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Neuropeptide receptor distributions in male and female *Eulemur* vary between female-dominant and egalitarian species

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Aggression and its neurochemical modulators are typically studied in males, leaving the mechanisms of female competitive aggression or dominance largely unexplored. To better understand how competitive aggression is regulated in the primate brain, we used receptor autoradiography to compare the neural distributions of oxytocin and vasopressin receptors in male and female members of female-dominant versus egalitarian/codominant species within the *Eulemur* genus, wherein dominance structure is a reliable proxy of aggression in both sexes. We found that oxytocin receptor binding in the central amygdala was predicted by dominance structure, with the members of three codominant species showing more oxytocin receptor binding in this region than their peers in four female-dominant species. Thus, both sexes in female-dominant *Eulemur* show a pattern consistent with the regulation of aggression in male rodents. We suggest that derived pacifism in *Eulemur* stems from selective suppression of ancestral female aggression over evolutionary time via a mechanism of increased oxytocin receptor binding in the CeA, rather than from augmented male aggression. This interpretation implies fitness costs to female aggression and/or benefits to its inhibition. These data establish *Eulemur* as a robust model for examining neural correlates of male and female competitive aggression, potentially providing novel insights into female dominance.

1. Introduction

Within the context of sexual selection theory, males have typically garnered attention across taxa as the more aggressive and socially dominant sex, both intrasexually and intersexually [1,2]; however, there has been mounting evidence that the females of certain species are the more competitive sex [3]. Female aggression is most often studied in the context of maternal or defensive aggression [4–6], whereas female competitive agonism and its neuroendocrine underpinnings are not well covered. In mammals, aggression links to activity in the limbic system and associated cortical networks (e.g. amygdala, nucleus accumbens, hypothalamus), as these areas are responsible for emotional arousal and responses to dangerous and threatening stimuli [2,7]. Within these regions, neuropeptides such as oxytocin (OXT)

and arginine vasopressin (AVP) are involved in regulating social behaviour, including aggression [8–10]. The corticolimbic system has been extensively studied in rodents to shed light on the role of these neuropeptides in aggressive behaviour [5,11,12]. Here, we extend this question to strepsirrhine primates by exploiting natural species variation in female (and male) aggression among the true or brown lemurs. The *Eulemur* genus uniquely includes both female-dominant and egalitarian or codominant species (figure 1) in which female competitive aggression, respectively, exceeds or meets that of males [14–17]. Codominance in *Eulemur* is characterized behaviourally both by the absence of a sex difference in aggression *and* by lower rates of aggression in both sexes, as compared to the relatively increased and female-biased rates of aggression in peers from female-dominant species [17]. We thus explore the relationship between neuropeptide receptor density and social dominance structure—a validated proxy of competitive agonism—across closely related species in this genus.

The amygdala is the hub of the mammalian corticolimbic system, responsible for recognizing sensory stimuli, integrating information and generating an emotionally salient response to relevant stimuli [7]. Aggressive behaviour is often linked to activation in the following three amygdalar nuclei: the basolateral amygdala (BLA), lateral amygdala (LA) and central amygdala (CeA; [18]). Whereas the BLA and LA receive sensory input from the cortex, thalamus and hippocampus [19,20], the CeA is the main output centre of the amygdala, integrating information from the BLA and LA to generate behavioural, endocrine and autonomic responses through connections with the hypothalamus, bed nucleus of the stria terminalis (BNST), lateral septum (LS) and other brain regions [21]. One functional route in this network of emotional regulation is via neurotransmitter action of OXT and AVP, following binding to their respective receptors. In the brain, the receptors mediating behavioural effects are the oxytocin receptor (OXTR; [22]) and vasopressin 1a receptor (AVPR1a [23]), found throughout the areas described above [13,24–30], including in *Eulemur* [13].

