., 1990; Hackett et al., 1998; Roberts et al., 2007], a structure that appears to be unique to primates and is connected mainly with higher-order frontal, parietal, temporal, and limbic cortical areas [Preuss, 2007].

In addition to these primate specializations, callitrichines share with other haplorhines a reduction of the main olfactory bulb and AOB compared to early primates (Fig. 6), which themselves had reduced these structures relative to their mammalian ancestors [Stephan et al., 1981; Barton, 2006]. In catarrhines, the major elements of the accessory olfactory system (VNO and AOB) are absent or vestigial in adults [Bhatnagar and Smith, 2007; Smith et al., 2014]. However, the VNO and AOB remain present in callitrichines and evidently in most other platyrrhines [Smith et al., 2004; Bhatnagar and Smith, 2007; Smith et al., 2011], and consistent with this, vomeronasal receptor genes that appear to be functional are present in callitrichines [Moriya-Ito et al., 2018]. Thus, the accessory olfactory system, including VNO and AOB, is probably functional in callitrichines, but not in catarrhines.

Callitrichines also possess a number of neuroanatomical specializations that evolved after their separation from other platyrrhines (Fig. 6). For one, marmosets and tamarins are reported to have higher densities of cones in the peripheral retina (particularly in the nasal retina) than do other platyrrhines or catarrhines [Troilo et al., 1993; Finlay et al., 2008]. In the somatosensory cortex, all anthropoid primates that have been examined, with the exception of callitrichines, have a pair of representations of the body surface's cutaneous receptors, occupying areas 3b and 1 of the primary somatosensory region (S1) [Kaas, 1983; Padberg et al., 2007]. The callitrichines, however, have only a single cutaneous representation, corresponding to area 3b [Carlson et al., 1986; Krubitzer and Kaas, 1990]. Callitrichines also lack monosynaptic projections of corticospinal neurons onto the motor neurons of the spinal cord ventral horn [Kondo et al., 2015]. In this, callitrichines differ from *Homo* and *Macaca*, among catarrhines, and at least *Cebus* among platyrrhines – all animals with well-developed digital opposability and grasping abilities [reviewed by Padberg et al., 2007]. These features of the somatosensory and motor systems may be related to callitrichine modifications of gross anatomy and locomotor behavior: it seems plausible that with the anatomical transformation of flattened nails into claw-like forms, and the behavioral change from digital grasping to gripping with the claws, there was a reduction in the role of sensory feedback from the digital pads and nail beds to the corticospinal system.

Callitrichines also have very small brains, much smaller in absolute terms than those of any other anthropoids, and among the smallest relative to body size [Isler et al., 2008]. While data on the size of higher-order cortical regions relative to the rest of the cortex are not available for comparing marmosets to other primates, visual inspection of recent marmoset cortical maps [Paxinos et al., 2012; Majka et al., 2016; Atapour et al., 2018] and quantitative analysis of regional size change [Chaplin et al., 2013] suggest that portions of the prefrontal cortex are smaller in marmosets than in other, larger-brained platyrrhines (*Cebus* [Cruz-Rizzolo et al., 2011]) and catarrhines (*Macaca* and *Homo* [Preuss and Goldman-Rakic, 1991a; Petrides and Pandya, 1999; Sallet et al., 2013; Markov et al., 2014; Neubert et al., 2014; Glasser et al., 2016]). Chaplin et al. [2013] identified the temporoparietal junction cortex and anterior cingulate cortex as additional regions that are relatively larger in macaques and humans than in marmosets.

*Marmosets Compared to Macaques*

It is useful to summarize some features shared by marmosets and macaques and those they do not share (Fig. 7). Marmosets and macaques share a number of features by virtue of being primates (reduced main olfactory bulbs, V1 blobs; multiple extrastriate areas divisible into dorsal and ventral streams, new higher-order association areas, addition of the dorsal pulvinar) and by virtue of being

