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Oxytocin and vasopressin enhance responsiveness to infant stimuli in adult marmosets

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ABSTRACT

The neuropeptides oxytocin (OT) and arginine-vasopressin (AVP) have been implicated in modulating sex-specific responses to offspring in a variety of uniparental and biparental rodent species. Despite the large body of research in rodents, the effects of these hormones in biparental primates are less understood. Marmoset monkeys (*Callithrix jacchus*) belong to a clade of primates with a high incidence of biparental care and also synthesize a structurally distinct variant of OT (proline instead of leucine at the 8th amino acid position; Pro^8-OT). We examined the roles of the OT and AVP systems in the control of responses to infant stimuli in marmoset monkeys. We administered neuropeptide receptor agonists and antagonists to male and female marmosets, and then exposed them to visual and auditory infant-related and control stimuli. Intranasal Pro^8-OT decreased latencies to respond to infant stimuli in males, and intranasal AVP decreased latencies to respond to infant stimuli in females. Our study is the first to demonstrate that Pro^8-OT and AVP alter responsiveness to infant stimuli in a biparental New World monkey. Across species, the effects of OT and AVP on parental behavior appear to vary by species-typical caregiving responsibilities in males and females.

Introduction

Despite structural and chemical similarities, oxytocin (OT) and arginine-vasopressin (AVP) differentially affect parental behavior depending on species, previous parental experience, sex, and breeding system. Evidence from uniparental species presents a clear role for OT in modulating parental behavior: increased oxytocinergic activity enhances maternal behavior (reviewed in Bosch and Neumann, 2012). Mothers with naturally high oxytocinergic activity engage in high levels of parental behavior (rat, Champagne et al., 2001; rat, Francis et al., 2000; macaque, Maestripieri et al., 2009), and females that would not ordinarily engage in parental behavior can be induced to do so with exogenous OT infusions (rat, Fahrbach et al., 1984; sheep, Kendrick et al., 1987; mouse, McCarthy et al., 1986; rat, Pedersen et al., 1982). Recent empirical and theoretical perspectives from research on humans suggest that OT exerts a multiplicity of effects on both male and female caregivers, including complex behavior such as bonding, coordination of affect, and alterations in the sensitivity of the caregiver to stimuli emanating from dependent offspring (reviewed in Feldman, 2015).

The AVP system also acts on parental care in ways that are sex- and species-specific: AVP exerts the same effects on parental behavior in males of biparental species as it does in females of uniparental species. In biparental male prairie voles and female rats alike, AVP increases and AVP V1a receptor antagonists (V1a-A) decrease parental behavior (Bosch and Neumann, 2012; Wang et al., 1994). The AVP system is also involved in modulating defensive parental aggression, and again it enhances this behavior in males of biparental rodents and females of uniparental species, though there are some strain differences (Bosch and Neumann, 2012; Nephew and Bridges, 2008; Young et al., 1997). In some species, such as the biparental California mouse, the AVP system is associated with parental care in males and females, but this association is weaker in females than it is in males, and AVP has been linked to aggression in males only (Bester-Meredith and Marler, 2001, 2003, 2012). Thus the effect of the AVP system on parental behavior, especially defensive aggression, depends not only on the sex of the individual, but also on differences in species-typical offspring care.

The OT and AVP systems are highly conserved among mammals, including primates, but New World monkeys (NWM) exhibit considerable inter-specific diversity in the OT gene and the OT and AVP receptors (OTR, V1a), while the AVP ligand remains unchanged (Lee et al., 2011; Ren et al., 2014, 2015; Vargas-Pinilla et al., 2015). Of particular interest is a clade of small-bodied monkeys (Callitrichidae). Marmosets (*Callithrix*) exhibit high rates of biparental care and a willingness to respond to isolated infants in distress (Lee et al., 2011; Nunes et al., 2001; Santos et al., 1997; Zahed et al., 2008), and they also produce an OT variant that substitutes leucine for proline at

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position eight (Lee et al., 2011). This variant (Pro^8-OT) is structurally distinct from the conserved Leu^8-OT, and variation in both *OXTR* and *AVPR1a* genes is associated with social behavior (Ren et al., 2015, 2014). This ligand-receptor-social system co-evolution suggests a functional role of neuropeptides in modulating social behavior, thus species in this clade can provide insight into relationships between neuropeptide systems and parental behavior. One study has shown that Leu^8-OT enhances passive food sharing to offspring in adult male marmosets (Saito and Nakamura, 2011), but Pro^8-OT and Leu^8-OT differentially affect marmoset behavior (Cavanaugh et al., 2014), and no studies have yet investigated the roles of Pro^8-OT or AVP in male and female marmosets.

