



Hedonic eating, obesity, and addiction result from increased neuropeptide Y in the nucleus accumbens during human evolution

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Contributed by C. Owen Lovejoy; received July 3, 2023; accepted July 25, 2023; reviewed by Clark S. Larsen and Robert M. Sapolsky

The nucleus accumbens (NAc) is central to motivation and action, exhibiting one of the highest densities of neuropeptide Y (NPY) in the brain. Within the NAc, NPY plays a role in reward and is involved in emotional behavior and in increasing alcohol and drug addiction and fat intake. Here, we examined NPY innervation and neurons of the NAc in humans and other anthropoid primates in order to determine whether there are differences among these various species that would correspond to behavioral or life history variables. We quantified NPY-immunoreactive axons and neurons in the NAc of 13 primate species, including humans, great apes, and monkeys. Our data show that the human brain is unique among primates in having denser NPY innervation within the NAc, as measured by axon length density to neuron density, even after accounting for brain size. Combined with our previous finding of increased dopaminergic innervation in the same region, our results suggest that the neurochemical profile of the human NAc appears to have rendered our species uniquely susceptible to neurophysiological conditions such as addiction. The increase in NPY specific to the NAc may represent an adaptation that favors fat intake and contributes to an increased vulnerability to eating disorders, obesity, as well as alcohol and drug dependence. Along with our findings for dopamine, these deeply rooted structural attributes of the human brain are likely to have emerged early in the human clade, laying the groundwork for later brain expansion and the development of cognitive and behavioral specializations.

neuropeptide Y | NPY | human evolution | human origins | reward pathway

The mesolimbic dopaminergic reward pathway is a primary element in the evolutionary selection of species-typical behaviors. This pathway directly integrates environmental context with internal physiological cues to yield potentially novel adaptive behaviors (1). Major elements of the pathway include regions of the striatum, ventral striatum, amygdala, hippocampus, lateral septum, and bed nucleus of the stria terminalis with dopaminergic projections from the ventral tegmental area. Dopamine (DA) within this system reinforces specific behaviors through its effects on motivation and reward (1, 2).

We previously reported that humans have increased dopaminergic innervation of the nucleus accumbens (NAc), ventral pallidum, and specific regions of the dorsal striatum relative to nonhuman primates, as measured by tyrosine hydroxylase-immunoreactive axons (3–6). Dopamine elevation in these regions likely plays a role in human-specific cognitive and behavioral specializations, as well as increased susceptibility to addictive behaviors and related neuropathological processes. Comparative analyses of the neurochemical profiles of structures within the reward system can provide valuable insight into the evolution of species-specific life history variables, such as mating strategy, diet, and the behavioral correlates thereof, while also shedding light on differential susceptibilities to neuropathologies. We therefore endeavored to enhance our understanding of this system based on a comparative analysis of neuropeptide Y (NPY) within the NAc across a wide range of primate species.

The NAc is the ventromedial portion of the ventral striatum. It exhibits connections to the amygdala and prefrontal cortex and is part of the mesolimbic dopaminergic reward pathway (7–10). The NAc has been demonstrated to play significant roles in food intake, reward and motivation, social and sexual behavior, and substance abuse. It is known to be involved in depression, anxiety, addiction (e.g., to alcohol, drugs of abuse, nicotine), attention deficit hyperactivity disorder, and posttraumatic stress disorder (11–14).

NPY is a 36 amino acid peptide that is conserved among vertebrates and a member of the pancreatic polypeptide (PP) family that was first described by Tatemoto et al. (15). It is found throughout the brain, with high densities in the hypothalamus, amygdala, NAc, hippocampus, and periaqueductal grey (16, 17). Five NPY receptors (Y1, Y2, Y4, Y5, and

Significance

Studies of human brain evolution have traditionally concentrated on the cerebral cortex, which is significantly larger than those of other primates. However, the more central and ancient portion of our brain is not enlarged and houses the nucleus accumbens, which is cardinal in the brain's reward pathway. The neurotransmitter neuropeptide Y promotes fat and sugar-seeking behavior when injected into the nucleus accumbens and is elevated in our species compared to other primates. Vigorous fat- and sugar-seeking behavior probably permitted our cerebral cortex to expand early in our evolution, but now appears to encourage syndromes associated with excessive fat and sugar intake, as well as drug and alcohol addiction. We are thus essentially wired for hedonic eating and addictive behaviors.

Author contributions: M.A.R. designed research; M.A.R., D.N.J., H.N.S., E.L.M., and M.K.E. performed research; K.A.P., W.D.H., P.R.H., and C.C.S. contributed new reagents/analytic tools; M.A.R. and E.N.M. analyzed data; and M.A.R. and C.O.L. wrote the paper.

Reviewers: C.S.L., The Ohio State University; and R.M.S., Stanford University.

The authors declare no competing interest.

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This article contains supporting information online at <https://www.pnas.org/lookup/suppl/doi:10.1073/pnas.2311118120/-DCSupplemental>.

Published September 11, 2023.

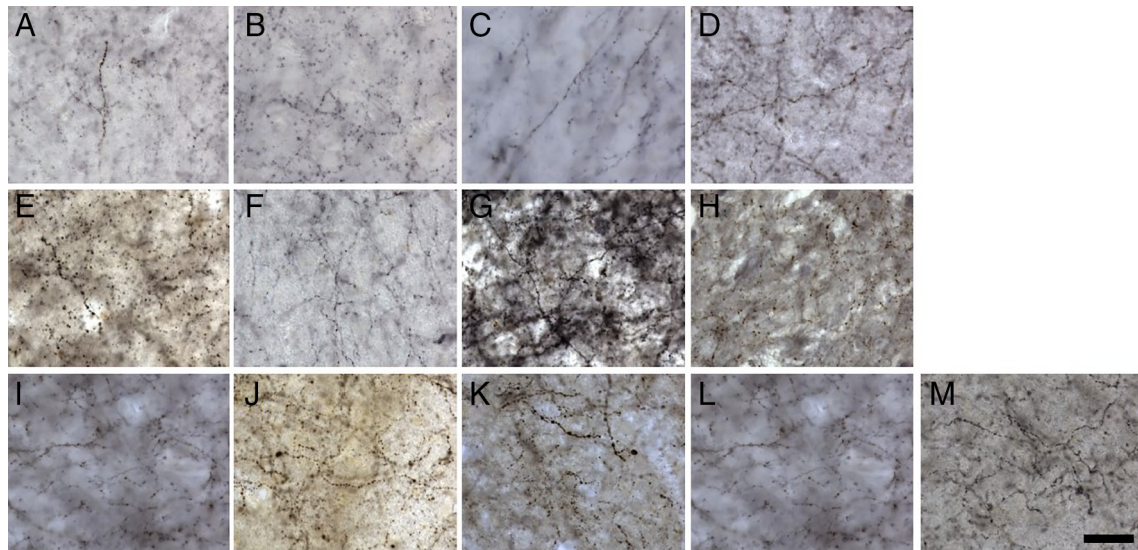


Fig. 1. Photomicrographs showing NPY-immunoreactive axons within the nucleus accumbens for each species included in this study. (A) marmoset; (B) tamarin; (C) owl monkey; (D) capuchin; (E) rhesus macaque; (F) pig-tailed macaque; (G) Japanese macaque; (H) moor macaque; (I) baboon; (J) gorilla; (K) chimpanzee; (L) bonobo; (M) human. Scale bar in M, 25 μ m and applies to all panels.