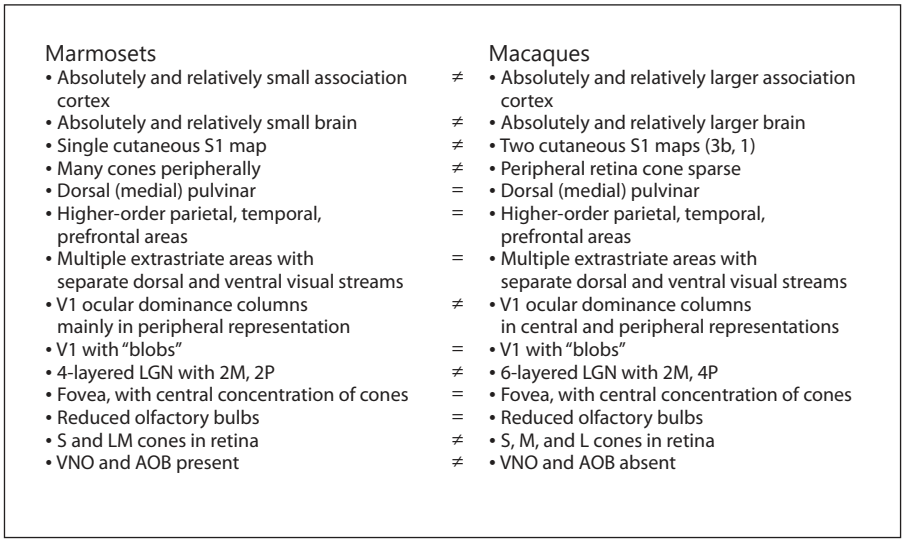


**Fig. 7.** A comparison of neuroanatomical features of marmosets and macaques discussed in the text, indicating points of similarity (=) and difference (≠).

anthropoid primates (a fovea, with a central concentration of cones). In addition, there are features of ancestral primates and ancestral anthropoids that marmosets and macaques do not share, notably the accessory olfactory system (present in marmosets, absent or vestigial in macaques and other catarrhines). The visual systems of marmosets and macaques also differ in a number of respects that mainly reflect catarrhine specializations, involving opsin proteins, the LGN, and the primary visual area. Finally, marmosets differ from macaques in ways that reflect callitrichine specializations, including differences in the retinal distribution of photoreceptors and in the sensorimotor cortex, and a likely reduction of brain size that disproportionately affected the higher-order association cortex.

Despite the limitations of the comparative neuroanatomical data set, it is clear that marmosets are, in a variety of ways, more different from humans than are macaques. That is not to say that macaques do not also differ from humans in significant ways – they clearly do. Even in the visual system, commonly considered to differ only in minor, quantitative ways between humans and macaques, one can in fact identify numerous differences at all levels of the visual system [Preuss, 2004; Preuss and Robert, 2014]. Every clade has its own mosaic of features, including its own specializations, and macaques are no exception. Nevertheless, for the purpose of modeling the human condition, macaques (along with other catarrhines) have the advantage of being much more closely related to humans than are marmosets, sharing about 20 million years of additional common ancestry (Fig. 1). Furthermore, human-macaque comparisons are uncomplicated by the platyrrhine and callitrichine specializations present in marmosets, and by the retention in marmosets of ancestral features lost in catarrhines (Fig. 6, 7).

## Additional Considerations

The foregoing discussion has focused on anatomical features of the nervous system, primarily because anatomy has received more comparative study than other dimensions of nervous system organization. As our knowledge of primate neurobiology grows, so will the number of different characters that can be evaluated, and, assuming we study a large enough variety of species, this knowledge will extend beyond anatomical features to include life history and behavior, on the one hand, and biochemistry, molecular biology, and genomics, on the other. Even with the limited information currently available, however, there is evidence for additional differences between callitrichines and catarrhines that likely bear on the utility of marmosets as stand-ins for humans in experimental studies.

I have noted above some differences in aspects of higher-order cortical organization between the small-brained marmosets and the larger-brained platyrrhines and catarrhines. The very small size of the marmoset brain makes it very likely that the functions of its cortical systems differ in important ways from those of larger-brained primates, if only because of the much more limited amount of neural machinery marmosets and other callitrichines

have to work with. In this regard, it is significant that two recent meta-analyses concluded that absolute brain size is a better predictor of cognitive function than is brain size relative to body size [Reader et al., 2011; Deaner et al., 2007] and a third indicated that absolute brain size is the best predictor of self-control [Maclean et al., 2014].

Given the small size and rapid development of marmosets, it is tempting to view marmoset life history as a condensed version of that of longer-lived primates. Yet there is evidence primates vary in patterns of postnatal growth and development. Bogin [2007] indicates that cercopithecoid and hominoid development includes an extended period of slow growth, defining a juvenile stage that has no counterpart in marmosets. This difference, and the specializations of human development recognized by Bogin – namely, the addition of childhood and adolescent stages – imply differences in the hormonal control of development [Bogin, 2009]. It is noteworthy that comparative studies of humans, macaques, and marmosets have identified remarkable species differences in the production of the androgen hormone dehydroepiandrosterone (DHEA) [Abbott and Bird, 2009], which is involved in sexual maturation. There is also a remarkable sex difference in marmosets, with adult males lacking a functional *zona reticularis* [Pattison et al., 2009], the component of the adrenal gland that produces most of the body's DHEA.