Our study investigated the roles of the OT and AVP systems in modulating parental responsiveness in marmosets. If these neuropeptides modulate the brain systems that control sensitivity to infant stimuli, then marmosets exposed to intranasal Pro^8-OT should exhibit increased responsiveness to and interest in infant stimuli compared to control stimuli, and marmosets exposed to OT receptor antagonists (OTA) should exhibit decreased responsiveness to and interest in infant stimuli. Also, because AVP affects parental behavior in males more so than in females in biparental rodents, we expected intranasal AVP to increase responsiveness to infant stimuli in marmoset males, but not females.

Methods

Subjects

We tested adult male (n = 8) and female (n = 8) marmosets (*Callithrix jacchus*). Marmosets were housed either in pairs or as the breeding pair of a family group (Table 1). One female (Arw) was pregnant during testing, three females (Kha, Lil, Nyl) were contracepted, and five males (Bat, Abu, Jax, Dac, Fab) were vasectomized (but not gonadectomized). Experimental procedures were approved by UNMC/UNO IACUC (#13-039-07-FC). Two males and two females had previous experience with infants as parents. Details of housing and husbandry protocols can be found in Schaffner et al. (1995).

Neuropeptide manipulations

OT and AVP systems were manipulated using five treatment conditions, using a combination of oral (via preferred food item) and intranasal deliveries: Pro^8-OT (150 μg/kg; CYIQNCPPG-NH_2) and AVP (133 μg/kg; CYFQNCPRG-NH_2) were each administered intranasally, and doses were based on previous research in NWMs (Cavanaugh et al., 2014; Jarcho et al., 2011; Smith et al., 2010). Intranasal delivery is a common method to administer small neuropeptide ligands to the brain non-invasively (Born et al., 2002; Neumann et al., 2013), but there are currently no pharmacological or behavioral data available for neuropeptide receptor antagonists administered intranasally. Instead, we chose ligands that are orally available and would be expected to cross the blood–brain barrier (Boccia et al., 2007; Pettibone et al., 1993; Serradeil-Le Gal et al., 1993). Doses for the OTR antagonist (OTA; 20 mg/kg; L-368,899 provided by Dr. Peter Williams, Merck) and the V1a antagonist (V1a-A; 20 μg/kg; SR49059) were based on previous research in NWMs and on the binding affinities of the antagonists for their respective receptors (Cavanaugh et al., 2014; Jarcho et al., 2011; Manning et al., 2012; Smith et al., 2010). Oral deliveries were administered 90 min prior to testing, and intranasal deliveries were administered 20 min prior to testing between 0800–1000 h. These treatment-testing intervals allowed for maximal absorption and concentration in cerebrospinal fluid (Boccia et al., 2007; Born et al., 2002). Treatments were arranged so that the experience of each marmoset was identical during all testing sessions: Pro^8-OT = oral control + intranasal Pro^8-OT; AVP = oral control + intranasal AVP; OTA = oral OTA + intranasal saline; V1a-A = V1a-A + intranasal saline; and SAL = oral control + intranasal saline. Each marmoset was tested under all five treatment conditions and received each treatment condition on two occasions. A one-week washout period occurred between the same treatments and a two-week washout between different treatments. The order of treatment was pseudorandomized and counterbalanced among subjects.

Table 1
Subject characteristics.

Pair (F/M)	Age (years)	Infant exposure*	Housing
Arw/Cle	4.0/1.7	Current	Pair + 2 infants
Kha/Dex	5.0/5.0	Current	Pair + 2 infants
Lil/Bel	2.1/5.0	No	Pair
Ell/Bat	4.1/4.2	No	Pair
Nyl/Odi	4.4/4.6	No	Pair
Tar/Abu	5.4/4.1	No	Pair
Vel/Jax	5.5/4.6	No	Pair
Art/Dac	5.4/4.2	No	Pair
Ath/Fab	4.6/5.7	No	Pair

Note. F = female, M = male, *No = no exposure to infants in cage for at least 24 months.