Y6) have been characterized to be G-protein-linked receptors regulated through $G_{i/o}$ proteins. Y1, Y2, and Y5 are the principal receptors within the brain, with Y1 densely expressed within the NAc (18, 19). NPY innervation of the NAc is derived from local interneurons and axons from GABAergic projection neurons in the arcuate nucleus (20).

NPY is associated with reward in the NAc and influences a variety of interconnected behaviors that moderate species-typical patterns. The reward function of NPY in the NAc is demonstrated by its induction of “conditioned place preference” in response to intracumbens NPY injections (21, 22). Infusions of NPY or a Y1 receptor agonist increase prosocial behaviors in mice (23). This may be due to the anxiolytic effects of NPY (24), or NPY may possibly increase the rewarding properties of the social encounter itself (23). NPY neurons within the NAc modulate anxiety-like behavior, with ablation of NPY neurons increasing, and activation of NAc NPY neurons decreasing anxiety-like behaviors (25).

Moreover, manipulation of NPY within the NAc has demonstrated that NPY has roles in alcohol and drug addiction, fat intake, and emotional behaviors (20, 26, 27). NPY has one of the most highly enriched transcripts in the human NAc, suggesting that this neuropeptide may uniquely contribute to human motivations and behaviors (28, 29). The present study explores the possibility of disproportionately greater NPY innervation of the NAc of humans as evidenced by a quantitative comparative analysis of humans, great apes, and both catarrhine and platyrrhine monkeys. We also evaluated neuron and glia densities and their ratios within the NAc to evaluate their scaling relationships.

Results

Immunostaining was robust for all individuals. Figs. 1 and 2 show examples of NPY-ir axons and neurons in the NAc of all species included in this study. Consistent with previous reports, NPY-ir

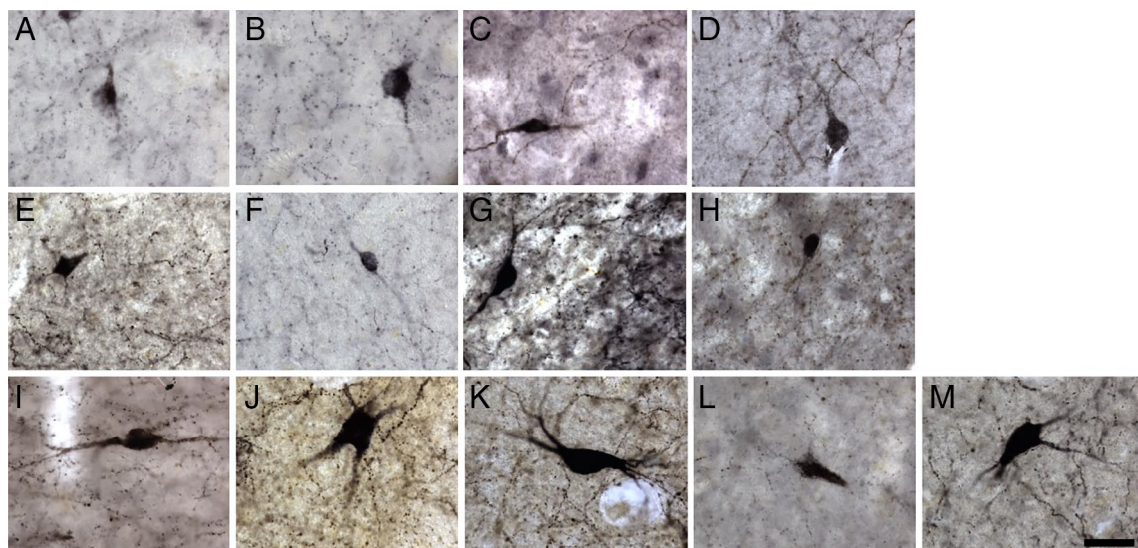


Fig. 2. Photomicrographs showing NPY-immunoreactive neurons within the nucleus accumbens for each species included in this study. (A) marmoset; (B) tamarin; (C) owl monkey; (D) capuchin; (E) rhesus macaque; (F) pig-tailed macaque; (G) Japanese macaque; (H) moor macaque; (I) baboon; (J) gorilla; (K) chimpanzee; (L) bonobo; (M) human. Scale bar in M, 25 μ m and applies to all panels.

Table 1. Summary data for total neuron density (Nv; expressed as neurons per mm³), glia density (Gv; expressed as glia per mm³), NPY axon length density/neuron density (ALv/Nv; expressed as μm/μm³) and percentage of NPY-ir neurons (% NPY cells; numbers in the table are expressed such that 0.009 = 0.9% of cells within the NAc are NPY-ir) within the NAc for each species

