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Acute oxytocin improves memory and gaze following in male but not female nursery-reared infant macaques

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Abstract

Rationale—Exogenous oxytocin administration is widely reported to improve social cognition in human and nonhuman primate adults. Risk factors of impaired social cognition, however, emerge in infancy. Early interventions—when plasticity is greatest—are critical to reverse negative outcomes.

Objective—We tested the hypothesis that oxytocin may exert similar positive effects on infant social cognition, as in adults. To test this idea, we assessed the effectiveness of acute, aerosolized oxytocin on two foundational social cognitive skills: working memory (i.e., ability to briefly hold and process information) and social gaze (i.e., tracking the direction of others' gaze) in one-month-old nursery-reared macaque monkeys (*Macaca mulatta*). We did not predict sex differences, but we included sex as a factor in our analyses to test whether our effects would be generalizable across both males and females.

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Results—In a double-blind, placebo-controlled design, we found that females were more socially skilled at baseline compared to males, and that oxytocin improved working memory and gaze following, but only in males.

Conclusions—These sex differences, while unexpected, may be due to interactions with gonadal steroids and may be relevant to sexually dimorphic disorders of social cognition, such as male-biased autism spectrum disorder, for which oxytocin has been proposed as a potential treatment. In sum, we report the first evidence that oxytocin may influence primate infant cognitive abilities. Moreover, these behavioral effects appear sexually dimorphic, highlighting the importance of considering sex differences. Oxytocin effects observed in one sex may not be generalizable to the other sex.

Keywords

infancy; primate; individual differences; intranasal oxytocin; cognitive; development

The neuropeptide oxytocin (OT) is reported to have wide-ranging positive effects on social behavior, including increasing prosocial behaviors, cognition, and attachment (Chang and Platt 2014; Guastella and MacLeod 2012; Quintana and Woolley 2016). However, most OT research is adult-focused and relatively little is known about OT in younger populations. While OT is not commonly studied in infancy, there are a number of reasons why OT is a strong candidate for supporting social cognitive development. For example, in human adults, OT appears to improve memory of faces (Guastella et al. 2008) and inferences of others' affective mental states (Domes et al. 2007). Together, these and other studies in adults suggest that OT may improve the ability to extract and remember social information.

Despite interest in the use of OT to improve social cognitive functioning (Chang and Platt 2014; Guastella and MacLeod 2012), we are limited in understanding how OT regulates social behavior, as well as the extent to which beneficial effects of OT may be generalizable to younger individuals (Taylor et al. 2015). This gap is particularly relevant considering that risk factors associated with impaired social cognitive skills begin to emerge during infancy. In addition, not all effects of OT have been positive, and, in some individuals, OT may exacerbate social dysfunction (for a review: Zik & Roberts, 2015). Thus there is a need to consider individual differences in responses to OT. The present study begins to bridge these gaps, investigating the influence of OT on two markers for detecting early perturbations in infant social cognitive development (Charman et al. 1997; Frischen et al. 2007; Wass 2015): working memory (i.e., briefly holding and processing information) and gaze following (i.e., co-orienting with others).

In humans, working memory—the ability to briefly retain information for seconds or minutes—is fundamental for successful social functioning. Working memory enables infants to retain information concerning their caregivers and other group members during social exchanges (Noland et al. 2010). In triadic interactions (e.g., communication with a partner regarding an object) infants must remember the partner and the item that is the focus of attention. From infancy, individual differences in working memory are remarkably stable and are positively correlated with cognition later in childhood (Cowan et al. 2006; Wass 2015). In fact, children with poor working memory struggle in novel social situations, such

as the transition to daycare or kindergarten (McQuade et al. 2013), and children's working memory is positively associated with their relationship quality (de Wilde et al. 2016). Thus, working memory enables the processing of information and is essential for social interactions.