Behavioral testing

After treatment, marmosets were released into the long arm of a T-maze that had a stimulus box at the end of each arm (Fig. 1). The infant stimulus box contained lifelike models of two infant marmosets on a branch, and a speaker that played distress (*cry*, *tsik*) and contact (*twitter*) calls recorded from two-week-old infants (Pistorio et al., 2006). The control stimulus box contained only a branch, and emitted 1 s bursts of pure tone at 5500 Hz, the dominant frequency of the recorded *cry* calls. Acoustic stimuli alternated for the duration of the test between 30 s of infant calls and 30 s of control tone, with a 5 s period of silence between tones and calls. The placement of the stimulus boxes (left vs. right) was counterbalanced across trials. We used three measures to index the behavior of marmosets toward infant stimuli: 1) responsiveness to infant cues — latency to first "peek" into the infant stimulus box, 2) sustained interest in infant stimuli — total duration of "peeks" into the stimulus boxes, and 3) preference for one stimulus — greater duration spent within 15 cm of one stimulus over the other. "Peeks" were scored when the marmoset's face was within 6 cm of a viewing hole and its gaze was oriented into the box. We also recorded behavioral indicators of stress/neophobia: alarm and contact vocalizations, latency to approach and investigate control stimuli, and total activity.

Statistical analyses

Behavioral data were averaged within treatment and analyzed using 5(treatment) × 2(stimulus type) × 2(sex) mixed factorial ANOVAs. Behavioral indicators of stress were tested for treatment effects using 5(treatment) × 2(sex) mixed factorial ANOVAs.

Results

Responsiveness to infant cues

The latencies for marmosets to perform the first peek in the stimulus boxes were affected by treatment condition, stimulus type, and sex ($F(4,64) = 3.15$, $p = .020$, $\eta^2 = .17$; Fig. 2). Male marmosets treated with Pro^8-OT peeked in the infant stimulus box significantly faster than when treated with saline ($t(8) = -3.16$, $p = .013$, $d_z = -1.05$), and faster than females treated with Pro^8-OT ($t(16) = -.247$, $p = .025$, $d_s = -0.12$). Additionally, females treated with AVP peeked in the infant stimulus box significantly faster than when treated with saline ($t(8) = -2.50$, $p = .037$, $d_z = -.83$) and faster than males treated with AVP ($t(16) = -3.14$, $p = .006$, $d_s = -1.48$). Latencies to the first peek in the control stimulus box, though, were unaffected by

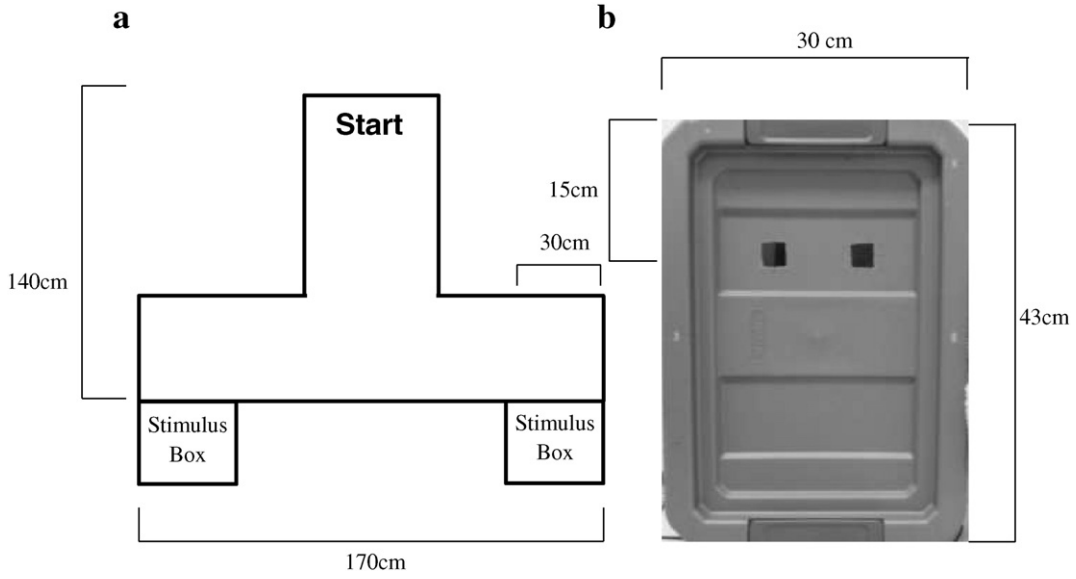

Fig. 1. T-maze apparatus (a) and stimulus box (b). Each stimulus box contained visual and auditory stimuli, accessed through two holes in each box.

