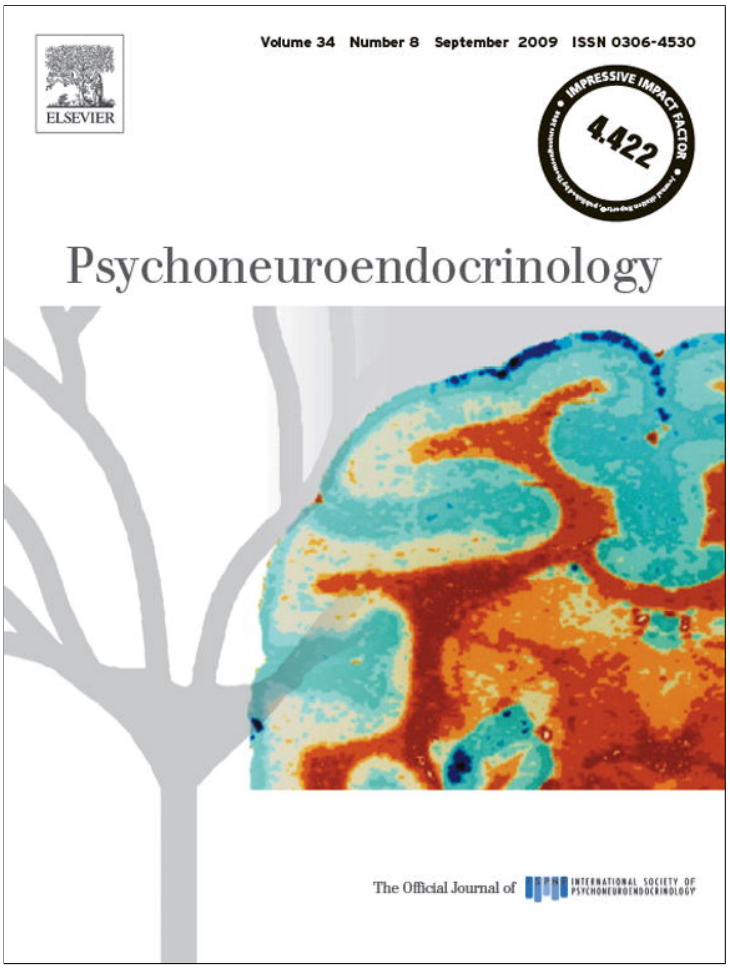

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Effects of elevated circulating cortisol concentrations on maternal behavior in common marmoset monkeys (*Callithrix jacchus*)

Wendy Saltzman [a,b,*], **David H. Abbott** [b,c]

[a] *Department of Biology, University of California, Riverside, CA 92521, United States*
[b] *National Primate Research Center, University of Wisconsin, Madison, WI 53715, United States*
[c] *Department of Obstetrics and Gynecology, University of Wisconsin, Madison, WI 53715, United States*

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Summary Both acute and chronic stress can impair maternal behavior and increase rates of infant abuse in several species. The mechanisms inducing these effects are unknown, but experimental manipulation of circulating corticosterone levels alters maternal behavior in rats, and circulating or excreted cortisol concentrations have been found to correlate either positively or negatively with maternal behavior in humans and nonhuman primates. In this study, therefore, we experimentally tested the hypothesis that both acute and chronic treatment with exogenous glucocorticoids would alter maternal behavior in a primate, the common marmoset (*Callithrix jacchus*). Multiparous females, approximately 3—5 weeks postpartum, received daily injections of either cortisol (hydrocortisone sodium succinate and hydrocortisone acetate; $N = 7$) or vehicle ($N = 7$) for 8 days, and maternal behavior was characterized under baseline conditions as well as during exposure to a noise stressor. Cortisol treatment successfully elevated both morning and afternoon plasma cortisol concentrations and suppressed circulating levels of adrenocorticotropic hormone. In home-cage observations, cortisol-treated females carried their infants significantly less than control mothers, and in noise-stressor tests, several hours after the first cortisol or vehicle treatment, cortisol-treated mothers inspected their infants significantly more often than controls. Aggression towards infants was infrequent and mild, and did not differ between treatment groups. These findings provide the first experimental evidence that cortisol elevations can alter maternal behavior in primates. As these effects were limited in scope, however, they suggest that other stress-responsive hormones or neuropeptides may additionally play a role in mediating the effects of stress on maternal behavior.

1. Introduction

Stress can impair maternal behavior and increase the likelihood of child abuse. In humans, it has long been appreciated

* Corresponding author at: Department of Biology, University of California, Riverside, CA 92521, United States. Tel.: +1 951 827 6356; fax: +1 951 827 4286.
E-mail address: Saltzman@ucr.edu (W. Saltzman).

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that a variety of acute and chronic psychosocial and environmental stressors, such as poverty, domestic violence, sexual assault, natural disasters, and lack of social support, may contribute to deficient maternal behavior and increased abusive behavior (e.g., Kotch et al., 1995; Brockington, 1996; Banyard et al., 2003; Tolan et al., 2006). Stress also contributes to the onset of several psychopathological conditions, including major depressive disorder, postpartum depression, and post-traumatic stress disorder, which in turn are associated with deficient maternal behavior, increased child abuse, and impaired mother–child relationships (e.g., Kotch et al., 1995; Lovejoy et al., 2000; Oyserman et al., 2000; Nonacs, 2002; Bailham and Joseph, 2003; Banyard et al., 2003; Brockington, 2004; Windham et al., 2004; Cohen et al., 2008). Compared to mothers without obvious signs or symptoms of depression, for example, mothers with clinically diagnosed depression engage in lower rates of positive behaviors and higher rates of negative and disengaged behaviors towards their children, and may be more likely to commit severe physical abuse (Lovejoy et al., 2000; Dawson et al., 2003; Windham et al., 2004).

Both acute and chronic stress have also been found to impair maternal behavior and increase infant abuse in animal models. In nonhuman primates, as in humans, anxiety and psychosocial or environmental stressors, such as lack of social support, crowding, and receipt of aggression, increase rates of infant abuse (Reite and Caine, 1983; Troisi and D'Amato, 1994; Maestripieri and Carroll, 1998a,b). In a study of group-housed pigtail macaques (*Macaca nemestrina*), for example, acute stress was the most common context for the spontaneous occurrence of infant abuse (Maestripieri and Carroll, 1998a). Similarly, mother rats (*Rattus norvegicus*) exhibited diminished maternal behavior and/or increased abusive behavior immediately following acute restraint stress (Yamada et al., 2002), during acute confinement in a novel chamber with limited bedding (Roth and Sullivan, 2005), and during exposure to chronic stressors involving wet bedding and forced foraging (Léonhardt et al., 2007) or limited nesting material (Ivy et al., 2008). Conversely, the spontaneous onset of maternal behavior in new rat mothers is associated with, and may in fact depend upon, a general reduction in fearfulness and anxiety as well as reduced hormonal and behavioral responses to stress (Neumann, 2003; Numan and Insel, 2003; Tu et al., 2005).