Another capacity that enables successful social engagement is gaze following, or looking where another individual looks. Gaze following allows infants to engage in successful social interactions, as well as to use more expert individuals' gaze direction to locate salient objects in their environment, increasing learning opportunities (Emery et al. 1997). In this context, gaze following is a developmental landmark for the emergence of more sophisticated social cognitive abilities, such as joint attention, i.e., infant and adult sharing attention to an object (Ferrari et al. 2000), theory of mind (Brooks and Meltzoff 2015), and social learning (Meltzoff et al. 2009). Gaze following is described as a cornerstone for social intelligence (Triesch et al. 2006), and impairments in gaze following are consistent and early predictors of later social deficits (Charman 2003).

Despite the importance of these skills, little is known about the best ways to reinforce their development in infants. Such support may increase infants' readiness for social interactions, particularly those infants at risk for neurodevelopmental disorders (Lefevre and Sirigu 2016). While both working memory and gaze following appear to be supported by enriched early social experiences in humans (de Wilde et al. 2016) and nonhuman primates (Simpson et al. 2016a), another approach may be through interventions aimed at manipulating specific brain mechanisms.

The present study addressed these questions through an investigation of the impact of nebulized OT on working memory and gaze following in one-month-old nursery-reared macaque monkeys. We chose macaques because they share many aspects of human physiology, development, cognition, and social complexity (Phillips et al. 2014) and exhibit pronounced individual differences in sociality across development (Dettmer et al. 2016; Sclafani et al. 2016). We tested macaque infants reared in a neonatal nursery by human caretakers, a population at risk for impaired social behaviors (e.g., Sclafani et al. 2015; Winslow, 2003), and who therefore may benefit the most from OT interventions. We chose to test one-month-olds to assess infants when they were still beginning to develop working memory and gaze following; therefore, an intervention would have the potential to produce positive changes in these skills. Consistent with reports that acute OT increases social interest in macaque infants (Simpson et al. 2014) and macaque adults (Chang and Platt 2014), we predicted that OT would improve infant macaque working memory and gaze following. We did not predict sex differences, but nonetheless included infant sex as a between-subjects factor in our analyses to confirm any effects would be generalizable across both sexes.

Methods

Subjects

We tested 24 healthy rhesus macaque infants (*Macaca mulatta*), 13 females and 11 males, at 1 month of age (M = 34 days, SD = 2, range = 30–40 days). Two additional infants were

tested but excluded due to failure to complete at least 10 test trials in the working memory assessment (i.e., inattention). All infants participated in the working memory task; 16 infants (9 females and 7 males) also participated in the gaze following task. Infants were healthy, separated from their mothers on the day of birth (typically by 8am), and reared in a nursery facility for unrelated studies. Infants were individually housed in incubators (51 × 38 × 43 cm) for the first two weeks of life and in larger cages thereafter. Both housing arrangements contained an inanimate surrogate covered with fleece fabric as well as loose pieces of fleece fabric and various plush and rubber toys. For the first month of life infants could see and hear, but not physically contact, other infants of similar age. Human caretakers were present for 13 hours each day and interacted with infants every 2 hours for feeding and cleaning.

Oxytocin Administration

We tested infants on two separate days. On each test day, following an established protocol (Simpson et al. 2014), we administered either OT (at 20 IU/mL; Bimeda- MTC Animal Health) or a sterile saline solution using a Pari Baby Nebulizer. This route of administration increases OT concentrations in CSF in adult monkeys (Modi et al. 2014). Experimenters administering the solution and carrying out the behavioral tests were blind to the condition (saline or OT). An independent assistant, who was not involved in testing, labeled the solutions “A” and “B” and did not reveal the identities of the solutions until all analyses were completed. Condition order was counterbalanced across subjects, so half of the infants first completed the OT, followed by saline the next business day; the other half first completed saline, followed by OT the next business day. Experimenters who collected the data and coded the videos were blind to the experimental condition (i.e., solution the infant received). During nebulization, infants were cradled in the arms of a trained experimenter, and a small nebulization mask was gently held over the infant’s nose and mouth. We delivered aerosolized OT or sterile saline solution for 7 minutes. Experimenters monitored nebulization amounts by measuring any remaining solution; infants received between .4 and 1.4 mL of OT [M = .92 mL (18.4 IU), SD = .26 mL (5.2 IU)] and .4–1.8 mL of saline (M = 1.17 mL, SD = .33 mL). Nebulization amounts did not differ across male and female infants for either saline, $t(24) = .005$, $p = .996$, $d = .002$, or OT, $t(24) = .810$, $p = .426$, $d = .32$, nor was the amount nebulized predictive of performance in either task, ps > .10. One hour after nebulization we carried out the social cognitive tasks. We chose a one-hour delay because previous studies indicated both changes in infant macaque behavior and peripheral (i.e., saliva) OT levels 60 min after aerosolized OT delivery (Simpson et al. 2014). In adult macaques, CSF OT was elevated 60 min after aerosolized OT delivery (Modi et al., 2014).