neuropeptide treatment condition (paired comparisons within sexes, all $t(8) < \pm 1.19$, $p =$ n.s., $d_z < .40$; male vs. female comparisons, all $t(16) < \pm 1.37$, $p =$ n.s., $d_s < .65$) demonstrating that the effects of neuropeptide treatment were specific to infant stimuli, and did not generalize to other novel auditory and visual stimuli. Oral neuropeptide antagonists had no effect on peek latencies ($t(8) < \pm 1.18$, $p =$ n.s., $d_z < .39$; $t(16) < \pm 1.37$, $p =$ n.s., $d_s < .64$).

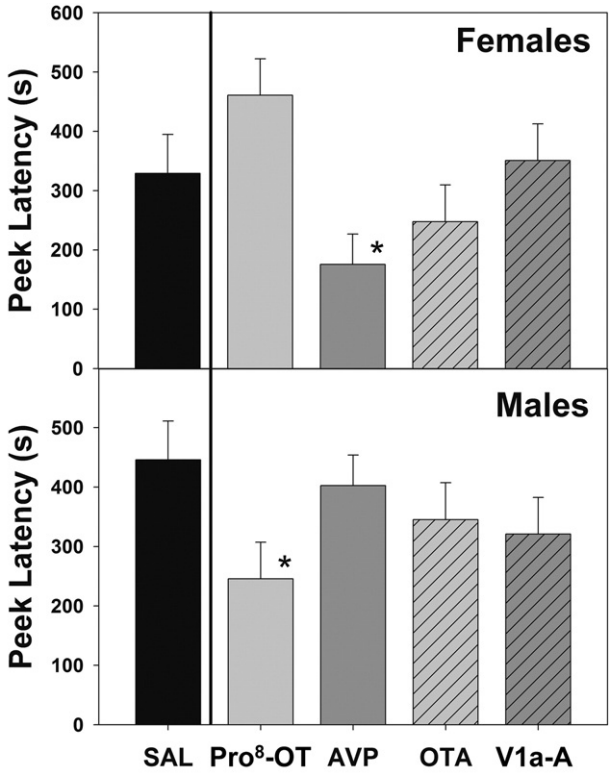

Fig. 2. Mean (±SEM) latency (s) to the first peek in stimulus boxes in female and male marmosets. Asterisks indicate significant differences compared to saline.

Sustained interest in infant stimuli

Marmosets spent more time investigating the infant stimulus box compared to the control stimulus box ($F(1,16) = 29.46$, $p < .001$, $\eta^2 = .65$; Table 2), but the duration of time that marmosets spent peeking in the stimulus boxes was not significantly affected by neuropeptide treatment, sex, or the interaction ($F(4,64) < .43$, $p =$ n.s., $\eta^2 < .09$).

Stimulus preferences

Males and females differed on time spent near each stimulus ($F(1,16) = 6.53$, $p = .02$, $\eta^2 = .29$; Table 2). Female marmosets spent more time in close proximity to the infant stimulus box compared to the control stimulus box ($t(8) = -3.09$, $p = .015$, $d_z = -1.03$), whereas males had no such preference. Neuropeptide treatment did not affect time spent near the infant box ($F(4,64) < .75$, $p =$ n.s., $\eta^2 < .04$).

Stress/neophobia measures

Neuropeptide treatment did not significantly affect rates of phee calling, alarm calling, latency to approach/investigate, or total locomotion (Table 3). This indicates that the effects of neuropeptide treatment on responsiveness to infant stimuli were not due to anxiety, general neophobia, or total activity.

Table 2
Sustained interest and preference for stimuli types.

Stimulus	Peek duration (s)		Proximity duration (s)	
	Infant	Control	Infant	Control
Male	4.0 (0.53)	1.9 (0.36)	147.7 (15.9)	153.6 (16.5)
Female	3.6 (0.53)	2.3 (0.36)	194.0 (15.9)*	140.1 (16.5)
Combined	3.8 (0.38)*	2.1 (0.26)	170.87 (11.23)	146.84 (11.67)

Note. Data presented are means ± SEM.
* Indicates a significant difference from control stimulus.