In rodents, the best-studied models, different types of aggression can have different neurobiological mechanisms. Aggression can be offensive, usually seen in cases of competition for resources, or it can be defensive, seen in response to threatening or fear-inducing stimuli [31,32]. The sex(es) of the actor and recipient, and the reproductive state of those individuals, also relate to how behaviour is modulated in the brain [33]. For instance, OXT release in male mice has been linked to a decrease in electroencephalogram activity in the amygdala, leading to reduced defensive aggression [34]. Likewise, OXT in non-lactating females decreases the rate of both defensive and offensive aggressive behaviour [4,35]; however, OXT in lactating females has the opposite effect, increasing maternal defensive aggression [36]. In the rodent CeA, more specifically, OXT regulates aggression in a sex-specific manner. OXT release in the CeA reduces intermale competitive aggression [37], but increases defensive maternal aggression in lactating rodents [38], and increases offensive interfemale aggression in a high-aggression phenotype [39]. These data indicate a potentially important distinction between OXT's regulation of aggression in males versus in females but without known corollaries in non-rodents.

Although AVP action in the amygdala and hypothalamus is more likely to stimulate aggression in males than in females [40], the role of AVP in regulating aggression in female rodents also is not well-resolved. In lactating female rats, AVP decreases maternal aggression, whereas injecting the same rats with an AVPR1a antagonist increases aggression [41]. In the BNST, there is a positive correlation between AVP expression and defensive territorial aggression by non-lactating females [42]. Given that neuropeptide system development is dependent on sex hormones during critical periods [43,44], androgen-mediated masculinization [45,46] may explain some of the variation seen between the sexes and reproductive states, potentially with broad applicability.

Millions of years of relatively isolated evolution on the island of Madagascar has resulted in exceptional species radiation and diversity among its endemic lemurs [47]. For example, as with other female strepsirrhines [17,48–50], females of the recently diverged *Eulemur* clade [51] show a suite of physically masculinized features consistent with prenatal exposure to androgens, including sexual size monomorphism, an elongated, pendulous clitoris that is traversed by the urethra, and elaborate scent glands [17,52]; nonetheless, the *Eulemur* clade also uniquely shows species-level variation in androgen-mediated female aggression and social dominance [17]. Notably, whereas the females of some species (e.g. *Eulemur flavifrons*) are extremely aggressive and virtually always dominate males [50,53], those of other species (e.g. *Eulemur fulvus*) are equally likely to initiate and receive aggression as are males, all at much lower frequencies [17]. The behavioural variability evident within *Eulemur* is accompanied by a related shift or 'relaxation' in hormonal function. Specifically, androgen concentrations in females are greater with female dominance than with codominance [17,54]. Otherwise, our two 'categories' of *Eulemur* species generally occupy similar ecological niches (e.g. [55–57]) and lack systematic differences in 'baseline' affiliation [58] or other behaviour [59]. *Eulemur* is thus an ideal taxon in which to examine the neuroendocrine basis of offensive aggression in both sexes.

Here, we ask if behavioural variation in *Eulemur* is related to neuropeptide signalling in the brain. In part, we conduct a broad survey of how neuropeptide receptor distributions vary (or not) between female-dominant and codominant species. More specifically, we test the relationship between our proxies of female aggression (i.e. species-level female dominance and codominance) and the distribution of OXTR and AVPR1a in the amygdala, limbic system (BNST, hippocampus, LS, hypothalamus) and cortex. We also test if sex predicts neuropeptide receptor density in the same regions; however, given that the neuropeptide system is responsive to prenatal androgens [43] and female lemurs show anatomical and behavioural evidence of hormonal masculinization [60], we do not expect to find sex differences in neuropeptide receptor density equivalent to those observed in rodents [61–64]. A better mechanistic understanding of female aggression in these lemurs should shed light on the evolution of female dominance or more specifically on its relaxation in certain species.