Callitrichines, like humans, engage in prosocial behaviors that are unusual among primates. These include cooperative breeding, in which adult males as well as females participate in carrying and sharing food with offspring, and alloparenting, in which other individuals, both related to and unrelated to the mother, contribute to the support of her offspring [Fernandez-Duque et al., 2009; Erb and Porter, 2017]. These have been cited as possible instances of convergent evolution in the human and callitrichine clades [Burkart and Finkenwirth, 2015], and there are other behavioral and cognitive similarities between humans and marmosets [Miller et al., 2016] that could be viewed in the same light. In evolutionary biology, convergence is considered to provide information about the similarities in selection pressures that shape similar phenotypes [Arendt and Reznick, 2008]. Convergence may not be what one is looking for in a human model, however, as convergently evolved features of social behavior or other phenotypes need not share homologous neural and genetic underpinnings [Arendt and Reznick, 2008]. Moreover, the proximate mechanisms regulating social behavior in callitrichines likely differ from those of humans in some important respects, considering that callitrichines mark their substrates, and sometimes other group members, with a mixture of urine and circumgenital secretions, and these chemical cues have been postulated to regulate the reproductive physiology of group individuals [Epple, 1970; Abbott et al., 1997; Lazaro-Perea et al., 1999; Smith et al., 2001]. As in many other mammalian groups, detection of such cues likely involves the accessory olfactory system, which is absent or vestigial in catarrhines, as discussed above.

Callitrichines are highly unusual among mammals in that their dizygotic twins exchange cell lines very early in development, resulting in genetically chimeric individuals [Benirschke et al., 1962; Gengozian et al., 1964]. Although the range of tissues that exhibit chimerism is controversial (compare Ross et al. [2007] and Sweeney et al. [2012]), it is clear that it involves hematopoietic tissues, such as blood and lymph cells, and possibly also germline tissues [Sweeney et al., 2012]. Chimerism could complicate the interpretation of genetic modification experiments because the presence of a modified gene in blood cells collected in routine assays would not necessarily indicate its presence in neural cells. In addition, the analysis of phenotypic responses in experiments involving brain damage, infection, inflammation, and aging could be complicated by the fact that macrophages and other components of the immune system that infiltrate brain tissue in these conditions are derived from hematopoietic cells.

There are numerous differences in the distribution of receptors in the cortex of marmosets compared to catarrhines (based mainly on studies of macaques and humans). These include differences in the regional and laminar distribution of adrenergic α1, muscarinic M1 and M2, and serotonergic 5-$HT_2$ receptors in the hippocampus [Kraemer et al., 1995] and in the laminar distribution of $GABA_A$ and 5-$HT_1$ receptors in the primary visual cortex [Gebhard et al., 1993]. Given the lack of evidence about receptor distribution in platyrrhines other than marmosets, it is unclear whether these represent differences between platyrrhines and catarrhines or between marmosets and catarrhines or, most likely, some combination of both. There is evidence for additional molecular and biochemical differences as well, for example, in the distribution and concentrations of manganese and zinc in marmoset and human brains [Knauer et al., 2017], and in the neuroendocrinology of stress and reproduction between platyrrhines and catarrhines [Bercovitch and Ziegler, 2002; Abbott et al., 2003].

The existence of differences such as these should not be surprising, given the longer period of shared ancestry between humans and macaques compared to humans

and marmosets (Fig. 1). The greater shared ancestry of humans and macaques is reflected in genomic similarities as well: the genome-wide identity of amino-acid coding nucleotide sequences is 94.0% for macaques and humans, compared to 91.7% for marmosets and humans [Harris and Rogers, pers. commun.; see also Worley et al., 2014]. Given that chimpanzees and humans, which are even more similar genetically, exhibit a remarkable diversity of genomic, molecular, and biochemical differences [e.g., Konopka et al., 2012; Bauernfeind et al., 2015; Reilly et al., 2015; Mora-Bermúdez et al., 2016; Li et al., 2017], there is a great deal of room for molecular and biochemical differences between marmosets and humans, and corresponding differences in nervous system organization and function. In fact, a recent comparison of human-marmoset orthologs [Harris, pers. commun.] provides evidence for selection acting on marmoset genes, identifying 49 potentially positively selected genes at $p < 0.01$ with a role in the brain, based on Gene Ontology Biological Process terms (the analysis employed HyPhy aBSREL [Smith et al., 2015] to evaluate the selection on orthologs identified in Ensembl v.91 [Herrero et al., 2016]).