Species	N	Nv	Gv	G/N ratio	ALv/Nv	% NPY cells
Marmoset	7	133,594 ± 79,126	130,843 ± 59,588	1.08 ± 0.31	114.44 ± 50.34	0.009 ± 0.006
Tamarin	6	93,162 ± 23,919	89,046 ± 14,741	1.02 ± 0.38	205.38 ± 78.59	0.011 ± 0.005
Owl monkey	4	101,139 ± 51,251	84,868 ± 48,672	0.81 ± 0.10	128.00 ± 38.72	0.005 ± 0.002
Capuchin	6	61,559 ± 44,520	137,895 ± 41,112	3.00 ± 1.76	277.00 ± 172.08	0.013 ± 0.006
Rhesus macaque	6	67,524 ± 22,498	110,359 ± 35,704	2.01 ± 1.44	209.11 ± 146.51	0.011 ± 0.007
Pigtailed macaque	6	48,222 ± 21,872	74,420 ± 25,454	1.64 ± 0.60	280.92 ± 91.48	0.013 ± 0.007
Japanese macaque	6	72,329 ± 27,335	95,866 ± 31,533	1.48 ± 0.59	224.87 ± 165.85	0.010 ± 0.007
Moor macaque	5	67,981 ± 8,753	85,036 ± 7,933	1.26 ± 0.10	157.36 ± 33.75	0.008 ± 0.002
Baboon	5	80,986 ± 32,398	124,442 ± 62,407	1.63 ± 0.68	179.40 ± 98.60	0.008 ± 0.005
Gorilla	6	55,224 ± 17,804	89,651 ± 43,994	1.58 ± 0.36	143.71 ± 34.61	0.008 ± 0.004
Chimpanzee	6	45,667 ± 17,949	83,931 ± 18,259	1.98 ± 0.66	245.40 ± 104.12	0.012 ± 0.005
Bonobo	4	100,050 ± 31,879	128,838 ± 59,692	1.32 ± 0.46	126.55 ± 57.43	0.019 ± 0.007
Human	7	31,141 ± 16,142	115,834 ± 57,884	4.32 ± 3.38	533.99 ± 212.85	0.014 ± 0.004

axons were dense within the NAc and NPY-ir cell morphology was consistent with what has been described as medium aspiny interneurons (30, 31). Table 1 provides summary data for the variables included in our analyses. Independent *t* tests were performed for all variables and species. One potential sex difference was detected, with male tamarins having higher NPY axon length density/total neuron density (ALv/Nv) relative to female tamarins (*t*₄ = 2.57, *P* = 0.03, not corrected for multiple comparisons). No other sex differences were detected (all *P* values > 0.05, not corrected for multiple comparisons). If corrected for multiple comparisons, the tamarin result would not be significant, suggesting that sex was not a confounding factor in these analyses. The ANOVA analysis for NPY-ir ALv/Nv showed a significant effect of species (*F*_{12,73} = 5.51, *P* < 0.001; Eta squared = 0.52). Bonferroni post hoc analyses revealed that humans have a higher NPY-ir ALv/Nv relative to the nonhuman primate species (all *P* values < 0.03; Fig. 3). No other species differences were detected. The ANOVA analysis for the percentage of NPY-ir neurons within the NAc exhibited no differences among species (*F*_{12,73} = 1.83, *P* > 0.05; Eta squared = 0.26; Fig. 4). The ANOVA analysis for total Nv showed a significant effect of species (*F*_{12,73} = 3.72, *P* < 0.001; Eta squared = 0.42). Bonferroni post hoc analyses revealed that marmosets have higher Nv relative to humans, chimpanzees, gorillas, and pig-tailed macaques (all *P* values < 0.05; Fig. 5). No other species differences were detected.

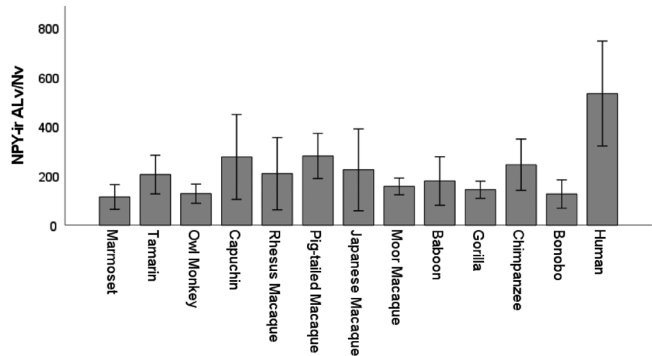


Fig. 3. Bar graphs showing NPY-ir ALv/Nv (NPY-ir axon length density/total neuron density expressed as μm/μm³) among species. ANOVA showed that human NPY ALv/Nv within the NAc was higher than that of all other species examined. Whiskers indicate ±1 SD.

The ANOVA analysis for total Gv in the NAc exhibited no differences among species (*F*_{12,73} = 1.46, *P* > 0.05; Eta squared = 0.22; Fig. 5). ANOVA for the glia-to-neuron ratio (G/N) in the NAc revealed a significant effect of species (*F*_{12,73} = 3.30, *P* = 0.001; Eta squared = 0.39; Fig. 6). Bonferroni post hoc analyses showed that humans possess an increased G/N ratio relative to marmosets, tamarins, owl monkeys, pig-tailed macaques, Japanese macaques, moor macaques, gorillas, and bonobos. No other species differences were detected.

Phylogenetic generalized least squares (PGLS) analysis indicated a significant positive scaling relationship between NPY-ir ALv/Nv in the NAc and brain weight (df = 13, regression slope of *b* = 0.18, 95% CI = 0.04 to 0.31, *P* = 0.02; Fig. 7A). Further phylogenetic analysis of covariance (pANCOVA) analysis demonstrated that NPY ALv/Nv in the human NAc was significantly higher than expected for the overall primate scaling trend (df = 3, *F* = 4.55, *P* = 0.05). Other species whose NPY ALv/Nv values plotted outside the 95% CI were also evaluated with pANCOVA, but these did not show conventionally significant *p*-values: gorilla (df = 3, *F* = 3.84, *P* = 0.07), bonobo (df = 3, *F* = 3.64, *P* = 0.08), pigtailed macaque (df = 3, *F* = 1.08, *P* = 0.32), capuchin (df = 3, *F* = 1.39, *P* = 0.26), tamarin (df = 3, *F* = 1.76, *P* = 0.21), and marmoset (df = 3, *F* = 1.30, *P* = 0.28).

PGLS analysis also indicated a significant positive scaling relationship between percentage of NPY neurons in the NAc and brain weight (df = 13, regression slope of *b* = 0.13, 95% CI = 0.01 to 0.26, *P* = 0.03; Fig. 7B). Further pANCOVA analysis demonstrated that the percentage of NPY neurons in the human NAc scaled as predicted relative to other species (df = 3, *F* < 0.01, *P* = 0.98). Other species whose percentage of NPY neurons values plotted outside the 95% CI were also evaluated with pANCOVA, but these did not show conventionally significant *p*-values: gorilla (df = 3, *F* = 1.9, *p* = 0.19), bonobo (df = 3, *F* = 3.09, *P* = 0.11), baboon (df = 3, *F* = 0.48, *P* = 0.50), pigtailed macaque (df = 3, *F* = 0.62, *P* = 0.45), moor macaque (df = 3, *F* = 0.44, *P* = 0.52), capuchin (df = 3, *F* = 1.02, *P* = 0.33), *Aotus vociferans* (df = 3, *F* = 3.91, *P* = 0.07), owl monkey (df = 3, *F* = 1.61, *P* = 0.23), and tamarin (df = 3, *F* = 2.37, *P* = 0.15).