Table 3
Neuropeptide manipulation does not affect behavioral indicators of stress.

Behavior	AVP	Pro^8-OT	AVPA	OTA	SAL	$F(4,64)$	p
Locomotion	25.7(4.6)	27.1(4.7)	28.7(6.2)	34.2(6.2)	27.8(5.6)	0.77	.548
Phee calling	6.9(1.8)	7.9(2.1)	9.0(2.1)	8.4(2.6)	8.6(2.0)	0.28	.887
Alarm calling	3.1(1.4)	3.5(1.7)	3.7(1.6)	6.4(2.7)	1.4(0.8)	1.62	.182
Approach control novel (s)	161.6(51.0)	148.6(34.4)	161.3(41.1)	160.8(35.5)	127.1(31.7)	0.174	.951
Peek in control novel (s)	328.4(43.6)	365.2(52.1)	320.5(47.0)	376.7(34.6)	356.0(45.0)	0.277	.892

Note. Data presented under treatment columns are means (±SEM).

Discussion

This study is the first to use Pro^8-OT or AVP to study parental responsiveness in a NWM, and our findings extend the growing molecular and behavioral evidence that neuropeptides modulate parental care in mammals. Neuropeptide agonists enhanced responsiveness to infant stimuli in marmosets, but the effects were sex-specific; Pro^8-OT enhanced responsiveness to infant stimuli in males, and AVP enhanced responsiveness to infant stimuli in females. These results were opposite our predictions, because we had expected AVP to affect males, but not females, as in rodents. Antagonist treatments at these doses did not affect any measures, and it appears that chronic, rather than acute, oral antagonist treatment may be necessary to affect marmoset social behavior (Cavanaugh et al., 2014; Smith et al., 2010), or that the timing of the oral antagonist treatments was sub-optimal. It is also possible that when only one receptor type is blocked (either OTR or V1a), responses to infant stimuli can be rescued by activation of the other receptor by endogenous neuropeptides, as has been demonstrated in prairie voles (Bales et al., 2004). Additionally, none of the neuropeptide manipulations affected anxiety-like behavior or neophobia, indicating that Pro8-OT and AVP affected responses to infant stimuli specifically.

Previous research has shown that not only do marmoset parents respond behaviorally to infant stimuli faster than non-parents (Sánchez et al., 2014; Zahed et al., 2008), but also that the neuropeptide systems in male marmoset brains are altered by parental experience (Kozorovitskiy et al., 2006; Woller et al., 2012). Our sample included both experienced and inexperienced marmosets, and we found that neuropeptides modulated responses to infant stimuli across both categories of marmosets. It is possible though, that experience caring for offspring can alter neuropeptide-induced changes in responsiveness. Our small sample of two fathers and two mothers did not allow for the assessment of parental status as a factor in our analyses, so this will be an important avenue for future research. Only one study has manipulated OT to study actual parental behavior in marmosets; intracerebroventricular Leu^8-OT increases tolerance for infant food stealing in marmoset fathers (Saito and Nakamura, 2011). The finding that Leu^8-OT enhances passive food sharing in marmoset fathers (Saito and Nakamura, 2011), and our finding that Pro^8-OT and AVP increase responsiveness to infant stimuli in male and female marmosets, respectively, indicate that neuropeptides are important facilitators of responsiveness to infant cues in marmosets.

The sex-specific effects of Pro^8-OT and AVP were unexpected, as AVP, rather than OT, is more closely associated with male parental and social behavior in biparental rodents (Bales et al., 2004; Wang et al., 1994). This finding highlights the potential for interspecific variation in the effects of neuropeptides based on species-typical patterns of offspring care. It has been proposed that OT enhances nurturing parental behavior, while AVP enhances defensive aggression (van Anders et al., 2011), and thus the response to neuropeptide manipulation may not necessarily vary by sex, but by the specific parental care roles played by males and females in different infant-rearing systems. For instance, AVP modulates parental defense behavior in males of biparental rodents (Young et al., 1997), and affects the same behavior in females of uniparental rodents (Bosch and Neumann, 2012). Thus the influence of OT and AVP on behavior in rodents is explained better as a result of the nurturing/defending responsibilities in parental care rather than as a sex difference. Though male and female marmosets respond to infant stimuli similarly, fathers contribute more to "nurturant" parental care (i.e. infant carrying) overall during the development of offspring (French et al., 2008; Sánchez et al., 2014). Furthermore, adult female marmosets respond aggressively toward intruders, especially when they reside in family groups with infants (Schaffner and French, 1997). In this light, the effects of neuropeptides on responsiveness to infant stimuli in marmosets align with what is known from rodents. That is, AVP tends to affect the sex that exhibits more aggression and defense (which may not necessarily be the male), and OT affects the sex that exhibits more nurturant care.