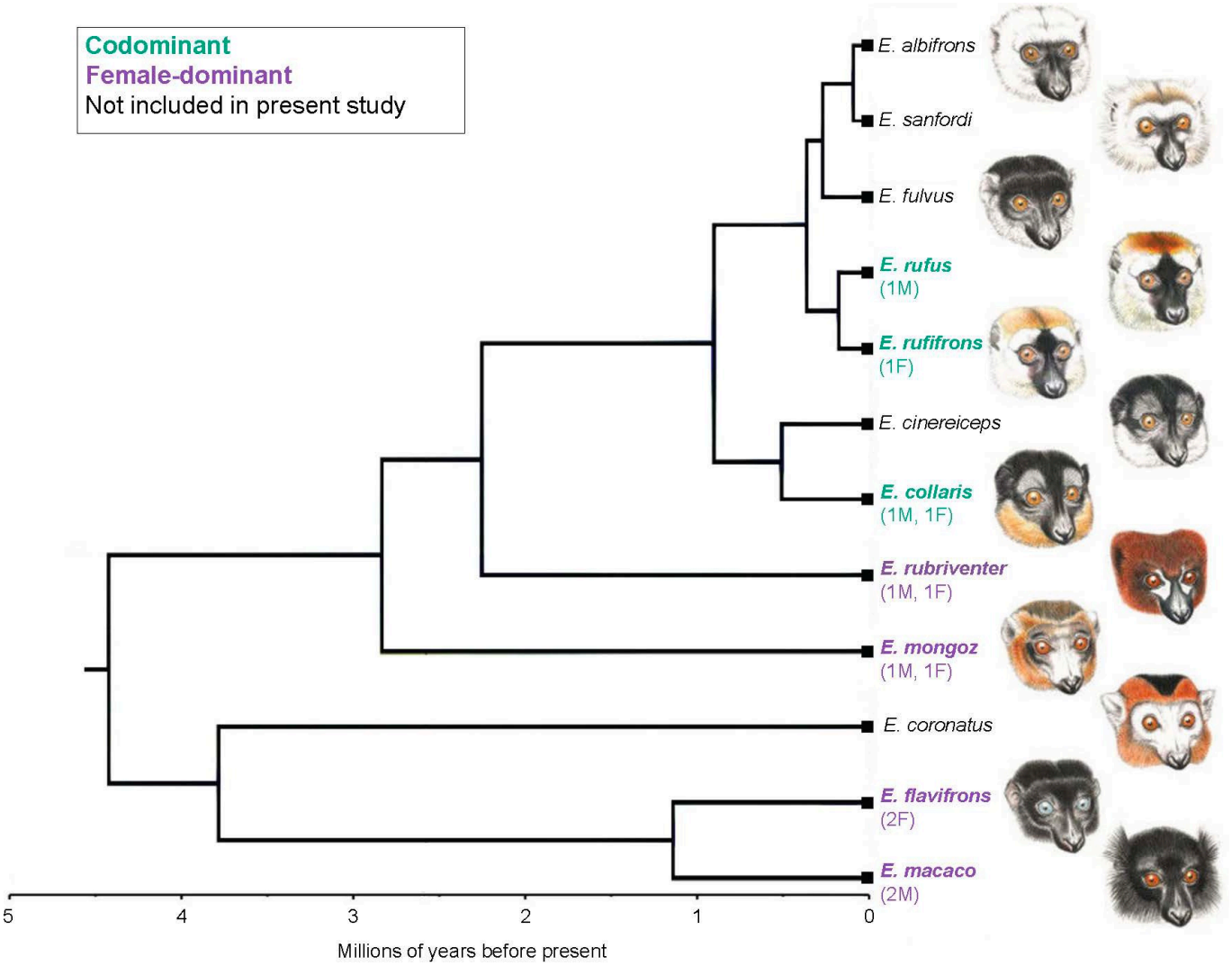

Figure 1. The phylogenetic relationships between and dominance structures of extant *Eulemur* species. The number and sex of specimens from each species are denoted in parentheses. This figure is adapted from [13].