The mechanisms by which stress impairs maternal behavior are not known. One possibility is that such effects are mediated by elevated concentrations of glucocorticoid hormones (i.e., cortisol and corticosterone) (Wingfield and Sapolsky, 2003). Few studies, however, have experimentally investigated the effects of glucocorticoids on maternal behavior. A recent series of experiments by Rees and colleagues (Rees et al., 2004, 2006; Graham et al., 2006) has indicated that glucocorticoids can either facilitate or inhibit aspects of maternal behavior in rats, depending on the reproductive history of the individual animal. In postpartum females, adrenalectomy decreased and corticosterone replacement increased licking of pups, time spent in the nest, and maternal memory (Rees et al., 2004; Graham et al., 2006). Conversely, in sensitized virgin female rats, adrenalectomy increased licking of pups and time spent crouching over pups, whereas corticosterone replacement had opposite effects (Rees et al., 2006).

Correlational studies in primates have suggested a similar dichotomy of associations between cortisol and maternal behavior. In women, salivary or plasma cortisol concentrations during the first few days postpartum were positively correlated with attraction to infant-related odors and affectionate behavior towards the infant in first-time mothers (Fleming et al., 1987, 1997). At roughly 6 weeks postpartum, higher salivary cortisol levels were similarly associated with more affectionate behavior towards infants in primiparous mothers aged 19–25 years old but were associated with less instrumental care-taking behavior in younger primiparous mothers (Krpan et al., 2005). Circulating or excreted cortisol concentrations have also been found to correlate negatively with specific aspects of maternal behavior in Western lowland gorillas (*Gorilla gorilla gorilla*; Bahr et al., 1998), Japanese macaques (*M. fuscata*; Bardi et al., 2003), and baboons (*Papio hamadryas anubis* sp.; Bardi et al., 2004; Ramirez et al., 2004). To our knowledge, however, effects of glucocorticoids on maternal behavior have not been tested experimentally in any primate species.

In the present study, therefore, we experimentally manipulated circulating cortisol concentrations in female common marmosets (*Callithrix jacchus*) to determine whether elevated cortisol levels alter maternal behavior. These small-bodied (~350 g) New World monkeys live in small groups (~3–16 individuals) in which the behaviorally dominant female gives birth, usually to fraternal twins or triplets, at roughly 6-month intervals (Digby et al., 2007). Infants are weaned at approximately 8–10 weeks of age (Tardif et al., 2003), and infant care is shared by all members of the social group, including the father and older siblings; however, mothers spend substantial amounts of time carrying their infants (e.g., approximately 30–40% of observation time during the first month postpartum and approximately 10–20% during the second month postpartum; Tardif et al., 1986; Ximenes and Sousa, 1996). This biparental and cooperative care of infants is unusual among primates and makes marmosets a particularly suitable model for human parental behavior. Moreover, stress has been reported to increase rates of infant abuse and infanticide by marmoset parents and to markedly reduce infant survival rates (Johnson et al., 1991).

We treated multiparous females with exogenous cortisol for 8 days during the mid-lactational period and examined both the acute and chronic effects on maternal behavior. Because glucocorticoid hormones are important regulators of fear and anxiety and may be especially likely to affect behavior under stressful, anxiogenic, or frightening circumstances (Korte, 2001; Schulkin et al., 2005), we characterized maternal behavior both under baseline conditions and during exposure to an auditory stressor.

2. Materials and methods

2.1. Animals

Subjects were 14 multiparous female common marmosets housed at the National Primate Research Center at the University of Wisconsin (UW) – Madison (WNPRC). Seven females were assigned to the cortisol treatment condition, and the remaining 7 served as vehicle-treated controls. Cortisol-treated and control animals did not differ in age (60.7 ± 8.5

months vs. 59.5 ± 7.9 months, respectively, mean ± SEM; $T = -0.110$, df = 12, $p = 0.915$), body mass (446 ± 16 g vs. 436 ± 13 g, $T = -0.467$, df = 12, $p = 0.649$), or parity (5 ± 1 litlitters vs. 5 ± 1 litters; $T = -0.402$, df = 12, $p = 0.695$) at the outset of data collection. Each female was housed with her mate and up to 8 offspring, including 1–2 infants and 1–7 older offspring.

Marmosets were housed indoors in aluminum and wire mesh cages (61 cm × 91 cm × 183 cm or 122 cm × 61 cm × 183 cm) that permitted visual, auditory, and olfactory contact between animals in different groups. The animals were fed Mazuri Hi-Fiber Callitrichid Diet (Mazuri, Richmond, IN) supplemented with vitamin D, at 1230–1330 h; however, food was typically available in the cages at all times. Water was available ad libitum. Lights were on from 0630 to 1830 h, and room temperature and humidity were maintained at approximately 23 °C and 30–70%, respectively.

All procedures were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* and were reviewed and approved by the Graduate School Animal Care and Use Committee of UW-Madison. WNPRC is accredited by AAALAC as part of the UW-Madison Graduate School.

2.2. Design

The experimental design is summarized in Table 1. We collected data on each female marmoset during a 10-day period, beginning when her youngest infants were 23–24 days old. Animals in the cortisol condition received an injection of hydrocortisone sodium succinate (Solu-Cortef, Pfizer, New York, NY; 40 mg/kg body weight in 0.8 ml/kg saline, SC) on day 1, followed by daily injections of hydrocortisone acetate (Sigma–Aldrich, St. Louis, MO; 90 mg, SC suspended in 0.45 ml sesame oil) on days 2–8. Initial doses were based on published studies on the squirrel monkey (*Saimiri sciureus*, another small-bodied New World monkey; Lyons et al., 2000, 2004), and modified based on pilot tests on female marmosets (unpublished data). We aimed to produce circulating cortisol concentrations in between peak levels occurring at the height of the circadian cycle (~275–400 μg/dl; George and Abbott, unpublished data) and those occurring in response to stress (e.g., ~550 μg/dl following social group formation and wounding, Saltzman et al., 1994; ~830 μg/dl during periods of inter-female aggressive interactions, George and Abbott, unpublished data) in female common marmosets. Hydrocortisone sodium succinate produces a marked, although relatively transient, elevation in circulating cortisol concentrations within 1 h, whereas hydrocortisone acetate produces delayed but more prolonged elevations in circulating cortisol levels (Lyons et al., 2000, 2004, unpublished data). Serial application of the two cortisol preparations allowed rapid induction of elevated circulating cortisol levels on the first day of treatment, permitting behavioral testing during acute cortisol excess, as well as appropriate daily maintenance of hypercortisolemia, permitting subsequent behavioral testing during chronic cortisol excess. Control animals received an injection of 0.9% saline (0.8 ml/kg, SC) on day 1 and daily injections of sesame oil (0.45 ml, SC) on days 2–8. All injections were given at 0800–0830 h.