Working Memory

One hour after nebulization we carried out the working memory task (Fig. 1–3), following methods used with human infants (Noland et al. 2010). Our testing apparatus consisted of a black cloth curtain (75-cm-wide × 120-cm-tall) draped to the floor, creating three target-zones around the edge of the curtain in which stimuli could appear, Fig. 1. In the middle of the screen, at eye-level for the infant (90 cm from the ground) a video camera filmed the infant through a 10-cm circular opening. A manually operated central distractor—a metal cup filled with colorful plastic beads—was positioned above the camera. There were two stimuli, both of which were familiar to the infants. A nonsocial stimulus—an array of

reflective bows and beads, covered in clear plastic—was rotated, producing both sound and movement. An experimenter served as the social stimulus, calling to the infant with infant-directed speech, and lipsmacking, an affiliative facial expression involving rapidly opening and closing the mouth, producing sound and movement.

At the start of the test session, one experimenter held the infant monkey in a comfortable position (i.e., swaddled in a pad or fleece sack) approximately 65 cm from the curtain, Fig. 1a. A second experimenter (the social target model) served as the source of the stimuli, Fig. 2. Working memory was measured using a modification of the peek-a-boo game. First, a target appeared in one of three locations: at the top, right, or left of the screen. It produced a "call" to the infant (infant-directed speech and lipsmacking, or rattle), Fig. 1b. The call continued until the infant oriented to the target, typically within 1-3 sec. When the infant oriented to the target, the target continued stimulating (lipsmacking or rattling) for approximately 2 sec. After that event, the target moved behind the curtain, out of view. At that time, the distractor (cup of colorful beads) was jingled, manually operated by the experimenter behind the curtain, to orient the infant toward the center of the curtain, immediately above the video camera, Fig. 1c. Once the infant looked at the distractor for approximately 1 sec, the distractor stopped rattling (no more sound or motion). Infants were then given 5 sec, during which time they were videotaped and could look wherever they wished, Fig. 1d. After the 5 sec response time, there was a brief inter-trial interval of approximately 10 sec, then the next trial began. Infants viewed up to 12 trials per test session, with 2 targets appearing in each of the three locations, in a randomized predetermined order. We measured working memory by examining the proportion of times the first-look during the response time was to the correct location, i.e., the location where the target most recently appeared prior to the delay, out of the total number of valid trials, which was coded offline by a blind coder, Fig. 3. A trial was considered valid if the infant looked to the target, then looked to the distractor, then looked to one of the three locations. If the infant did not look to one of the three target locations, then the trial was considered invalid, and was not included in the score (17% of trials were excluded for failure to look to the distractor or target zones; total trials completed: $M = 20$, $SD = 3$, range: 13–24). A session was only included if the infant completed at least 3 trials. Infants viewed up to 12 trials per test session, with 2 targets appearing in each of the three locations, in a randomized predetermined order, such that no more than two trials in a row were in the same location. In total this test session took approximately 5 minutes, and there was one session for each condition (OT and saline).