In addition to their effects on social behavior, OT and AVP can have anxiolytic and anxiogenic properties, respectively. In humans, intranasal oxytocin decreases hypothalamic–pituitary–adrenal (HPA) activation during social stress and increases trust (Heinrichs et al., 2009; Van IJzendoorn and Bakermans-Kranenburg, 2012). Similarly, intranasal OT decreases HPA activation in squirrel monkeys during social isolation (Parker et al., 2005). However, we found that neither OT nor AVP treatment had any effect on behavioral indicators of stress/anxiety, including the latency to approach or investigate the novel control stimulus, suggesting that the effects of neuropeptide treatment on the latency to respond to infant stimuli were specific to parental-like behavior. A potential explanation for why OT produces anxiolysis in other primates but not in marmosets comes from work done in rodents that use localized neuropeptide manipulations to specific brain nuclei. When manipulations are diffuse across the brain, upregulation of the OT system decreases and upregulation of the AVP system increases anxiety like behavior in rats and mice (Bosch and Neumann, 2008; Gimpl and Fahrenholz, 2001). Moreover, OT agonists inhibit, and AVP agonists excite the same distinct populations of neurons in the amygdala (Huber et al., 2005). When neuropeptide manipulations are localized to the MPOA, a region implicated in the control of parental care, upregulations of the AVP and OT systems increase maternal behavior without affecting anxiety-like behavior (Bosch and Neumann, 2012, 2008). Furthermore, in another socially relevant nucleus, the PVN, upregulations of the AVP and OT systems increase maternal defense. In the central amygdala though, OT and AVP have differential effects; OT decreases and AVP increases defensive behavior (Bosch and Neumann, 2012). In rodents, OT and AVP in the amygdala are critical for fear and social recognition (Ferguson et al., 2001), but OT receptors have not been found in the amygdala of marmosets (Schorscher-Petcu et al., 2009), though V1a receptors are present (Schorscher-Petcu et al., 2009; Wang et al., 1997). Thus it is possible that intranasal neuropeptides at the doses used here activate only those circuits that control parental behavior, leaving anxiety-like behavior unchanged.

Conclusions

We showed that neuropeptides modulate responsiveness to infant stimuli in marmosets. Specifically, OT increased responsiveness to infant stimuli in males, whereas AVP increased responsiveness to infant stimuli in females. Neither OT nor AVP receptor antagonist treatment affected marmoset behavior, and none of the OT or AVP system manipulations affected anxiety-like behavior. When compared to previous work in uniparental and biparental rodents, our findings are best described as a consequence of specific social/parental responsibilities; OT

affects the behavior of the parent that engages in the most parental care, and AVP affects the behavior of the parent that engages in defensive behavior. The differential effects of OT and AVP on male and female behavior are especially interesting in marmosets, because recent molecular studies in New World monkeys, particularly those in the family *Callitrichidae*, have shown that the V1a and OTR genes are quite different from human receptors, and the OT and the OT-OTR genes have coevolved (Ren et al., 2014, 2015; Vargas-Pinilla et al., 2015). It is yet unknown whether Pro^8-OT is more or less selective for the marmoset OTR compared to Leu^8-OT and the OTR in most mammals, or how well Pro^8-OT binds to the marmoset V1a. Experiments exploring these molecular mechanisms are needed in order to fully understand the behavioral results of neuropeptides in marmosets presented here and elsewhere. The present study, in conjunction with previous reports on marmosets and humans, supplements the body of work in uniparental and biparental rodents and primates, by highlighting the diversity and subtlety in the way in which neuropeptides affect parental behavior.

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