2. Material and methods

(a) Subjects and specimens

The brain specimens (11 hemispheres, one whole brain) for this study were derived, opportunistically, from 12 adult lemurs (six male, six female; 16.6–34 years of age), representing four female-dominant and three codominant *Eulemur* species (figure 1). The subjects had been housed socially at the Duke Lemur Center (DLC), in Durham, NC, primarily in male–female pairs, in indoor/outdoor enclosures (23.2–951.3 m^2), and had received species-appropriate diets [52]. Female-dominant species were those in which the females had outcompeted the males in at least 60% of agonistic interactions [17].

(b) Specimen collection

The DLC houses the largest collection of lemurs outside of Madagascar; we acquired the brain specimens from the DLC's tissue bank. Because lemurs are the most endangered mammals on the planet [65], their brains had been collected and fresh-frozen following natural mortality or necessary euthanasia (for humane reasons). Euthanasia and postmortem necropsies were conducted by DLC veterinarians, following routine protocols approved by Duke's Institutional Animal Care and Use Committee (A216-20-11). We excluded specimens obtained from subjects that had shown any unusual neurological symptoms.

We stored the brain specimens at −80°C and, using a cryostat (Leica CM 3050S), sectioned them at −20°C into 20 µm slices. We mounted tissue sections onto SuperFrost Plus slides (Brain Research Laboratories, Newton, MA) and stored them at −80°C until use in receptor autoradiography.

(c) Receptor autoradiography

Our receptor autoradiography methods have been previously detailed [13]. Briefly, we used a competitive binding protocol for OXTR and AVPR1a developed and optimized for non-human primate brain tissue [66]. After light fixation and washes, we

incubated the slides for 1 h in either radiolabelled ^{125}I-ornithine vasotocin analogue (50 µCi ^{125}I-OVTA; PerkinElmer, Waltham, MA) or ^{125}I-linear AVP antagonist (50 µCi ^{125}I-LVA; PerkinElmer, Waltham, MA), along with non-radiolabelled ligands for the opposing receptor, where appropriate, for competitive binding. We then exposed slides to autoradiographic film, along with autoradiographic standards, for quantification of optical binding density (OBD). Because no lemur brain atlas exists, we used adjacent sections stained with acetylcholinesterase to identify brain regions where receptor binding was present. Grebe *et al*. also previously performed confirmatory analyses to validate the competitive binding protocol and to sequentially identify regions that showed appreciable receptor binding [13].

(d) Selection of regions of interest

Given the necessarily small sample size of lemur brains and the uniqueness of this dataset, we consider our study to be partly hypothesis-driven (i.e. relating to the female masculinization hypothesis) [48,60,67] and partly exploratory; we therefore included more regions of study than those, such as the amygdala and hypothalamus, for which we would have generated *a priori* predictions based on their prominence in regulating aggression in other species. Regions of interest for the present analysis thus included manually selected brain areas with appreciable binding of either OXTR or AVPR1a, determined by measurement of average intensity, in the cortex, limbic system and hypothalamus. The regions meeting these criteria included the prefrontal cortex (PFC), olfactory tubercle (OT), piriform cortex (Pir), entorhinal cortex (EC), primary visual cortex (V1), BLA, CeA, LA, BNST, LS, dentate gyrus (DG), hippocampus, arcuate nucleus of the hypothalamus and ventromedial hypothalamus. The olfactory bulb was excluded because it is rarely recovered during standard necropsy.

(e) Quantification of ligand binding

To quantify OBD in all regions of interest, we used MCID Image Analysis software (Interfocus Imaging, Linton, UK). For each region, we took OBD measurements in three consecutive slices to calculate an average OBD and account for anterior to posterior variation. Each OBD measure is divided by the region's area to normalize it to the region's size. After the initial OBD measurement, we subtracted background measures from the calculated OBD to account for any global differences in non-specific binding across subjects.