PGLS analyses showed a significant negative relationship between total Nv in the NAc with brain weight (df = 13, regression slope of *b* = -0.21, 95% CI = -0.30 to -0.11, *P* < 0.01; Fig. 8A) and no significant scaling of Gv in the NAc with brain weight (df = 13, regression slope of *b* = -0.008, 95% CI = -0.10 to 0.08, *P*

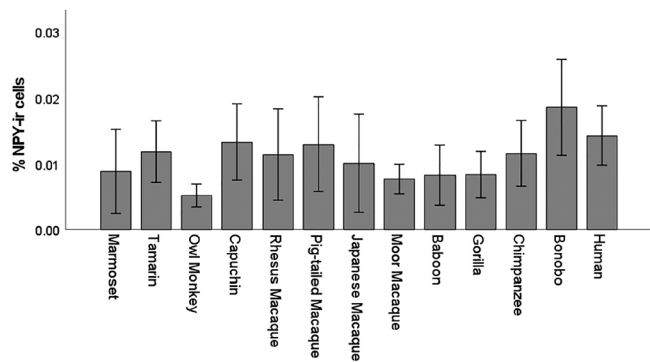


Fig. 4. Bar graphs showing % NPY-ir neurons (NPY-ir neuron density/total neuron density) among species within the NAc. ANOVA analysis did not detect a difference among species. Whiskers indicate ± 1 SD. Note that numbers on the y-axis are expressed such that 0.01 = 1% of neurons within the NAc are NPY-ir.

= 0.86; Fig. 8B). Consequently, the G/N ratio increases in relation to brain enlargement across primates ($df = 13$, regression slope of $b = 0.36$, 95% CI = 0.20 to 0.52, $P < 0.01$; Fig. 8C). pANCOVA analysis indicated that humans do not differ from the overall primate trend in neuron and glia densities ($df = 3$, $F = 0.86$, $P = 0.37$; $df = 3$, $F = 0.36$, $P = 0.56$, respectively), but do deviate from the overall primate trend in having an elevated G/N ratio in the NAc ($df = 3$, $F = 4.60$, $P = 0.05$).

Discussion

In the present study, we compared the density of total neurons, glia, glia-to-neuron ratios, and NPY-ir axons and neurons in the NAc of a large sample of anthropoid primates. The NAc is both a component of the ventral striatum and a critical node in the brain's reward system. We found that NPY innervation, as measured by ALv/Nv, is significantly greater in the human NAc than it is in all other primate brain regions we examined. An elevated ALv/Nv reflects increased axons within the NAc, with an increased ratio of axons relative to neurons. Presumably, this reflects increased axon collaterals (e.g., ref. 32), but whether that is the result of innervation derived from local neurons or the arcuate nucleus is not clear. The increased NPY in the human NAc is in contrast with data we previously reported for NPY ALv/Nv in other brain regions. In the neocortical regions that we have previously examined (Brodmann's areas 10, 24, 44, 22), humans and great apes share greater innervation relative to monkey species (33). However, only humans and chimpanzees share higher NPY

ALv/Nv in their dorsal striatum (gorillas and monkeys do not). We also have examined cortical NPY-ir neuron densities in Brodmann's area 22. There, we found no differences among human and nonhuman primate species (34).

As predicted, Nv scaled inversely with brain weight while Gv was independent of brain size. This is consistent with what has been reported for neocortical regions, with Gv being more constant, whereas Nv exhibits more freedom to vary, both among species and from one brain region to another within species (35). Significantly, and consistent with our previous findings (5), humans deviated from the overall primate trend in having increased G/N ratios in the NAc when controlling for brain size. The current analysis included additional species and different individuals compared to our earlier report. Similar to what has been observed in neocortical regions, G/N differences among species appear to be driven by neuron numbers rather than altered glia densities. This elevation in G/N may provide increased metabolic support for this highly interconnected region (10, 36, 37). The NAc has connections with the medial and orbital prefrontal cortex, thalamus, midbrain, and amygdala (8, 37). There is a difference in the connectivity of the ventral striatum between humans and macaques, with the suggestion that these differences may underlie species-typical behaviors relative to motivation and response (38).

The human brain is unique among primates. It is three times larger than expected for an anthropoid of our body mass and constitutes approximately 20% of our adult basal metabolic rate (BMR), and up to 66% of BMR during childhood (39). This constant demand for potential energy stores (fat and glycogen) is remarkable (40, 41) and contrasts with adult nonhuman primates which devote only 9% of their BMR to their brain (42).

A dietary supply of both fat and long-chain polyunsaturated fatty acids is therefore critical for human brain development. Moreover, humans also maintain higher body fatness than does any other primate (43–47). Van den Heuvel et al. (20) found that NPY injections into the NAc of rats induce a specific preference for fat, but not sugar or standard chow in these rodents, an effect that is thought to be mediated by Y1 receptors on enkephalinergic neurons (reviewed in ref. 48). Pandit et al. (49) measured the effects of NPY infusion into the lateral hypothalamus, NAc, and ventral tegmental area on the motivation for, and consumption of, sucrose. They reported that both motivation and consumption were increased with NPY infusions into the NAc, an effect that was dopamine-dependent. If the elevated NPY in the human NAc as reported here (*vide supra*) is responsible for inducing preference for both fat and sweet intake as it does in these rodents (20, 49), then a strong preference for foods with bioavailable fat stores would likely have been permissive or even requisite for the precipitous expansion of the human brain during the Plio-Pleistocene. Moreover, it would be reasonable to assume that such a change in dietary drive could have accompanied other pivotal shifts in sociobehavioral strategies that conferred an advantage for our early ancestors, contributing to the demographic success of our lineage.