Gaze Following

Immediately following the working memory task, we carried out a gaze following task (Fig. 4). We used an experimental design adapted from human infants (Scaif and Bruner 1975) and monkey infants (Simpson et al. 2016a). A familiar caretaker handled the infants. An actor sat approximately two feet in front of the infant, and two evaluators sat approximately four feet behind the actor, one evaluator was slightly to the left and the other slightly to the right of the actor. The actor sat at eye level with the infant and engaged in various attention-getting behaviors to facilitate eye contact. Upon making eye contact, the actor looked right, left, up, or down, moving her head 90°, consistent with the direction of gaze, and held this

position for approximately 5 sec. The direction of the actor's gaze was counterbalanced so the infant saw 5 trials of each direction (20 trials total). We chose to use movement of the head, rather than just the eyes, because while older infants can use more subtle cues, younger infants need more obvious cues to follow gaze (Ferrari et al. 2000). Prior to the test session, one evaluator (first-evaluator) was assigned to call out the direction of the infant's first gaze shift, after the actor's movement. If a monkey did not shift his or her eyes for five sec, then the eye movement was recorded as "straight ahead". To ensure accuracy, a second evaluator either agreed or disagreed with the first evaluator's statement of gaze direction (for similar live-scoring methods, see Simpson et al. 2016a). Upon instances of the infant failing to attend to the actor's movement, the trial was repeated. In cases in which the evaluators disagreed, the trial was repeated to ensure 100% agreement. The first and second evaluator roles were altered between observers and occurred equally from the left and right side positions. We tested infants over two successive days, once following nebulization of OT and once following nebulization of saline, each with 20 trials. Both evaluators and the infant handler were blind the condition (OT, saline). In total, this task took approximately 10 minutes.

Analysis

Inter-observer reliability for the working memory assessment was computed with Cohen's Kappa (κ) between two coders, on a random selection of 20% of the videos. Agreement was high for infants' first anticipatory looks left (κ = .91), right (κ = .90), and up (κ = 1.0). Inter-observer reliability for the gaze following task was 100% (κ = 1.00); trials with disagreements were repeated until both observers agreed. In the working memory task, we found no main effects or interaction effects for the factor Stimulus type (social, nonsocial), or effects of condition order (i.e., receiving OT then saline, or receiving saline then OT), so we pooled across these variables to increase power (for details, see Table 1). See Supplementary Materials for details. In the gaze following task, there was a main effect of Condition Order, so we retained this variable in the analysis.

For each measure we first assessed whether, overall, infants' proportion of correct responses was above chance with a one-sample *t* test. In the working memory task, there were three possible target locations (Fig. 1), so chance was ⅓ or .33, and in the gaze following task, the model looked in one of four locations, so chance was ¼ or .25. Next, we carried out a 2 (Sex: male, female) × 2 (Condition: saline, OT) mixed design analysis of variance (ANOVA) on the proportion of correct responses in each task. We followed up significant interactions with paired samples *t* tests, looking within each sex to see whether proportions differed between conditions, with independent samples *t* tests to directly compare males and females within each condition, and with one-sample *t* tests comparing each sex and condition to chance. All *t* tests were two-tailed.

Results

Working Memory

We performed a 2 (Sex) × 2 (Condition) mixed design analysis of variance (ANOVA) on the proportion of correct responses. While there were no main effects of either Sex or Condition,

$F(1,22) \leq 1.33$, $ps > .261$, there was a Sex × Condition interaction, $F(1,22) = 4.36$, $p = .049$, $\eta^2_p = .165$, Fig. 5a. Males showed a trend of better memory in the OT versus saline condition, $t(10) = 2.19$, $p = .053$, $d = .66$, whereas females performed similarly across OT and saline conditions, $t(12) = .69$, $p = .502$, $d = .19$. However, when compared directly, males and females did not differ from one another within either the saline condition, $t(22) = 1.17$, $p = .25$, $d = .48$, or OT condition, $t(22) = .21$, $p = .21$, $d = .09$, suggesting only weak, if any sex differences.

A one-sample *t* test on the proportion of correct responses confirmed that, overall, infants performed above chance ($M = 45\%$ correct, $SD = 14\%$), $t(23) = 4.23$, $p < .001$, $d = .86$. To explore group differences further and to determine whether looking differed from chance, we carried out one-sample *t* tests for each sex and condition. Males were at chance with saline (mean difference from chance 12.31%; 95% CI [2.70–21.92]), $t(10) = 1.48$, $p = .171$, $d = .34$, but were above chance with OT (mean difference from chance 19.09%; 95% CI [6.59–31.60]), $t(10) = 3.40$, $p = .007$, $d = 1.03$. Females, in contrast, were above chance with saline (mean difference from chance 12.31%; 95% CI [2.70–21.92]), $t(12) = 2.79$, $p = .016$, $d = .77$, but did not differ from chance with OT (mean difference from chance 8.37%; 95% CI [−4.79–21.54]), $t(12) = 1.39$, $p = .190$, $d = .38$.