(f) Statistical analyses

To investigate the relationship between receptor binding and dominance structure, we used linear mixed models (LMMs) with replicate OBD measurements nested within individual, as a random effect, and including sex as a factor. Controlling for species was not possible in our analyses due to small sample sizes within species. We performed separate models for each region of interest and calculated Cohen's *d* values to measure effect size, with positive values representing greater binding in female-dominant species. We performed all analyses in R (v. 2024.04.2) and fit LMMs with the lme4 package [68].

3. Results

(a) Neuropeptide receptor binding in regions of interest

In the corticolimbic system, we observed OXTR binding in some (e.g. PFC, BLA, CeA, LA), but not all (BNST, LS, DG) regions, whereas AVPR1a binding was evident in all regions of interest (figures 2 and 3). Compared with OXTR binding, there were generally higher levels of AVPR1a binding, consistent with a prior report [13].

(b) Relationship to dominance structure

Dominance structure significantly predicted OXTR binding in the CeA (LMM: $t = -2.755$, $p = 0.033$; figure 3A,B): members of codominant species showed greater OXTR binding in this region (mean OBD = 29.66 ± 1.06) than did members of female-dominant species (mean OBD = 9.46 ± 2.55). This finding was associated with a large effect size ($d = -1.23$) [69], indicating minimal overlap of the two groups' distributions and a high probability of codominant individuals having greater OXTR density in the CeA compared with female-dominant individuals [70]. Neither dominance structure nor sex were significant predictors of OXTR or AVPR1a binding in any other region ($p > 0.05$).

4. Discussion

We provide the first evidence in lemurs consistent with a neural basis for species variation in aggression. Specifically, OXTR in the CeA was related to female dominance in the genus *Eulemur*, with members of both sexes within codominant species showing greater OXTR density in this region than their peers in female-dominant species. Although we did not examine the direct action of neuropeptides in *Eulemur*, the greater density of OXTR represents a greater potential for OXT to influence neuronal activity in the region. We interpret our results as indicating that the CeA in codominant species is more sensitive