Each female marmoset underwent an air-horn test (see below) with one of her infants, followed immediately by blood sample collection, at 1100–1230 h on day 1 of treatment, 3–4 h after the first injection (hydrocortisone sodium succinate or saline), to characterize the acute effects of elevated cortisol concentrations on maternal behavior and responsiveness to stress. Marmosets subsequently underwent a second, identical air-horn test on day 8 to characterize the effects of chronically elevated cortisol levels. To further characterize the effects of cortisol treatment on maternal behavior, we collected behavioral data on each female with one of her infants in their home cage (see below) at 1430–1530 h on days 3 and 6 and at 0930–1030 h on days 4 and 7. For females with two infants, we alternated which infant was used in air-horn tests and home-cage observations.

Basal blood samples were collected (see below) at 0900–0930 h on days 0 (the day before the first injection), 3, 6, and 9 (approximately 25 h after the final injection), and at 1515–1545 h on days 0, 4, and 7. All blood samples were assayed for plasma cortisol, and the morning samples collected on days 0 and 9 as well as the samples collected immediately after air-horn tests on days 1 and 8 were additionally assayed for plasma adrenocorticotropic hormone (ACTH). Because marmosets ovulate and conceive approximately 10–20 days postpartum (Saltzman et al., 1997a; Tardif et al., 2003), we assayed samples collected on days 0 and 9 for progester-

Table 1 Schedule of experimental procedures.

Day of experiment	Injections (cortisol group/control group)	Observations	Blood samples
Day 0	–	–	0900–0930 h[a,b,c] 1515–1545 h[a]
Day 1	Hydrocortisone succinate/saline 0800–0830 h	Air-horn test 1100–1230 h	1115–1230 h[a,b]
Day 2	Hydrocortisone acetate/oil 0800–0830 h	–	–
Day 3	Hydrocortisone acetate/oil 0800–0830 h	Home cage 1430–1530 h	0900–0930 h[a]
Day 4	Hydrocortisone acetate/oil 0800–0830 h	Home cage 0930–1030 h	1515–1545 h[a]
Day 5	Hydrocortisone acetate/oil 0800–0830 h	–	–
Day 6	Hydrocortisone acetate/oil 0800–0830 h	Home cage 1430–1530 h	0900–0930 h[a]
Day 7	Hydrocortisone acetate/oil 0800–0830 h	Home cage 0930–1030 h	1515–1545 h[a]
Day 8	Hydrocortisone acetate/oil 0800–0830 h	Air-horn test 1100–1230 h	1115–1230 h[a,b]
Day 9	–	–	0900–0930 h[a,b,c]

[a] Plasma was assayed for cortisol.
[b] Plasma was assayed for ACTH.
[c] Plasma was assayed for progesterone.

one, to determine whether or not subjects were in either the luteal phase of the ovarian cycle or early pregnancy. Finally, we weighed each mother and infant at 0800–0930 h on days 0, 5, and 9 to obtain a gross index of body condition.

2.3. Home-cage observations

Approximately 5 min prior to the beginning of observations, the subject's mate and offspring were captured in a nest box and released into a cage in another room; the female subject remained in her home cage. We then released one of her infants back into the home cage with its mother and immediately collected behavioral data on the mother and infant for 15 min.

Behavioral data were collected on a laptop computer using the JWatcher event-recorder program (Blumstein and Daniel, 2007) by a trained observer sitting in full view of the animals, which had been habituated to the observer during the preceding 2 weeks. Table 2 describes the behaviors that were scored and analyzed. A variety of behaviors were recorded each time they were performed by the mother (solicit, inspect, lick, vocal threat, attack, bite, cuff, approach, scratch self, autogroom, long-call, chirp) or the infant (ngä). For several other behaviors we scored the duration of each bout performed by the mother (carry, reject, bristle strut). In addition, every minute, upon an audible signal from a timer, we scored whether the mother was locomoting, whether she was in proximity to the infant, and whether the infant was suckling. Several additional behaviors (approach by infant, ear-tufts flick, facial submit, genital present, groom infant, huddle, lipsmack, squawk, avoid, scent mark; see Saltzman et al. (1997b) for definitions) were observed very rarely and were therefore omitted from analyses.

2.4. Air-horn tests

The female subject and one of her infants were captured from their home cage and released into a standard housing cage (61 cm × 91 cm × 183 cm) inside a small room containing no other animals, for 15 min. Immediately prior to testing, the room was sprayed with air freshener (Vanilla Indulgence, AirWick, Parsippany, NJ) to increase the novelty of the environment and to provide a comparable presentation of the testing environment across animals. Approximately 5.5, 7.5 and 12.5 min after initial release of the animals into the test cage, a celebration air horn (Unique Inc., Philadelphia, PA; ~115 dB) was blasted once (duration ~1 s) by an observer sitting next to the cage, approximately 1 m from the test animals. A similar, unpredictable noise paradigm has been used previously to induce stress in pregnant rhesus monkeys, and was found to elevate plasma glucocorticoid levels significantly in the mothers as well as to induce persistent alterations in brain catecholamine activity, hypothalamic–pituitary–adrenal axis function, and behavior in their offspring (Clarke and Schneider, 1993; Clarke et al., 1994; Schneider et al., 1998). Behavioral data were collected throughout the 15-min test by a second, trained observer seated behind a one-way mirror, using the JWatcher program as described above. After 15 min had elapsed, the mother was manually captured from the test cage and a blood sample was collected (see below). The

Table 2 Behaviors scored in home-cage observations and air-horn tests.

Behavior	Measure	Definition
Approach	Frequency	Move to within 10 cm of infant
Solicit	Frequency	Position body directly above or against infant and/or attempt to pull infant onto body
Carry	Duration	Infant has all four limbs on any part of female's body
Reject	Duration	Rub, pull, or otherwise try to force juvenile off body (excludes biting)
Inspect	Frequency	Push face against or towards infant and/or use hands to investigate infant (excludes grooming)
Lick	Frequency	Common usage; lick any part of infant's body
Vocal threat (erh-erh)	Frequency	Low-pitched, staccato chattering; performed in the context of offensive or defensive aggression (Epple, 1968; Stevenson and Poole, 1976)
Attack	Frequency	Lunge at or pounce on infant aggressively
Bite	Frequency	Direct biting motions towards infant
Cuff	Frequency	Swift, superficial blow, scratch, or push performed aggressively
Bristle strut	Duration	Arching posture and/or strut locomotion and/or general piloerection
Scratch self	Frequency	Common usage; direct scratching towards any part of body
Autogroom	Frequency	Use hands and/or mouth to pick through own fur, mouth, or other body part
Long-call (phee)	Frequency	Long, high-pitched, whistle-like contact call; most commonly performed during separation from a familiar groupmate(s) (Epple, 1968)
Chirp	Frequency	Any tsee, tsik, twitter, or chirp vocalization; associated with high arousal; may be used as alarm/mobbing calls (Epple, 1968; Cross and Rogers, 2006)
Ngä (infant)	Frequency	Infant emits relatively low-pitched, atonal, infantile squeal; associated with distress or used as a contact call
Locomotion	1-Min scan	Engaged in locomotion or other whole-body movement
Proximity	1-Min scan	Any part of female's body is <10 cm from infant
Suckling	1-Min scan	Infant's mouth is on female's nipple and/or infant's face is in vicinity of female's nipple

mother and infant were subsequently reunited with their family in their home cage.