Gaze Following

We performed a 2 (Sex) × 2 (Condition) × 2 (Condition Order) mixed design ANOVA on the proportion of correct trials. There was a main effect of Condition Order, $F(1,12) = 13.31$, $p = .003$, $\eta^2_p = .526$, in which infants performed better overall if they first participated in the OT condition ($M = 42\%$ correct, $SD = 6\%$) compared to if they first participated in the saline condition ($M = 30\%$ correct, $SD = 8\%$). While there were no main effects of either Sex or Condition, $F(1,12) \leq 1.96$, $ps > .20$, there was a large Sex × Condition interaction, $F(1,12) = 9.35$, $p = .010$, $\eta^2_p = .438$, Fig. 5b. Only for males, there was an large increase in gaze following when given OT versus saline, $t(6) = 2.64$, $p = .038$, $d = 1.00$. In contrast, females showed a trend in the opposite direction, with better gaze following with saline versus OT, $t(8) = 2.00$, $p = .081$, $d = .67$. There were no sex differences in the saline condition, $t(14) = 1.25$, $p = .233$, $d = .51$, but in the OT condition there was a trend of males outperforming females, $t(14) = 1.90$, $p = .079$, $d = .96$.

A one-sample *t* test on the proportion of correct responses confirmed that, overall, infants performed above chance ($M = 73\%$ correct, $SD = 19\%$), $t(15) = 10.42$, $p < .001$, $d = 2.61$. To explore group differences further, and to determine whether looking differed from chance, we carried out one-sample *t* tests for each sex and condition. Males were at chance with saline (mean difference from chance 6.43%; 95% CI [−4.15–17.01]), $t(6) = 1.49$, $p = .188$, $d = .53$, but were above chance with OT (mean difference from chance 17.86%; 95% CI [8.28–27.43]), with a notably large effect size, $t(6) = 4.56$, $p = .004$, $d = 1.73$. Females, in contrast, performed above chance with both saline (mean difference from chance 13.89%; 95% CI [4.52–23.26]), $t(8) = 3.42$, $p = .009$, $d = 1.14$, and OT (mean difference from chance 8.89%; 95% CI [2.29–15.48]), $t(8) = 3.11$, $p = .014$, $d = 1.04$.

Discussion

Acute, aerosolized OT improved male nursery-reared infant monkeys' social cognitive skills across two tasks—working memory and gaze following—both with notably large effect sizes. Only two other studies have experimentally manipulated OT levels in infant primates. One study reported that acute aerosolized OT increased newborn monkeys' affiliative behaviors during an imitation recognition task in which a human imitated them (Simpson et al. 2014). In the other study, chronic aerosolized OT, delivered between 2 to 6 months of age, increased male 6-month-old macaques' attention to emotional facial expressions, but decreased the time they spent looking at the eye region of neutral faces (Parr et al. 2016). The present study extends these findings, showing OT not only influences social attention and motivation, but also affects infants' cognitive skills.

Our findings are consistent with studies reporting positive associations between endogenous OT and infant sociability. In human newborns, higher OT levels in cerebrospinal fluid (CSF) positively correlate with social engagement (Clark et al. 2013). Similarly, in juvenile and sub-adult macaques (18- to 36-month-old), CSF OT levels were positively associated with affiliative social behaviors (Winslow et al. 2003). Further, in human children, plasma OT levels are a highly heritable trait, positively associated with social functioning (Parker et al. 2014) and negatively associated with trait anxiety (Carson et al. 2015). In sum, while this evidence is only correlational, it suggests that infants and children naturally vary in their OT levels, with higher OT levels associated with greater sociality.