Although these early human precursors had brains only slightly larger than those of contemporary bonobos and chimpanzees, they were nevertheless highly differentiated from these phyletic relatives by already exhibiting well-developed upright walking and a near canine monomorphism well before 4 MA (50, 51). This reduction in male canine size clearly heralded a dramatic shift in group behavior as the canine is a "social tooth" (52). There is typically a high level of sexual dimorphism in canine size among nonhuman primates, with males having larger canines. Canine monomorphism is found only in monogamous nonhuman primate species, but this

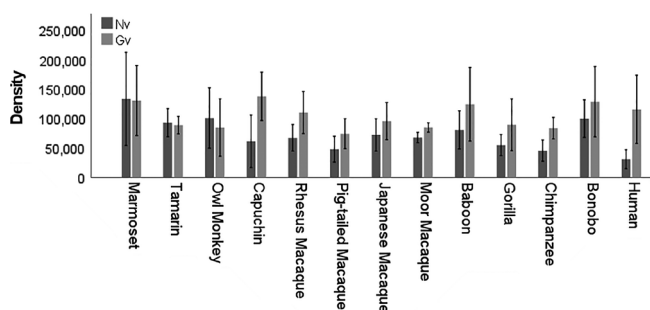


Fig. 5. Bar graphs showing both NAc total Nv and Gv densities among species (both Nv and Gv are expressed as number of cells per mm^3). ANOVA analyses detected a significant difference among species for Nv, but not Gv. Post hoc analyses of the significant Nv finding revealed that marmosets had significantly higher Nv relative to pig-tailed macaques, gorillas, chimpanzees, and humans. No other significant differences were detected. Whiskers indicate ± 1 SD.

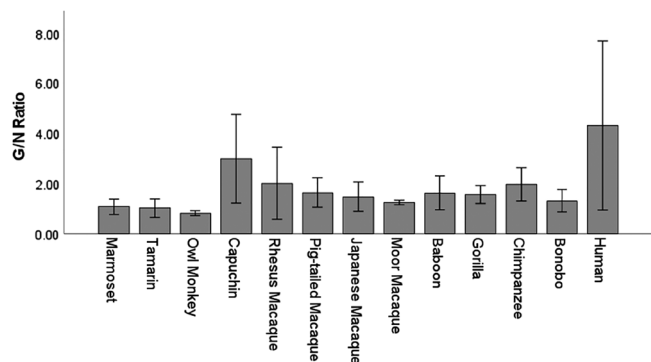


Fig. 6. Bar graphs showing NAC glia-to-neuron (G/N) ratios among species. The ANOVA detected a significant effect of species, with humans having higher G/N ratios relative to many, but not all, species. Whiskers indicate ± 1 SD.

is the result of a different process than what occurred in hominins. In hylobatids, females have robust canines that are comparable in size to those of the males, a result of female canine enlargement. In contrast, the neotropical callitrichids and owl monkeys display a combination of canine size reduction in males and some size increase in females (51). Canine monomorphism favoring increased crown size in both sexes suggests territoriality. Incidentally, for a species to become bipedal which results in a requisite increase in search intensity, territoriality would require maintenance of an enlarged male canine.

The unusually “feminized” male canine, with a distinctive diminished size in both males and females, observed in early bipeds implies both monogamous pair bonding and substantially increased affiliative behavior. This social shift would have been enabled by an increasingly dopamine-dominated striatum and reduction of striatal acetylcholine (4). Under this unique social routine, reproductive success would have been strongly favored by fat-targeted search routines sufficient to improve dietary support during pregnancy and an earlier cessation of lactational amenorrhea, obviously favoring fitness in both females and provisioning males. Moreover, these hominins exhibited remarkable demographic success at the same time that all other apes have since been undergoing virtual population collapse (53, 54). Brain expansion in later hominins encouraged by a preference for fat was therefore

likely an important component of their uniquely successful social adaptation.

It has been hypothesized that the adoption of fire for cooking was pivotal in supporting the full expansion of the human brain. Cooking increases the energy that can be obtained from most foods, with a 45 to 78% increase in caloric gain from proteins (i.e., chicken, egg) (55, 56). While it is tempting to suggest that the adoption of cooking was the initial introduction of targeted fat consumption, it is more likely that search routines favoring fat-rich foods came first and were instead largely permissive to further brain expansion made possible by the wholesale changes in social behavior described earlier. Moreover, it is likely that fire sufficiently controlled for regular cooking is considerably far more recent than significant brain expansion in hominids (57, 58).

Importantly, our previously reported hypothesis that increasing intraaccumbal NPY positively influences prosocial behaviors (4) is also consistent with early dietary specialization. As noted, even at nearly 5 Ma upright hominins possessed reduced, nondimorphic male canines, demonstrating a major shift in social behavior from aggressive to more affiliative (52, 59). This shift could have included monogamous pair bonding (4, 52, 59–61). Of note is that the experience of sweet taste is associated with romantic feelings and an increase in prosocial behaviors (62–65), while bitter taste has been associated with moral disgust (66). It is not known how the experience of fat consumption influences social or other behaviors, but these results would lead to the prediction that fat intake may increase positive social behaviors as well as brain nutrient supply.

A greater reliance on intraaccumbal NPY to guide species-specific search behaviors may well have simultaneously become responsible for our variety of food-related pathologies. The roles of NPY in orexinergic activity as well as the impact of anxiolytic medications, including directed reward-seeking of hyperpalatable foods, make elevated NPY prone to inducing hedonic eating (67). This includes stress and compulsive eating, which augment the risk of obesity (68). In fact, the NAc has been referred to as a “hedonic hot-spot”—a region that amplifies the drive for palatable taste (69). NPY-ir neurons in the arcuate nucleus of the hypothalamus project to the NAc and are involved in hedonic eating (20, 70), and injection of NPY into the NAc increases the desire for palatable