2.5. Collection of blood samples

Marmosets were manually captured from their home cage (or, following air-horn tests, from the test cage) and restrained in a marmoset restraint device (Hearn, 1977) while 0.1–0.4 ml blood was collected from the femoral vein into a heparinized syringe and immediately placed on ice. Less than 3 min elapsed from initial disturbance to the animal (investigator's entry into the home cage or test room) until the completion of blood collection for 94% of the samples. The remaining eight samples were collected in 4.5 ± 0.7 min (mean ± SEM) of disturbance to the animal. These blood-sampling procedures do not elevate plasma cortisol concentrations in marmosets in our colony that have previously undergone frequent blood collection (Saltzman et al., 1994, 1998). Blood samples to be assayed for ACTH were processed as described by Orth (1979): samples were initially centrifuged at 4200 rpm for 15 min at 4 °C, and the plasma fraction was removed and centrifuged again at 9000 rpm for 10 min at 4 °C. The plasma fraction was again removed and stored at −80 °C. Samples to be assayed only for cortisol (or for cortisol and progesterone) were centrifuged at 2000 rpm for 10 min, and the plasma fraction was removed and stored at −20 °C.

2.6. Hormone assays

All blood samples were assayed in duplicate for plasma cortisol using an antibody-coated-tube radioimmunoassay (RIA) kit (GammaCoat, DiaSorin Corp., Stillwater, MN) that had been fully validated for use with marmoset plasma, as previously described (Saltzman et al., 1994). Assay sensitivity at 90% binding was 0.1 ng/tube (1.0 μg/dl), and intra- and inter-assay coefficients of variation (CVs) of a plasma pool assayed in quadruplicate in each assay (36% binding) were 9.6% and 10.6%, respectively.

Plasma ACTH concentrations were measured by an RIA that had been fully validated for marmoset plasma (Saltzman et al., 2004). All samples were run in a single assay. Assay sensitivity at 90% binding was 0.5 pg/tube (6.7 pg/ml), and the intra-assay CV of a plasma pool assayed in triplicate (33% binding) was 4.6%.

Plasma progesterone concentrations were measured in duplicate using a heterologous enzymeimmunoassay that was fully validated for marmoset plasma (Saltzman et al., 1994). Assay sensitivity at 90% binding was 3.6 pg/tube (2.7 ng/ml), and intra- and inter-assay CVs of a plasma pool assayed in duplicate in each assay (40% binding) were 4.8% and 13.5%, respectively.

2.7. Analysis

Plasma cortisol, ACTH, and progesterone concentrations were analyzed by ANOVA, with day and time of day treated as repeated measures and treatment condition (cortisol, vehicle) as a between-groups variable. Marmosets were considered to be pregnant or in the luteal phase of the ovarian cycle if plasma progesterone concentrations exceeded 10 ng/ml (Harlow et al., 1983). Mothers' and infants' body weights were similarly analyzed by ANOVA. For mothers with two infants, we used the twins' mean weight for each time point.

Most of the behavioral data were not normally distributed and contained many zero scores; therefore, behavior was analyzed nonparametrically. For behaviors scored in home-cage observations, we first performed a Friedman test on each treatment group separately to examine possible differences across the four observations (days 3, 4, 6, and 7). If behavior scores did not show a clear pattern of change across days for either group, we compared the two groups' mean scores from all four observations using a Mann–Whitney *U*-test. For behaviors scored in each air-horn test (days 1 and 8), we compared data from the cortisol and control groups using Mann–Whitney *U*-tests, with separate analyses performed for the first 5.5 min (prior to the first noise exposure) and the subsequent 9.5 min (during and after the three noise exposures). We also compared behavior scores between the pre- and post-noise periods for each group separately using Wilcoxon tests.

Analyses were performed using Systat 5 for the Macintosh and Systat 12 for Windows (San Jose, CA). Results were evaluated at the 0.05 level (two-tailed).

3. Results

3.1. Cortisol

On the day before the first cortisol or vehicle injection, basal plasma cortisol concentrations were significantly higher in the morning than in the afternoon, as expected ($F[1,12] = 40.858$, $p < 0.001$), but did not differ between female marmosets in the cortisol and control groups (main effect of group: $F[1,12] = 0.726$, $p = 0.411$; groups × time interaction: $F[1,12] = 0.139$, $p = 0.716$; Fig. 1A and B).

Cortisol treatment successfully elevated marmosets' circulating cortisol levels. Morning (0900–0930 h) plasma cortisol concentrations differed significantly between the two treatment groups ($F[1,12] = 196.197$, $p < 0.001$) and across days (days 0, 3, 6, and 9; $F[3,36] = 124.829$, $p < 0.001$), and showed a significant groups × days interaction ($F[3,36] = 84.477$, $p < 0.001$; Fig. 1A). Morning cortisol levels increased progressively in both cortisol-treated ($F[3,18] = 123.215$, $p < 0.001$) and control females ($F[3,18] = 6.416$, $p = 0.004$), but this pattern was much more pronounced in the cortisol-treated animals. Compared to their baseline levels on day 0, cortisol-treated marmosets exhibited a 7-fold increase in morning cortisol levels by day 9, whereas controls exhibited only a 0.8-fold increase.

Afternoon cortisol levels were similarly influenced by treatment condition ($F[1,11] = 195.326$, $p < 0.001$), days (days 0, 4, and 7; $F[2,22] = 80.374$, $p < 0.001$), and a groups × days interaction ($F[2,22] = 69.525$, $p < 0.001$; Fig. 1B). When analyzed separately, cortisol-treated animals exhibited a progressive rise in afternoon cortisol concentrations across days ($F[2,12] = 92.949$, $p < 0.001$) whereas control animals did not ($F[2,10] = 2.486$, $p = 0.133$). Compared to afternoon baseline levels on day 0, afternoon cortisol concentrations on day 7 increased by 11-fold in cortisol-treated marmosets but only by 0.6-fold in controls. Consequently, following the initiation of cortisol or vehicle treatment, mean morning plasma cortisol levels were significantly higher than mean afternoon levels in control animals ($T = 8.271$,