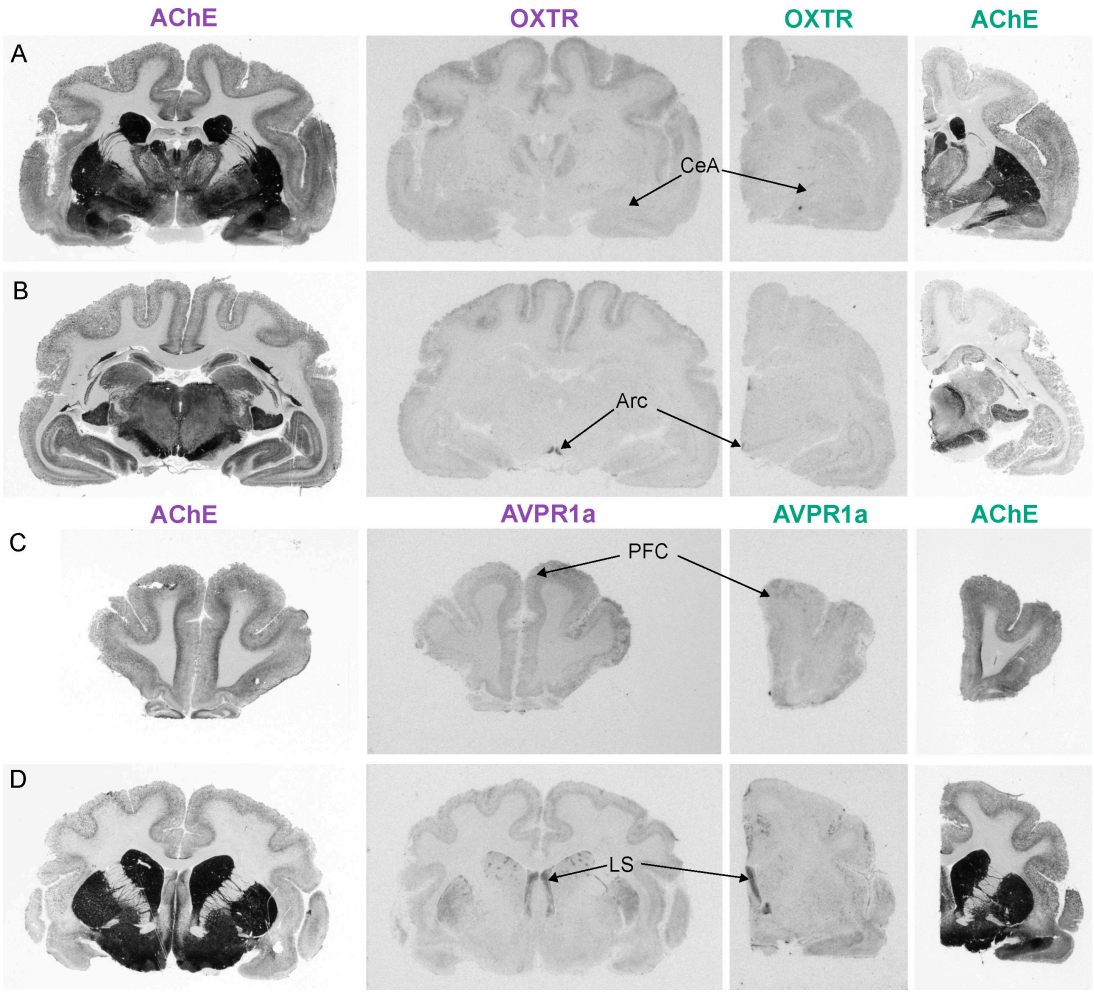

Figure 2. Autoradiograms of OXTR (panel rows A and B) and AVPR1a (panel rows C and D) binding across regions of interest in a female-dominant individual (*Eulemur macaco* whole brain; purple text headers) and a codominant individual (*Eulemur rufifrons* left hemisphere; teal text headers). Autoradiograms are aligned with images of adjacent sections stained with acetylcholinesterase (AChE) to show anatomical structures. Selected regions of interest are indicated to show binding patterns across species: shown are the (A) central amygdala (CeA), (B) arcuate nucleus of the hypothalamus (Arc), (C) prefrontal cortex (PFC) and (D) lateral septum (LS).

to local OXT release than the CeA in the more aggressive, female-dominant species. Because this region functions to drive neural output from the amygdala [21] and OXT inhibits offensive aggression in male and non-lactating female rodents [4,37], it is plausible that pacifism in codominant species owes, mechanistically, to suppression of the output of aggressive behaviour through increased OXTR binding in the CeA.

It is worth noting that OXTR binding in the CeA was relatively low across all *Eulemur* species, and possibly could be pharmacologically confounded with AVPR1a binding in the region, despite the competitive binding protocol used [66]; however, there was both a large effect size in CeA OXTR ($d = -1.23$) and a significant relationship between dominance structure and CeA OXTR ($p = 0.033$; figure 3A,B). Conversely, AVPR1a in the CeA showed a small effect size in the opposite direction ($d = 0.37$) and no relationship with dominance ($p > 0.05$; figure 3A). Similarly, although our sample size of female-dominant ($n = 8$) and codominant ($n = 4$) individuals is small, the large effect size of CeA OXTR is consistent with a strong relationship between receptor density in that brain region and dominance structure. Thus, we interpret our finding as being biologically relevant rather than spurious or driven by AVPR1a cross-talk.

Although we controlled for sex and did not find sex to be a significant predictor of OXTR binding in the CeA, our species sample sizes did not allow for robust sex-based comparisons. Nonetheless, when considering the results from both sexes together, the neuroanatomical and behavioural findings suggest that the recently evolved 'egalitarian' phenotype reflects suppression of aggression in both sexes, rather than increased male aggression. These data lend support to prior suggestions—based on phylogeny, on the pervasiveness of female dominance in lemurs, and on both pre- and post-natal androgen mediation of aggression—that female dominance/aggression is ancestral [17,60,71], whereas egalitarianism/lack of aggression is a derived trait in strepsirrhine primates. Moreover, these data shed new light on a potentially contributory neural mechanism for behavioural endocrine relaxation, in adulthood, in codominant species.