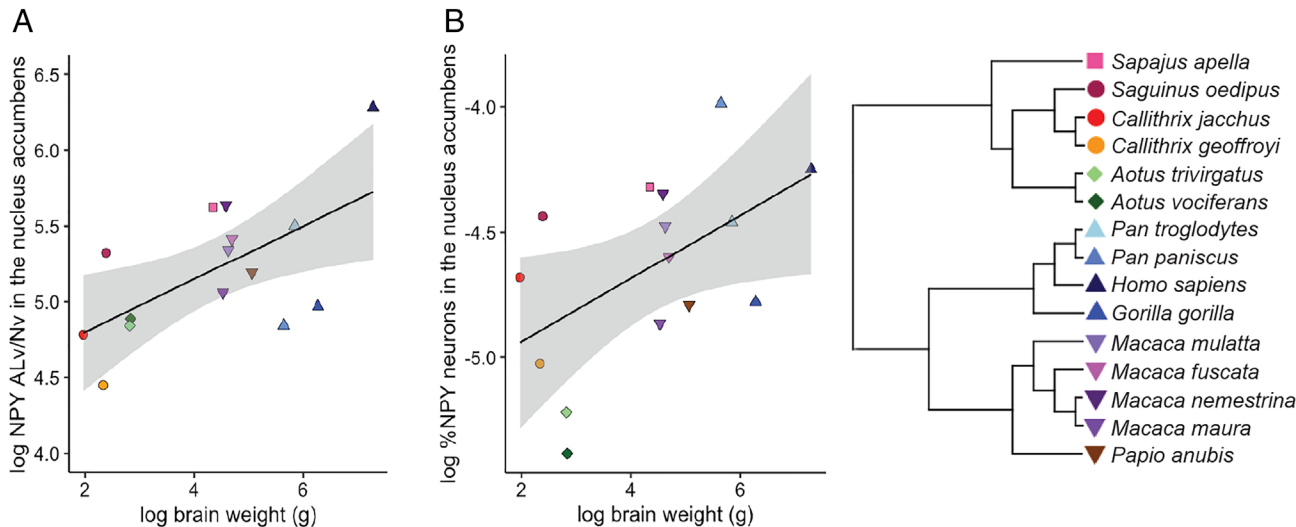


Fig. 7. PGLS regressions of NYP AL/Nv (NPY-ir axon length density/neuron density; $\mu\text{m}/\mu\text{m}^3$) in the NAc against brain weight shown with 95% CI (A), and %NPY neurons in the NAc against brain weight shown with 95% CI (B). The phylogenetic tree in this figure provides the color/shape legend for species values in all plots of PGLS analyses.

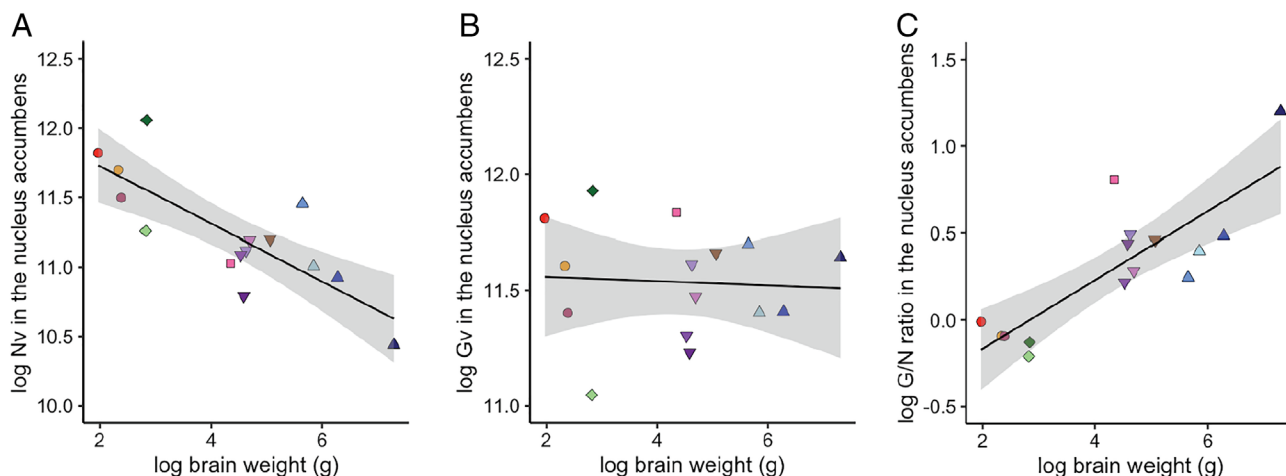


Fig. 8. PGLS regressions of Nv (neuron density per mm^3) in the NAc against brain weight shown with 95% CI (A), Gv (glia density per mm^3) in the NAc against brain weight shown with 95% CI (B), and G/N ratio in the NAc against brain weight shown with 95% CI (C). pANCOVA revealed that humans deviated from the primate trend in having significantly increased G/N ratios.

food in rodents (49). Of interest, stress increases NPY within the arcuate nucleus and this may also contribute to stress-related food consumption (reviewed in ref. 71). A naturally elevated concentration of NPY innervation in the ancestral hominin NAc could have predisposed us to hedonic eating, overconsumption, and obesity, with implications particularly for modern societies with their virtual overabundance of freely available hyperpalatable foods. While a fat-seeking preference would have been an advantage that supported survival in an environment where resources were not abundant, this predilection has become a distinct disadvantage in a modern environment.

Eating disorders and substance abuse occur together in humans with a high frequency (72–75). NPY injections into the NAc lead to increased ethanol consumption (76), and NPY actions within the NAc appear to be involved in the dopamine-mediated positive reward by increasing extracellular dopamine levels (22). This strongly suggests that NPY reinforces addictive substances through its actions in the NAc (77), possibly involving the Y1 and Y5 receptors (77, 78). We previously reported that humans have higher dopaminergic innervation in the NAc relative to all other primates (5). Of note, humans have an increased vulnerability to addiction relative to other mammals (79). Domesticated species have a higher propensity toward substance addiction compared to their nondomesticated counterparts, but even domesticated species do not exhibit rates of addiction comparable to those of humans (79, 80). Taken together, the combination of increased NPY and DA within the human NAc may have permitted enhanced encephalization in the human clade but may also have simultaneously rendered humans exceptionally vulnerable to eating disorders and substance abuse, maladies that appear likely to have had deep evolutionary origins. More broadly, this shift in our NAc may also account for our reward pathway's unique responsiveness to an almost unbridled array of stimuli with progressively elevating thresholds. These likely rely on inhibitory GABAergic effects to provide a constant resetting of the pathway to maintain responsiveness (81). While it is impossible to determine the precise order of events, an intriguing possibility is that an increase in NPY-driven fat intake may have played a pivotal role in providing nutrients required for brain expansion throughout the Plio-Pleistocene. It may also have been responsible for increasing the reward pathway's expansion of potential

targets; that is, our pathway's capacity to respond to everything from food to sports, art, music, etc., has likely been a central creative force throughout human evolution during the past several million years.

Materials and Methods

The study sample included postmortem brain specimens from 74 individuals representing 13 primate species, including humans (*Homo sapiens*, $n = 7$), bonobos (*Pan paniscus*, $n = 4$), chimpanzees (*Pan troglodytes*, $n = 6$), gorillas (*Gorilla gorilla*, $n = 6$), baboons (*Papio anubis*, $n = 5$), pigtailed macaques (*Macaca nemestrina*, $n = 6$), rhesus macaques (*Macaca mulatta*, $n = 6$), Japanese macaques (*Macaca fuscata*, $n = 6$), moor macaques (*Macaca maura*, $n = 5$), capuchins (*Sapajus (Cebus) apella*, $n = 6$), owl monkeys (*Aotus*, spp., $n = 4$), tamarins (*Saguinus oedipus*, $n = 6$), and marmosets (*Callithrix* spp., $n = 7$). The sex and age of each specimen are listed in Table 2. No living animals were used in this study. All postmortem brains from nonhuman primates were acquired from donations by zoological or research institutions. The animals had been maintained in AAALAC- or AZA-accredited facilities and died from either natural causes or from humane euthanasia for quality of life unrelated to the current research study. The research presented here is in accordance with the American Society of Primatologists Principles for the Ethical Treatment of Nonhuman Primates. The acquisition and processing of postmortem human and nonhuman brain materials are exempted from the requirement of approval by institutional animal care and human subject use committees.