## Conclusions

Given the variability of primate brain organization, how do we choose the model or models most relevant for understanding the human brain and behavior? In view of the decreasing diversity of primate species available for research, and the growing imperative to generate genetically modified primate models, we are likely faced with the choice of marmosets or macaques or some combination of both. Therefore, it is important to evaluate the relative merits of marmosets and macaques, as non-human primate models for understanding the human brain and behavior. From the standpoint of cost and convenience, marmosets have some clear advantages, such as their rapid rate of growth and reproduction, which provide the potential for the speedier development of genetically modified models and for the speedier completion of developmental and aging studies. From a purely biological standpoint, however, macaques have clear advantages over marmosets: they have more in common with us, owing to our closer phylogenetic relationship.

There are additional points in favor of macaques. Compared to marmosets, we have much more experience with macaque husbandry and with the assessment of macaque neurobiology and behavior, including changes across the lifespan. It should be remembered, too, that the very characteristics of marmosets that make them convenient experimentally for the purposes of genetic modification, studies of development and aging, and cortical mapping – their small size, rapid development, and short lifespan, which are all likely related to the callitrichine specialization of dwarfing – are ways in which marmosets differ from humans but in which macaques are more like humans (Fig. 2). Finally, while it is clear that marmosets offer advantages for genetic modification, it is not clear that these advantages involve anything more than cost and speed of development: the same procedures appear to be feasible in macaques, and in fact China's brain project, which includes gene-editing approaches, focuses on macaques [Poo et al., 2016].

From a research-resources perspective, if the question is how best to understand the features of human brain organization that cannot be studied directly in humans, the best solution (in lieu of even broader studies) would be to study both macaques and marmosets. Studying multiple species is necessary for reconstructing evolutionary history and, in particular, for disambiguating features shared among larger groups from the specializations of subgroups. So, for example, features shared by both macaques and marmosets are likely to have been present in the immediate ancestry of catarrhines (including humans), whereas features present only in macaques, for example, might be shared derived features of macaques, or of cercopithecoids, or of catarrhines, or of anthropoids, and so forth down the phylogenetic tree – there is no way to tell by studying only macaques. Analogous considerations apply to research limited to marmosets. Therefore, we should view marmoset and macaque research as complementary [see also Mitchell and Leopold, 2015; Miller, 2017]. If we could only study one animal from which to extrapolate results to humans, the choice would necessarily be macaques, given their longer period of shared ancestry with humans – the likelihood of a given feature of macaques having a homologue in humans is greater than for a given feature of marmosets. However, it would be extremely unfortunate if we were forced to make that choice, as it would be inimical to good science.

If the question is, what animal is best for genetic modification, measured as the rate at which translatable results can be obtained, the answer is less clear, depending as it does on two unknown quantities: the rate at which models can be developed and the likelihood that a model will yield results that translate to humans. Marmosets probably have the edge with respect to model development, whereas macaques probably have the edge in trans-

latability. We could perhaps narrow this knowledge gap by carrying out parallel pilot experiments in macaques and marmosets to try to estimate those rates. However, obtaining translatable results for a single gene in one species is no guarantee that other genes will yield favorable results in that species. Moreover, it is entirely possible that neither macaques nor marmosets will provide translatable results for a given gene of interest, but that some other primate (or even non-primate) species will. The most reasonable strategy would be to hedge our bets, devoting some resources to marmosets, while maintaining a robust investment in macaques. One hopes, too, that we will ultimately be able to expand the range of primate and non-primate species to which we can apply gene editing and other advanced research techniques.

Practitioners of genetic modification, hoping for a rapid transition from mice to primates and wishing to regard marmosets as "the new mouse," might find these prescriptions unsatisfactory. But just as the mouse model, convenient as it is, has run afoul of the diversity of mammalian biology, so might the marmoset model run afoul of the diversity of primate biology. Be careful what you wish for.


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## Disclosure Statement

The author has no conflicts of interest to declare.

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