Neurobiology underlying oxytocin's influence on social cognition

From a neurobiological standpoint, the effect of OT on working memory is interesting, but difficult to interpret. OT null mutant mice have profound deficits in some cognitive abilities, such as social amnesia, without apparent deficits in nonsocial memory (Ferguson et al. 2000). In a social recognition task, mice lacking the OT gene have difficulties recognizing conspecifics (Choleris et al. 2003). This test requires repetitive, brief (5-min) exposure tests to the same stimulus mouse in the home cage of a resident, with a new mouse introduced in a fifth and final test. OT-knockout mice have difficulties in recognizing the new individual, most likely due to memory deficits. While most studies have examined short-term memory under social conditions (Maroun and Wagner 2016), it is possible that OT effects on the working memory system of infant macaques may be less specific for social stimuli.

More recently, researchers have described the neuroanatomical distribution of OT receptors binding and mRNA in rhesus macaques (Freeman et al. 2014). The nucleus basalis of Meynert is one structure with a high density of OT receptors, a region that provides important input to the neocortex, in particular the visual cortex (Gattass et al. 2014), involved in recognition memory (Aigner et al. 1987), and the basolateral amygdala and which may contribute to some aspects of selective attention and attentional effort, functions that are sensitive to OT treatment (Ebitz et al. 2013). Interestingly, dense OT binding was also found in the superior colliculus (Freeman et al. 2014). Thus, in the present study, some aspects of the OT effects in relation to orienting attention and gaze responses may be attributed to the modulatory effects of OT on these circuits that mediate orienting movements in response to specific visual cues (Wurtz and Goldberg 1972).

While unexpected, we did find an order effect in the gaze-following task: infants performed better if they first participated in the OT condition compared to if they first participated in the saline condition. One possible explanation for this difference is that the gaze following task my have been mildly stressful, particularly in the first test session, and since OT has been shown to be anxiolytic (e.g., Yoshida et al. 2009), it is possible that learning was improved following OT especially in this first test session. Whatever the cause, this difference highlights the importance of counter-balancing, as we did here.

Sex differences in oxytocin sensitivity

A number of individual factors have been reported to influence sensitivity to exogenous OT in human adults, including sex (MacDonald 2013). While we did not predict sex differences, we explored whether males and females differentially responded to OT. Our findings are the first reported evidence of sex differences in sensitivity to OT in a nonhuman primate. Notably, in both tasks, females performed above chance in the saline condition, with particularly large effect sizes for gaze following, indicating females were performing well above chance; in contrast, males performed at chance with saline. This pattern suggests that, in at least some tasks, female infants display higher levels of social cognitive functioning than males. This may be due to different maturation rates in males and females for certain cognitive abilities and their associated neural circuits. For example, female monkeys are more advanced than males in their working memory, which appears shaped by perinatal hormones (Bachevalier and Hagger 1991). This might explain why female monkeys in the present study appeared to have superior baseline working memory compared to males.

These baseline sex differences may also be the reason why males appear more sensitive to the positive effects of OT on working memory and gaze following relative to females. This result extends previous findings that female infant monkeys exhibit greater social interest than males—including more looking to faces and more affiliative behaviors—even in carefully controlled early rearing environments (Simpson et al. 2016b). These findings are also consistent with reports in human infants in which females demonstrate greater social interest. For example, compared to males, female infants orient more to faces (Connellan et al. 2000) and voices (Osofsky and O'Donnell 1977), and make more eye contact (Hittelman and Dickes 1979). In fact, sex differences in sociality are widespread not only among humans, but throughout mammals, indicating possible evolutionary roots (Christov-Moore et al. 2014). Furthermore, a recent study of a large sample of rhesus macaques (n=481) reported female macaques were more likely to gaze-follow than males (Rosati et al. 2016), consistent with our findings. Interestingly, these sex differences were evident across a wide variety of ages, from infancy through adulthood, and grew larger with age, paralleling findings in humans (e.g., Bayliss et al., 2005; Deaner et al. 2007).