All individuals were adult and free of gross neuropathology. Sexes were balanced as much as possible given the rarity of some of the samples. Human brain specimens were provided by the Northwestern University Alzheimer's Disease Center Brain Bank and NIH NeuroBioBank. All human specimens were obtained from adult individuals who were free of neuropathology on gross examination and showed no evidence of histopathological degenerative lesions. Postmortem interval did not exceed 17 h for any specimen. The moor macaques were perfused transcardially with 4% paraformaldehyde following methods described previously (82, 83) as part of unrelated experiments. All other brains were fixed by immersion in 10% buffered formalin for at least 10 d and then transferred to a 0.1 M phosphate-buffered saline (PBS, pH 7.4) solution containing 0.1% sodium azide and stored at 4 °C until histological processing.

Sample Processing. Postmortem brain weights were obtained at necropsy or upon receipt in the laboratory. Prior to sectioning, samples were cryoprotected in a graded series of sucrose solutions (10%, 20%, and 30%) until saturated. Brain samples were frozen on dry ice and sectioned at 40 μm using a freezing sliding microtome (SM2000R, Leica, Chicago, IL). Each section was placed into an individual centrifuge tube containing freezer storage solution (30% each distilled water,

Table 2. Specimens included in analyses

Species	Common name	Sex	Age (y)
<i>Callithrix geoffroyi</i>	Geoffroy's marmoset	M	5.7
<i>Callithrix jacchus</i>	Common marmoset	M	6
<i>C. jacchus</i>	Common marmoset	M	4.5
<i>C. jacchus</i>	Common marmoset	M	2.75
<i>C. jacchus</i>	Common marmoset	F	6.2
<i>C. jacchus</i>	Common marmoset	F	6.1
<i>C. jacchus</i>	Common marmoset	F	5.1
<i>Saguinus oedipus</i>	Cotton-top tamarin	M	10.9
<i>S. oedipus</i>	Cotton-top tamarin	M	8.4
<i>S. oedipus</i>	Cotton-top tamarin	M	9.5
<i>S. oedipus</i>	Cotton-top tamarin	F	9.9
<i>S. oedipus</i>	Cotton-top tamarin	F	11
<i>S. oedipus</i>	Cotton-top tamarin	F	16
<i>Aotus trivirgatus</i>	Northern owl monkey	M	>18
<i>Aotus spp.</i>	Owl monkey	M	18
<i>Aotus spp.</i>	Owl monkey	F	3
<i>Aotus vociferans</i>	Spix's night monkey	F	5
<i>Sapajus (Cebus) apella</i>	Tufted capuchin	M	2.9
<i>S. apella</i>	Tufted capuchin	M	16.6
<i>S. apella</i>	Tufted capuchin	M	15.9
<i>S. apella</i>	Tufted capuchin	F	12.6
<i>S. apella</i>	Tufted capuchin	F	17.5
<i>S. apella</i>	Tufted capuchin	F	18.3
<i>Macaca mulatta</i>	Rhesus macaque	M	8
<i>M. mulatta</i>	Rhesus macaque	M	13
<i>M. mulatta</i>	Rhesus macaque	M	13
<i>M. mulatta</i>	Rhesus macaque	F	14
<i>M. mulatta</i>	Rhesus macaque	F	11
<i>M. mulatta</i>	Rhesus macaque	F	12.5
<i>M. nemestrina</i>	Pigtailed macaque	M	15.73
<i>M. nemestrina</i>	Pigtailed macaque	M	4.28
<i>M. nemestrina</i>	Pigtailed macaque	M	2.5
<i>M. nemestrina</i>	Pigtailed macaque	F	15.1
<i>M. nemestrina</i>	Pigtailed macaque	F	9
<i>M. nemestrina</i>	Pigtailed macaque	F	5.95
<i>M. maura</i>	Moor macaque	M	10
<i>M. maura</i>	Moor macaque	M	8
<i>M. maura</i>	Moor macaque	F	5
<i>M. maura</i>	Moor macaque	F	7
<i>M. maura</i>	Moor macaque	F	8
<i>M. fuscata</i>	Japanese macaque	M	19
<i>M. fuscata</i>	Japanese macaque	M	11
<i>M. fuscata</i>	Japanese macaque	M	9
<i>M. fuscata</i>	Japanese macaque	F	19
<i>M. fuscata</i>	Japanese macaque	F	14
<i>M. fuscata</i>	Japanese macaque	F	10
<i>Papio anubis</i>	Olive baboon	M	13
<i>P. anubis</i>	Olive baboon	M	6
<i>P. anubis</i>	Olive baboon	M	7
<i>P. anubis</i>	Olive baboon	F	12

Table 2. (Continued)

Species	Common name	Sex	Age (y)
<i>P. anubis</i>	Olive baboon	F	9.5
<i>Gorilla gorilla</i>	Gorilla	M	40
<i>G. gorilla</i>	Gorilla	M	21.5
<i>G. gorilla</i>	Gorilla	M	49
<i>G. gorilla</i>	Gorilla	M	34
<i>G. gorilla</i>	Gorilla	M	11
<i>G. gorilla</i>	Gorilla	M	16
<i>Pan troglodytes</i>	Chimpanzee	M	40.5
<i>P. troglodytes</i>	Chimpanzee	M	40
<i>P. troglodytes</i>	Chimpanzee	M	17
<i>P. troglodytes</i>	Chimpanzee	F	45
<i>P. troglodytes</i>	Chimpanzee	F	41
<i>P. troglodytes</i>	Chimpanzee	F	35
<i>P. paniscus</i>	Bonobo	M	34
<i>P. paniscus</i>	Bonobo	M	25
<i>P. paniscus</i>	Bonobo	F	25
<i>P. paniscus</i>	Bonobo	F	52
<i>Homo sapiens</i>	Human	M	59
<i>H. sapiens</i>	Human	M	56
<i>H. sapiens</i>	Human	M	44
<i>H. sapiens</i>	Human	M	44
<i>H. sapiens</i>	Human	M	42
<i>H. sapiens</i>	Human	F	25
<i>H. sapiens</i>	Human	F	53

ethylene glycol, and glycerol and 10% 0.244 M PBS), numbered sequentially, and maintained at -20°C until histological or immunohistochemical processing was performed. A 1:10 series for all samples was stained with 0.5% cresyl violet to reveal cell somata. Nissl-stained sections were used to obtain total neuron (Nv) and glial (Gv) densities and to define area boundaries.