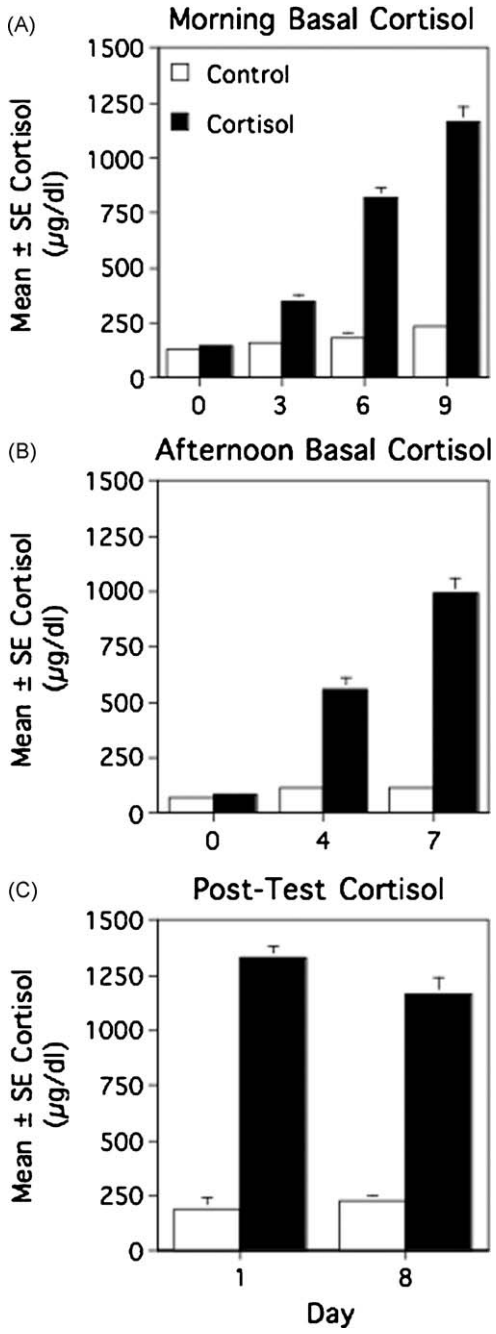

Figure 1 Mean ± SEM morning basal (A), afternoon basal (B), and post-air-horn test plasma cortisol concentrations (C) in cortisol-treated and vehicle-treated (control) female marmosets. See text for statistical results.

df = 6, $p < 0.001$) but not in cortisol-treated animals ($T = 0.094$, df = 6, $p = 0.929$).

Plasma cortisol concentrations immediately following air-horn tests did not differ consistently between days 1 and 8 of treatment ($F[1,12] = 1.848$, $p = 0.199$; Fig. 1C). Post-test cortisol levels were significantly higher in cortisol-treated animals than in controls ($F[1,12] = 375.356$, $p < 0.001$), however, and the two groups tended to show different patterns of change from day 1 to day 8: cortisol-treated marmosets tended to have lower post-test cortisol levels on day 8 than day 1, whereas the control animals showed the opposite pattern. This difference was not quite significant, though ($F[1,12] = 4.274$, $p = 0.061$). We were not able to assess the magnitude of stress-induced changes in cortisol concentrations, as we did not determine cortisol levels at the same time of day under baseline conditions.

3.2. ACTH

Comparison of morning basal ACTH concentrations on day 0 (the day before the first hydrocortisone or vehicle injection) and day 9 (the day after the final injection) revealed a significant groups × days interaction ($F[1,12] = 10.631$, $p = 0.007$; Fig. 2A): ACTH levels decreased across days in cortisol-treated animals ($T = 3.399$, df = 6, $p = 0.015$) but did not change reliably in controls ($T = -1.579$, df = 6, $p = 0.166$). Nonetheless, basal ACTH concentrations did not differ significantly between the two treatment groups on either day 0 ($T = -1.617$, df = 12, $p = 0.132$) or day 9 ($T = 1.751$, df = 12, $p = 0.105$).

Plasma ACTH concentrations immediately after air-horn tests did not differ between day 1 and day 8 (main effect of days: $F[1,11] = 0.053$, $p = 0.822$; groups × days interaction: $F[1,11] = 0.269$, $p = 0.614$) but, as expected, were significantly lower in cortisol-treated animals than in controls ($F[1,11] = 16.806$, $p = 0.002$; Fig. 2B). We were not able to characterize the magnitude of stress-induced changes in

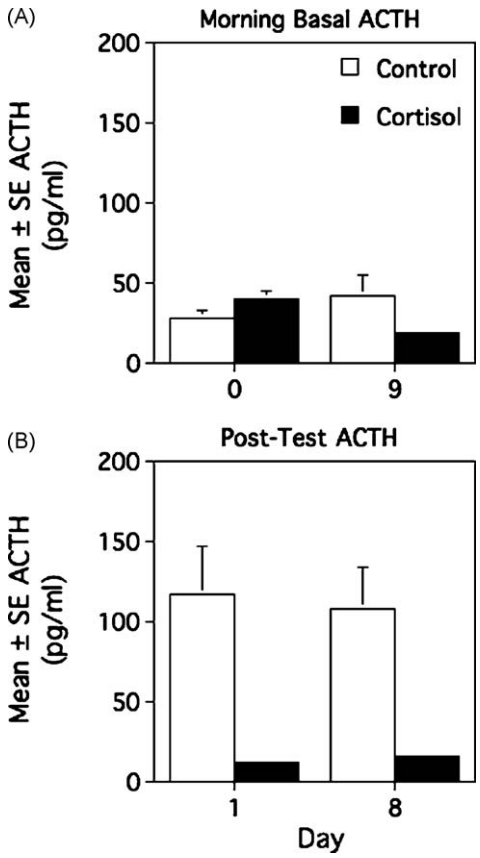

Figure 2 Mean ± SEM morning basal (A) and post-air-horn test plasma ACTH concentrations (B) in cortisol-treated and vehicle-treated (control) female marmosets. See text for statistical results.

ACTH concentrations, as we did not determine ACTH levels at the same time of day under baseline conditions.

3.3. Progesterone

Each female's plasma progesterone concentrations on days 0 and 9 were well above 10 ng/ml (range: 44.7–165.3 ng/ml), indicating that all females had undergone a postpartum ovulation prior to the beginning of data collection and were still pregnant or in the luteal phase of the ovarian cycle at the end of data collection. Progesterone concentrations increased significantly from day 0 to day 9 (76.95 ± 7.68 ng/ml vs. 107.09 ± 7.06 ng/ml, respectively; $F[1,12] = 12.640$, $p = 0.004$), typical of the early- to mid-luteal phase in this species (Harlow et al., 1983). Progesterone levels did not, however, differ reliably between cortisol-treated and vehicle-treated marmosets (main effect of group: $F[1,12] = 0.064$, $p = 0.804$; groups $\times$ days interaction: $F[1,12] = 0.257$, $p = 0.622$).

3.4. Behavior in the home cage

When tested in their home cage with one of their own infants, cortisol-treated females did not show any significant behavioral changes across the 4 days of observations. Control females showed significant changes only in frequency of chirping (Friedman test; chi-square = 8.786, df = 3, $p = 0.032$) and time spent carrying their infant (Friedman test; chi-square = 7.971, df = 3, $p = 0.047$); however, these behaviors did not show a clear pattern of change across time. Therefore, for each behavior we compared total scores from the four observation periods between the two groups. Results are summarized in Table 3.