Comparing this regulatory mechanism of aggression with results from rodent studies further supports that aggression in female *Eulemur* may share mechanisms with aggression regulation in male, rather than female, rodents. Oxytocinergic action in the rodent CeA suppresses offensive male aggression [37], but promotes maternal and defensive female aggression [38,39]. In both male and female *Eulemur*, we see the suppressive effect of OXT akin to that seen in male rodents, aligning with female masculinization, *sensu* [45], of both the physiological and behavioural traits of *Eulemur*. Offensive female aggression within lemur groups does not require the presence of offspring; instead, it promotes social dominance [17], making it functionally and

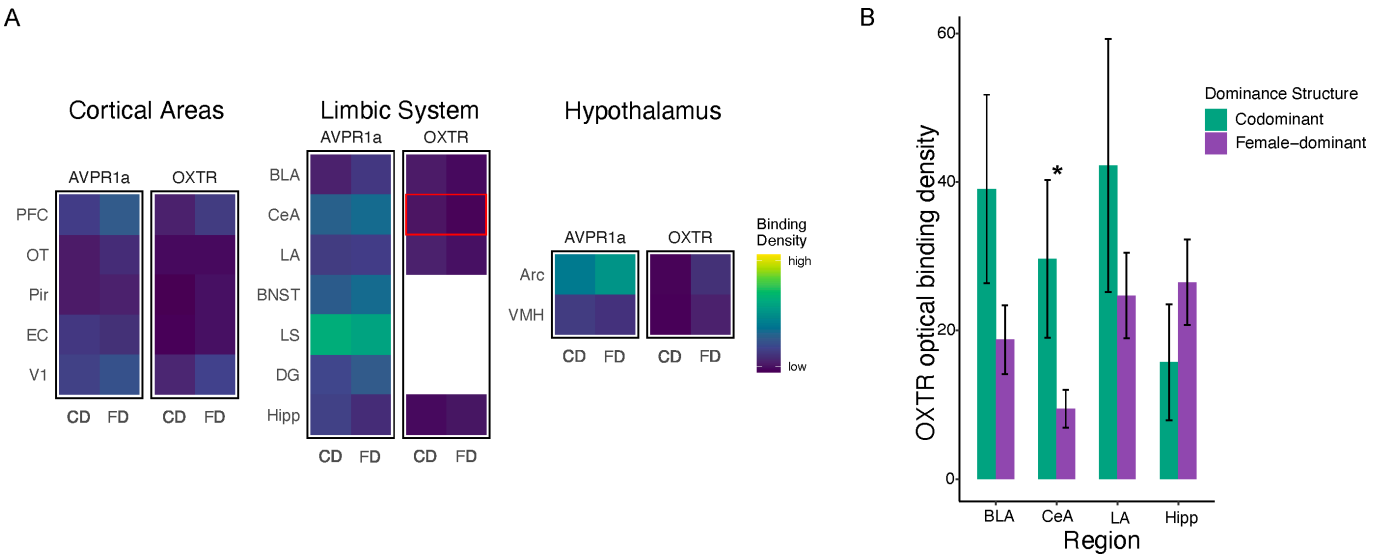

Figure 3. Neuropeptide binding densities in corticolimbic and hypothalamic areas in *Eulemur* species. Panel A shows relative binding densities of AVPR1a and OXTR across all included regions. Columns depict average binding density in specimens from codominant (CD) and female-dominant (FD) species, respectively. Red box indicates a significant relationship between receptor density and dominance structure. Blank cells indicate no measurement available for radioligand binding in that region. Panel B shows average OXTR binding density in codominant and FD species in limbic regions where OXTR binding was detected. Error bars represent s.e.m. The asterisk indicates a significant ($p < 0.05$) relationship between receptor density and dominance structure.

contextually similar to offensive intermale aggression in rodents. It follows that the underlying neurobiology of aggression in female lemurs would also align with that observed in male rodents.