Immunohistochemistry. A 1:10 series of sections from each individual that included the NAC was immunostained for NPY following a protocol that we have previously used in human and nonhuman primate species (4, 33, 34). Briefly, floating tissue sections were immunostained using the avidin-biotin-peroxidase method. Sections were pretreated for antigen retrieval in a 0.05% citraconic anhydride solution (pH 7.4) in a water bath (85°C) for 30 min (84). Endogenous peroxidase was quenched using a solution of 75% methanol, 2.5% hydrogen peroxide (30%), and 22.5% distilled water for 20 min. Sections were preblocked in a solution of 0.1 M PBS, 0.6% Triton X-100, 4% normal serum, and 5% bovine serum albumin. Sections were then placed in primary antibody (rabbit anti-NPY polyclonal antibody, ab30914, Abcam, Cambridge, MA, USA) at a dilution of 1:5,000 in PBS for 48 h at 4°C . Following this, sections were incubated in a biotinylated secondary antibody (1:200) in a solution of PBS and 2% normal serum. The sections were then incubated in an avidin-peroxidase complex (PK-6100, Vector Laboratories, Burlingame, CA) followed by a 3,3'-diaminobenzidine-peroxidase substrate with nickel enhancement (SK-4100, Vector Laboratories).

Data Collection and Analysis. Nissl-stained sections and sections immunostained for NPY were analyzed using an Olympus BX-51 photomicroscope equipped with a Ludl X, Y motorized stage, Heidenhain z-axis encoder, StereoInvestigator software (MBF Bioscience, Williston, VT, USA), and a digital camera that projects images onto a 24-inch LCD flat panel monitor. Subsampling techniques were used to determine sampling parameters for each species in order to ensure coefficients of error below 0.10 (85). The NAC

was outlined at low magnification ($2\times$ objective lens) and NPY-immunoreactive (-ir) axons were quantified using the "SpaceBalls" probe at $100\times$ magnification (N.A. 1.4) under Koehler illumination using a 7- or 8- μm -diameter hemisphere and a guard zone of 2%. The SpaceBalls probe provides a total axon length estimate that is divided by the planimetric volume of the sampled region to yield an axon length density (ALv). Three to four sections that spanned the NAc were quantified per individual. Section thickness was measured at every sampling site with an average of $14.91 \pm 3.84\ \mu\text{m}$ thickness. An average of 63.58 ± 12 sampling sites was used per individual with sampling grids that ranged from $275\ \mu\text{m} \times 275\ \mu\text{m}$ to $700\ \mu\text{m} \times 700\ \mu\text{m}$. This yielded 405.03 ± 144.65 axon/hemisphere intersections per individual. The average coefficient of error (Gundersen $m = 1$) was 0.06 ± 0.009 .

NPY-immunoreactive (-ir) neuron densities (Nv) were calculated using the optical disector as described previously (86). An average of 56.48 ± 20 sampling sites was used per individual with sampling grids that ranged from $450\ \mu\text{m} \times 450\ \mu\text{m}$ to $900\ \mu\text{m} \times 900\ \mu\text{m}$. This yielded 241.17 ± 107.27 NPY-ir neurons per individual. The average coefficient of error (Gundersen $m = 1$) was 0.07 ± 0.018 .

Adjacent Nissl-stained sections were used to obtain total neuron densities (total Nv) and glia densities (Gv) using the optical disector with a fractionator sampling scheme (5), following the sampling parameters above. Neurons were recognizable based on the presence of a robustly Nissl-stained cytoplasm, a large nucleus, a distinct nucleolus, and lightly stained proximal dendritic processes (35). Glia contains less endoplasmic reticulum and lack a distinct nucleolus. The average coefficient of error (Gundersen $m = 1$) was 0.07 ± 0.003 .

Because the species included in this study have vastly different brain sizes, we used the ratio of NPY-ir ALv to total Nv (ALv/Nv) for comparative analyses of species. Using total Nv as the denominator provides a variable that accounts for the fact that axons innervate neurons regardless of brain size. The ratio of NPY-ir Nv to total Nv represents the percentage of neurons expressing NPY. NPY ALv/Nv and the ratio of NPY-ir Nv to total Nv (% NPY neurons) were compared among species using one-way ANOVAs. Bonferroni post hoc tests were used to evaluate significant findings.

Additional analyses were conducted using R studio software (R core Team, Vienna, Austria, version 4.2.2, <https://www.R-project.org/>) including PGLS and pANCOVA. PGLS regression was performed to determine the allometric scaling

relationship among species mean values for NPY innervation in the NAc and brain weight as well as species mean values for the percentage of NPY-ir neurons in the NAc and brain weight while accounting for the covariance structure of evolutionary relatedness (87). pANCOVA was performed to test whether species mean values for NPY ALv/Nv and percentage of NPY-ir neurons in the NAc differed significantly from allometric predictions. Additionally, PGLS and pANCOVA were performed to examine the relationship between cell densities and brain weight across species. An α level was set at 0.05 for all statistical tests.

Data, Materials, and Software Availability. All study data are included in the article and/or *SI Appendix*.

ACKNOWLEDGMENTS. This research was funded by the NSF (BCS-1846201 to M.A.R. and SMA-1542848 and EF-2021785 to C.C.S. and W.D.H.). E.N.M. was supported by the NSF Graduate Research Fellowship Program (1746914). We thank both reviewers and Larry J. Young for comments on previous drafts of this manuscript. We would also like to thank Melanie A. McCollum for helpful discussion, Morgan Chaney for statistical advice, and Cheryl D. Stimpson and Bridget Wicinski for expert technical assistance. We are grateful to each of the following for the use of brain materials: The NIH NeuroBioBank, National Chimpanzee Brain Resource (NIH grant NS092988), The Great Ape Aging Project (supported by NIH grant AG014308), the National Primate Research Center at the University of Washington (NIH grant RR000166), the Oregon National Primate Research Center (NIH P51 OD011092), the Northwestern University Alzheimer's Disease Center Brain Bank (supported by Alzheimer's Disease Core Center grant AG013854, from the National Institute on Aging to Northwestern University, Chicago, IL).

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