Cortisol-treated mothers spent less time carrying their infants (Mann–Whitney $U = 42.000$, $N = 7,7$, $p = 0.025$) but approached their infants more often than control mothers (Mann–Whitney $U = 10.500$, $N = 7,7$, $p = 0.025$). Mothers in both treatment groups generally retrieved their infants within several seconds of the infants' reintroduction into the home cage; however, control mothers consistently carried their infants throughout the remainder of each observation period, whereas cortisol-treated mothers were more likely to reject and retrieve their infants repeatedly, sometimes up to 20 times in a single 15-min observation period. Cortisol-treated females tended to spend less time in proximity to their infants, to spend more time rejecting their infants, to inspect their infants more frequently, and to engage in locomotion more frequently than control females; however, these differences did not quite reach statistical significance (see Table 3). Moreover, infants of cortisol-treated mothers showed a non-significant trend towards emitting ngä vocalizations more often than infants of control mothers.

All forms of contact aggression towards the infant (attack, bite, cuff) occurred very infrequently and were therefore summed for analysis (''contact aggression''). Frequencies of contact aggression, as well as frequencies of licking the infant, soliciting the infant, vocal threats, chirping, long-calling, autogrooming, scratching, and locomotion by the mother, frequency of suckling by the infant, and amount of time spent bristle strutting by the mother, did not differ between the two groups (Table 3). Three of the four mothers that performed contact aggression, however, were cortisol-treated, comprising 43% of cortisol-treated mothers versus 14% of controls.

3.5. Behavior during air-horn tests

When tested in a novel cage on day 1, several hours after the first cortisol or vehicle injection, most mothers in both treatment groups exhibited behavioral inhibition both before and after exposure to the noise stressor, engaging in few

Table 3 Behavior scores (median, range) of cortisol-treated and vehicle-treated (control) female marmosets when tested in their home cage with one of their own infants on days 3, 4, 6, and 7 of treatment.

Behavior	Cortisol group	Control group	p (Mann–Whitney U-test)
Approach infant[a]	0.033 (0.000–0.767)	0.000 (0.000–0.000)	0.025
Carry infant[b]	0.992 (0.242–0.997)	0.996 (0.994–0.998)	0.025
Reject infant[b]	0.002 (0.000–0.234)	0.000 (0.000–0.019)	0.056
Inspect infant[a]	0.633 (0.183–3.267)	0.267 (0.033–1.333)	0.064
Proximity to infant[c]	1.000 (0.364–1.000)	1.000 (1.000–1.000)	0.062
Lick infant[a]	0.167 (0.000–0.367)	0.017 (0.000–0.267)	0.137
Solicit infant[a]	0.067 (0.017–0.800)	0.067 (0.033–0.067)	0.256
Contact aggression (bite + cuff + attack)[a]	0.000 (0.000–0.333)	0.000 (0.000–0.050)	0.230
Vocal threat[a]	0.300 (0.000–0.517)	0.100 (0.000–1.783)	0.797
Chirp[a]	1.767 (0.117–32.617)	0.700 (0.100–5.200)	0.277
Long-call[a]	0.917 (0.000–3.083)	0.567 (0.000–3.083)	0.898
Autogroom[a]	0.017 (0.000–0.083)	0.017 (0.000–0.617)	0.547
Scratch[a]	0.133 (0.000–0.500)	0.133 (0.000–0.833)	0.846
Bristle strut[b]	0.341 (0.034–0.711)	0.141 (0.014–0.965)	0.749
Locomotion[c]	0.153 (0.033–0.309)	0.073 (0.000–0.172)	0.085
Suckling by infant[c]	0.034 (0.000–0.333)	0.241 (0.000–0.527)	0.396
Ngä by infant[a]	0.000 (0.000–1.333)	0.000 (0.000–0.000)	0.062

[a] Number of occurrences per minute across all four observations.
[b] Proportion of time across all four observations.
[c] Proportion of instantaneous scans across all four observations.

Table 4 Behavior scores (median, range) of cortisol-treated and vehicle-treated (control) female marmosets in a test cage with one of their own infants before (pre) and after (post) the first of three exposures to a noise stressor on days 1 and 8 of treatment.

Behavior	Test Day	Cortisol Gp Pre	Control Gp Pre	P-Value Pre[a]	Cortisol Gp Post	Control Gp Post	P-Value Post[a]
Inspect infant[b]	Day 1	0.472 (0.000–3.220)	0.000 (0.000–1.278)	0.475	0.675 (0.000–5.864)	0.000 (0.000–0.315)	0.050
	Day 8	0.195 (0.000–4.918)	0.364 (0.000–1.441)	0.690	0.104 (0.000–3.294)	0.000 (0.000–1.138)	0.549
Chirp[b]	Day 1	4.074[c] (0.000–14.428)	1.700 (0.000–12.061)	0.370	1.084 (0.000–9.255)	2.063 (0.000–5.523)	0.872
	Day 8	0.000 (0.000–17.827)	0.000 (0.000–12.741)	0.724	0.104 (0.000–8.511)	0.104 (0.000–3.575)	0.641
Long-call[b]	Day 1	1.887 (0.000–6.612)	2.364[c] (0.000–6.856)	0.872	1.499 (0.623–3.188)	4.951 (0.000–7.497)	0.337
	Day 8	0.000 (0.000–4.494)	0.360 (0.000–3.399)	0.946	0.206 (0.000–3.387)	0.000 (0.000–3.092)	0.322
Carry infant[d]	Day 1	0.969 (0.929–0.996)	0.992 (0.958–0.997)	0.173	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.000
	Day 8	0.993 (0.979–0.997)	0.992 (0.963–0.995)	0.700	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.000
Bristle strut[d]	Day 1	0.941 (0.764–0.988)	0.965 (0.907–0.986)	0.522	1.000 (0.684–1.000)	1.000 (0.000–1.000)	0.902
	Day 8	0.963 (0.000–0.987)	0.934 (0.000–0.985)	0.480	1.000 (0.809–1.000)	0.664 (0.000–1.000)	0.119
Locomotion[e]	Day 1	0.100 (0.000–0.600)	0.200 (0.000–0.600)	0.613	0.111 (0.100–0.222)	0.211 (0.000–0.333)	0.255
	Day 8	0.000 (0.000–0.400)	0.000 (0.000–0.400)	1.000	0.111 (0.000–0.333)	0.111 (0.000–0.222)	0.843
Suckling by infant[e]	Day 1	0.000 (0.000–1.000)	0.000 (0.000–0.800)	0.528	0.000 (0.000–0.259)	0.000 (0.000–0.333)	0.674
	Day 8	0.000 (0.000–0.200)	0.000 (0.000–1.000)	0.424	0.000 (0.000–0.000)	0.000 (0.000–0.900)	0.142