We attribute the neuroanatomical difference between female-dominant and codominant species to the suite of dominance-related behaviour, notably enhanced aggression, submission and increased scent-marking, known to distinguish these species [17]; nevertheless, we acknowledge that other factors could be related to OXTR density in the CeA. For instance, OXT action in the CeA also plays a role in affective states, such as fear and anxiety (e.g. [72]), and cognitive abilities, such as social discrimination (e.g. [73]). These alternatives seem unlikely to explain our findings in *Eulemur*, however, given that the semi-free-ranging lemurs at the DLC—a forested facility, focused on conservation and public education—have lives that bear little resemblance to the 'normal or chronic pain conditions' that induce fear and anxiety in cage-reared rodents (e.g. [68]). Moreover, whatever negative affective states may be associated with subordination in *Eulemur* most likely would be evidenced predominantly as stress in the males of species experiencing exceptionally aggressive females [50]. Likewise, despite species differences in scent-marking frequencies (as a form of competition), all members of *Eulemur* retain pronounced scent glands, complex chemosignals and specialized olfactory communication skills used in social discrimination [52]. It is specifically because of the variation seen in dominance structure despite close genetic relatedness, recent divergence times and similar ecological characteristics that we selected the *Eulemur* genus as our prime system in which to study the neuroendocrine basis of aggression. We cannot, however, rule out that phylogenetic relatedness could be influencing OXTR density in the CeA independently of any behavioural differences. Unfortunately, the pharmacological manipulations necessary to rule out such alternatives are logistically challenging to implement in endangered species [58].

Our results raise questions about the functional significance of aggressively mediated female dominance and the evolutionary circumstances under which the costs of aggression may exceed the benefits. Exploration of the socioecological conditions precipitating the shift from female dominance to a more egalitarian social structure in *Eulemur*, including the potential costs of high androgen concentrations to females (e.g. [50,74]), would further our understanding of the evolution of lemur social systems. Our interpretation further supports the female masculinization hypothesis of female dominance [17,50,60] and invites future research into the nature of brain masculinization in female-dominant species [75].

In closing, we suggest that when investigating the neurobiology of social behaviour, it is important to consider the broader biology of the chosen model. In the case of aggression in female rodents, most studies include either lactating mothers or induced forms of aggression, such as those arising from social isolation or from the resident–intruder paradigm [4,6,76]. Although such paradigms may have predictive value, they may not faithfully replicate all forms of ecologically relevant aggression, potentially limiting the broad applicability and translatability of neural findings [77,78]. By comparison, our sample includes lemurs that lived in naturalistic social groups and freely expressed aggression, throughout their lives, in a species-typical manner. Our data highlight the ecological relevance of lemur aggression and suggest that species within the *Eulemur* clade are robust primate models for understanding the neurobiology of aggression. The current study demonstrates the value of broadening species representation in neuroscience and provides new information about the neurobiological underpinnings of female combative aggression.

Ethics. Animal protocols at the DLC were approved by the Duke University Institutional Animal Care and Use Committee (A216-20-11).
Data accessibility. Data and code are available from the Dryad Digital Repository [79].
Declaration of AI use. We have not used AI-assisted technologies in creating this article.

Authors' contributions. A.S.: conceptualization, formal analysis, funding acquisition, investigation, writing—original draft; M.R.G.: conceptualization, formal analysis, investigation, writing—original draft; N.G.: conceptualization, data curation, funding acquisition, methodology, writing—review and editing; A.S.: funding acquisition, investigation, writing—review and editing; S.M.F.: funding acquisition, investigation, methodology, writing—review and editing; M.P.: investigation, methodology, writing—review and editing; K.B.: funding acquisition, supervision, writing—review and editing; H.P.: investigation, supervision, writing—review and editing; C.M.D.: conceptualization, funding acquisition, investigation, project administration, supervision, writing—review and editing.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interest declaration. We declare we have no competing interests.

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