[a] Results of Mann–Whitney *U*-test comparing cortisol and control groups pre or post.
[b] Number of occurrences per minute.
[c] Significantly different from corresponding "post" value ($p < 0.05$, Wilcoxon test).
[d] Proportion of time.
[e] Proportion of instantaneous scans.

overt behaviors except vocalizations (Table 4). All mothers carried their infants throughout the entire test, but most of them engaged in few other behavioral interactions with their infants. Cortisol-treated females emitted more chirp vocalizations per min during the 5.5 min before the first noise exposure than during the 9.5 min after (Wilcoxon test, $Z = -2.023$, $N = 6$, $p = 0.043$), whereas control females long-called more frequently after than before the first noise exposure (Wilcoxon test, $Z = 2.023$, $N = 6$, $p = 0.043$). No other behavior differed significantly between the pre- and post-test periods for either group. The only significant behavioral difference between groups was that after (but not before) the first noise exposure, cortisol-treated mothers inspected their infants more frequently than controls (Mann—Whitney $U = 7.000$, $N = 6{,}6$, $p = 0.050$). Mothers did not orient in any particular direction on hearing the air horn.

When re-tested with the noise stressor on day 8 of treatment, all mothers again carried their infants throughout the entire test but performed few other overt behaviors except vocalizations (Table 4). No behaviors differed significantly between the pre- and post-stressor periods for either treatment group or between cortisol-treated and control animals (Table 4).

3.6. Body weight

Mothers' body weights did not differ reliably across days (days 0, 5, and 9; $F[2,18] = 0.721$, $p = 0.500$) or between cortisol-treated and control animals (main effect of group: $F[2,9] = 0.719$, $p = 0.513$; groups $\times$ days interaction: $F[4,18] = 0.554$, $p = 0.699$). Infant weights increased progressively from day 0 (51 ± 2 g) to day 5 (57 ± 3 g) to day 9 (62 ± 3 g; $F[2,20] = 135.544$, $p < 0.001$); however, neither absolute weights ($F[1,10] = 0.269$, $p = 0.616$) nor the pattern of change across time ($F[2,20] = 0.615$, $p = 0.551$) differed between infants of cortisol-treated and control mothers.

4. Discussion

In this study we administered exogenous cortisol to multiparous female marmosets during the mid-lactational period and assessed the effects on maternal behavior under both baseline and test conditions. The results provide, to our knowledge, the first experimental evidence supporting the hypothesis that elevated cortisol concentrations alter — or specifically, disrupt — maternal behavior in a primate species, but indicate that these effects do not appear to be traumatic. Elevated cortisol induced an aspect of maternal neglect (spending less time carrying infants), but no significant infant abuse.

Effects of exogenous cortisol on maternal behavior were more pronounced under baseline conditions than during exposure to a noise stressor. When tested in their home cage with one of their own infants, cortisol-treated females spent significantly less time carrying the infant than did controls. At the same time, they approached the infant significantly more often and showed clear, although non-significant, tendencies to engage in more visual/olfactory inspection of the infant and to spend more time rejecting the infant. When marmosets were tested during exposure to a noise stressor in an unfamiliar environment, the only difference between groups was that cortisol-treated females inspected their infants more frequently than control females in the first of two stress tests. These latter findings should, however, be interpreted with caution. We were unable to characterize the incremental effects of the air-horn test on cortisol and ACTH concentrations, because we did not obtain baseline values at the same time of day, and therefore cannot definitively conclude that the test constituted an effective stressor.

Our results are consistent with correlational findings in several other primate species. In captive Western lowland gorillas, mothers' postpartum urinary cortisol concentrations, divided by prepartum urinary cortisol levels ("postpartum stress index"), correlated negatively with the proportion of time that mothers spent in ventro-ventral supported contact with their infants, especially during locomotion (Bahr et al., 1998). Similarly, among captive savannah baboons, mothers with higher urinary cortisol concentrations postpartum spent less time maintaining contact with their infants than those with lower urinary cortisol levels (Bardi et al., 2004). Among captive Japanese macaques, in contrast, mothers' fecal cortisol levels postpartum were not significantly associated with time spent in contact with the infant, but were positively correlated with the frequency of maternal rejection of infants (Bardi et al., 2003). Importantly, in all of these studies on nonhuman primates, as in the present experiment, all or virtually all of the animals studied were experienced (multiparous) mothers.

Correlational findings in women have been more variable. In a comprehensive series of studies, Fleming et al. found that circulating or salivary cortisol concentrations correlated with aspects of maternal behavior, maternal attitudes, or maternal mood, but that the specific correlations differed with women's age and parity. During the first few days postpartum, for example, salivary or circulating cortisol levels of first-time mothers were positively associated with the mothers' frequency of affectionate contact with their infants and attraction to infant odors, whereas cortisol concentrations of experienced mothers were associated with increased care-taking activities and an enhanced ability to recognize their own infants' odors, but also with increased anxiety (Fleming et al., 1987, 1997). Moreover, among primiparous mothers, salivary cortisol concentrations approximately 6 weeks postpartum correlated negatively with instrumental care-taking activities and fatigue in teenaged mothers, correlated positively with affectionate behavior towards infants in "young mothers" (19—25 years old) and did not correlate with maternal behavior, but were positively associated with fatigue and negative moods in "mature mothers" (26—40 years old; Krpan et al., 2005).

In sum, these findings from humans and nonhuman primates suggest that elevated cortisol concentrations may have generally stimulatory effects on maternal behavior in younger, less experienced mothers, especially in terms of increasing mothers' attraction to and affectionate behavior towards infants. Among older, more experienced mothers, in contrast, elevated cortisol levels may have fewer and qualitatively different effects on maternal behavior and may be more closely associated with negative affect. In nonhuman primates, including the marmosets in our study, high cortisol levels specifically appear to inhibit experienced mothers' contact with and carrying of infants.

Although the present study focused primarily on effects of chronic cortisol elevations, the design additionally permitted

us to examine the effects of acute cortisol treatment, as we first observed each mother and infant in an air-horn test 3—4 h after the initial cortisol or vehicle injection. At this time point, cortisol-treated mothers already had significantly higher plasma cortisol levels and significantly lower ACTH levels than controls. Nonetheless, cortisol-treated females showed no behavioral differences from controls during the first 5 min in the test cage, prior to their first exposure to the noise stressor, and only one significant difference (increased rates of investigating their infant) during/after noise exposure. These results suggest that acute, unlike chronic, cortisol elevations may have limited effects on maternal behavior in this primate. It is important to note, however, that we did not evaluate maternal behavior under undisturbed conditions in the home cage shortly after the first cortisol or vehicle treatment.

Importantly, we found no clear evidence that exogenous cortisol increased mothers' aggression towards their infants. Common marmosets have been reported to show elevated rates of killing or abusing their own offspring under stressful conditions and to have markedly decreased infant survival rates during chronic stress (Johnson et al., 1991). In addition, female marmosets exhibit low attraction to and low tolerance of other females' infants, and may commonly commit infanticide, during late pregnancy, when circulating cortisol concentrations are elevated (Saltzman, 2003; Saltzman and Abbott, 2005). In the present study, however, frequencies of most aggressive behaviors, including attack, bite, cuff, genital present, and ear-tufts flick, were extremely low. Most females were never observed performing any of these behaviors during either home-cage observations or air-horn tests, but three of the four females that performed contact aggression towards their infants were cortisol-treated. Mothers did occasionally perform vocal threats to their infants, but frequencies of this behavior did not differ between cortisol-treated and control females. Thus, our findings do not provide strong support for the hypothesis that elevated cortisol levels increase aggression towards infants by marmoset mothers, and suggest that stress-related increases in child- or infant abuse in this and other species (e.g., humans: Brockington, 1996; Tolan et al., 2006; macaques: Reite and Caine, 1983; Troisi and D'Amato, 1994; Maestripieri and Carroll, 1998a,b) may not be mediated by glucocorticiods alone.

The mechanisms by which cortisol may alter maternal behavior are not known. One possibility is that cortisol acts directly on neural regions involved in the control of maternal behavior. The neuroanatomical basis of maternal behavior has not been characterized in primates. In rodents, however, several key brain regions involved in the control of maternal behavior, such as the medial preoptic area, bed nucleus of the stria terminalis, and medial amygdala, contain type-II glucocorticoid receptors, which are activated when glucocorticoid levels are elevated (Ahima and Harlan, 1990; Numan, 2007). Additionally or alternatively, cortisol might act indirectly through actions on other hormone, neurotransmitter, or neuropeptide systems. In rats, for example, glucocorticoids increase the expression of corticotropin-releasing hormone (CRH) in the central nucleus of the amygdala (Schulkin et al., 2005). The amygdala plays a crucial role in the onset of maternal behavior in rats (Numan, 2007), and intracerebroventricular administration of CRH may inhibit aspects of maternal behavior in rodents (Pedersen et al., 1991; Gammie et al., 2004) as well as in common marmosets (Saltzman, Boettcher, Post, Abbott, unpublished data). Cortisol might also influence maternal behavior indirectly through broader effects on cognition, perception, emotionality, or arousal (Fleming et al., 1987, 1997). Finally, effects of exogenous cortisol on mothers' behavior might be mediated via effects on their infants. We were unable to systematically examine effects of maternal cortisol treatment on infant behavior in this study, for logistical reasons; however, exposure to elevated glucocorticoid levels in breast milk has persistent effects on behavior, cognition, and neural development in rats (e.g., Catalani et al., 2000, 2002) and is thought to influence infant temperament in humans (Glynn et al., 2007).

Several aspects of our experimental design should be kept in mind when interpreting our results. First, we used experienced breeding females, each of which had successfully reared at least one infant prior to the litter used in this experiment. Experienced mothers in several species exhibit lower rates of infant abuse or neglect than first-time mothers and may therefore be less vulnerable to stress-induced disruptions of maternal behavior; however, no such differences have been found in common marmosets (e.g., Tardif et al., 1984; Bardi and Petto, 2002). Second, we collected data roughly halfway through the lactational period rather than during the early postpartum period. In rats, hormonal influences are more apparent in the initial onset of maternal behavior (i.e., during the early postpartum period) than in the subsequent maintenance of maternal behavior (Numan and Insel, 2003). In human mothers, however, cortisol levels have been found to correlate with aspects of maternal behavior as late as 6 weeks postpartum (Krpan et al., 2005), and in macaques and baboons, cortisol levels may correlate with maternal behavior over the first 2—3 months postpartum (Bardi et al., 2003; Ramirez et al., 2004). Thus, effects of cortisol on maternal behavior may not be restricted to the early postpartum period in primates.

A third caveat is that plasma cortisol concentrations in our cortisol-treated animals increased progressively across successive days of treatment and, by the end of the 8-day treatment period, were substantially higher than levels typically found at the peak of the circadian cycle or in response to stress in female common marmosets (see Section 2). We have, however, documented endogenous plasma cortisol levels similar to those of our cortisol-treated animals, in female marmosets treated with a high dose of exogenous ACTH (Pattison et al., 2007). Moreover, plasma cortisol levels across most days of cortisol treatment in this study were within the physiological range (basal to stressed states), and we found very few behavioral changes across the 4 days of home-cage observations, suggesting that the exceptionally high cortisol levels at the end of the study did not affect behavior differently than the more physiological levels generated earlier.

It should also be noted that marmosets and other small-bodied New World monkeys exhibit several unusual features of the hypothalamic—pituitary—adrenal axis. Circulating cortisol concentrations are an order of magnitude higher than those in Old World primates, and virtually all of this cortisol circulates unbound or loosely bound to albumin, as marmosets, like other New World primates, have extremely low

circulating levels of corticosteroid-binding globulin (Pugeat et al., 1984; Robinson et al., 1985; Klosterman et al., 1986). The high circulating cortisol levels appear to be compensated for by partial glucocorticoid resistance (Chrousos et al., 1986), associated with overexpression of the intracellular FK506-binding protein (FKBP51), which inhibits translocation to the nucleus of glucocorticoid bound to either the mineralocorticoid or glucocorticoid receptor (Denny et al., 2000; Scammell et al., 2001) and hence impairs functionality of the glucocorticoid receptor (Her et al., 2005).

In several species, treatment with exogenous glucocorticoids either raises or lowers concentrations of corticosteroid-binding globulin (CBG), presumably altering the bioavailability of glucocorticoids (e.g., Feldman et al., 1979; Schlechte and Hamilton, 1987; Berdusco et al., 1993). Because marmosets, in contrast, do not have appreciable amounts of CBG (Pugeat et al., 1984; Robinson et al., 1985; Klosterman et al., 1986), all of the exogenous (and endogenous) cortisol measured in our animals is likely to be biologically active, and the cortisol concentrations measured in our assays should be highly correlated with levels of cortisol available to the tissues.

In conclusion, our results provide the first experimental support for the hypothesis that cortisol can disrupt maternal behavior in primates, especially in terms of reducing mothers' time in contact with or carrying their infants. This effect was apparent only under basal, rather than test, conditions, however, and we found no strong evidence that elevated cortisol levels increased mothers' aggression towards infants. Thus, disruption of maternal behavior and escalation of infant neglect, but not necessarily infant abuse, by stress or stress-related psychiatric disorders, as reported in several primate species, might be mediated at least to some extent by elevated cortisol levels. Additional studies are needed to characterize the roles of other stress-responsive hormones, neurotransmitters, and neuropeptides, such as epinephrine, norepinephrine, CRH, and the endogenous opioids, in modulating primate maternal behavior under stressful conditions.

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Conflict of interest

Both authors declare that they have no conflict of interest regarding this research.

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