Despite a growing number of exogenous OT studies in macaques (e.g., Chang and Platt 2014; Ebitz et al. 2013; Liu et al. 2015), we know of no reports of sex differences, although this may be due to the necessity of small sample sizes (i.e., 2–6 individuals) and therefore insufficient power to detect sex differences, or a sole focus on only males (e.g., Parr et al. 2016). Thus, the sex differences reported here were admittedly unexpected; however, a review of the literature reveals that our findings are largely consistent with a handful of

studies in human and nonhuman primate adults (MacDonald 2013). For example, a recent study in male rhesus macaque adults reported that OT improved gaze-following responses to video stimuli (Putnam et al. 2016). Among healthy human adults, OT increased the reward or salience of positive social interactions in males but had the opposite effect in females (Feng et al. 2014). Another study reported OT enhanced females' focus on positive social attributes and males' focus on negative ones (Gao et al. 2016). Similarly, among older adults (> 60 years), males but not females showed improved facial emotion recognition following OT, but not following a placebo (Campbell et al. 2014). In human adults with generalized anxiety disorder, males but not females treated with OT for 3 weeks exhibited clinical improvements, while females showed the opposite pattern (Feifel et al. 2011). Similarly, we found OT to have either no effect or a negative effect on female infants' performance. Specifically, we found that female infants showed performance above chance in their working memory in the saline condition, but were no longer above chance in the OT condition. Similarly, while females were above chance in their gaze following responses for both saline and OT conditions, they showed a trend of decreasing performance with OT. Although this latter effect did not reach significance, it suggests there may be a small negative effect of OT in females. In sum, while OT may be beneficial for males, for females it may either fail to have a positive influence or may negatively impact them.

Another intriguing dimension to consider is the relation between sex difference in OT sensitivity and psychological disorders. Many disorders in which OT has been proposed as a potential treatment occur more often in one sex than the other, and are linked to individual differences in sociability (Christov-Moore et al. 2014). This link highlights the need to further understand the extent to which findings in one sex are generalizable. For example, autism spectrum disorder (ASD), characterized by disruptions in social behavior, is male-biased and associated with sexually dimorphic levels of OT (Carter 2007). While initial clinical trials in ASD seem promising, the results overall remain mixed, with some studies finding null results (for a review: Lefevre and Sirigu 2016). In trying to interpret these and other contradictory results, a consideration of sex may be useful, as it seems likely that, in at least some cases, OT treatment may be appropriate for one sex but not the other (Feng et al. 2014).

Sex differences in OT effects may reflect not only a differential sensitivity, but also complex interactions between gonadal steroids and OT (Choleris et al. 2003). In fact, estrogen may regulate the production of OT at the hypothalamic level (Choleris et al. 2003; Gabor et al. 2012). Early and chronic administration of OT in rodents can lead to different effects in males and females, with disturbed social behavior in males but not female adults (Bales and Carter, 2003). It is possible that the impact of OT administration in early development may occur within a sensitive period, potentially critical also for the organizational and synergic actions of steroid hormones. Administration of OT at a neonatal age may produce long-term changes in epigenetic regulation of the OT system (Lefevre and Sirigu 2016). However, most studies on administration of OT in early life have been carried out in rodents; thus, we must be cautious in generalizing such findings to primates.

Conclusions

Remarkably, overall, we found that one-month-old macaques demonstrated good working memory and gaze following abilities, performing above chance in both tasks, and acute OT improved these abilities in male, but not female infants. To our knowledge, this finding is the earliest documentation that infant monkeys are capable of these advanced social skills at such a young age. However, the present study is not without limitations. First, we only included two tasks, so it is difficult to know whether our results are generalizable to other aspects of social cognition, including facial expression recognition and action understanding. Second, we cannot be confident from the present results that our effects are specific to the social realm. While we found no evidence that these effects are limited to the social domain for working memory, we think further tests are necessary with nonsocial controls to explore whether OT may influence perception or cognition more generally rather than specifically to social stimuli. In addition, it is unclear to what extent OT, if administered chronically or at different doses, may have different effects (Rault et al., 2013). Finally, the present study focused on infants who were raised by human caretakers. This unique rearing may have impacted infants' early OT systems (Corcoran et al. 2012; Winslow et al. 2003); studies in mother-reared infants are necessary to determine the generalizability of our results. Nonetheless, the present results extend previous findings of positive social effects of OT in infant monkeys (Simpson et al. 2014), suggesting OT effects also appear in more cognitive tasks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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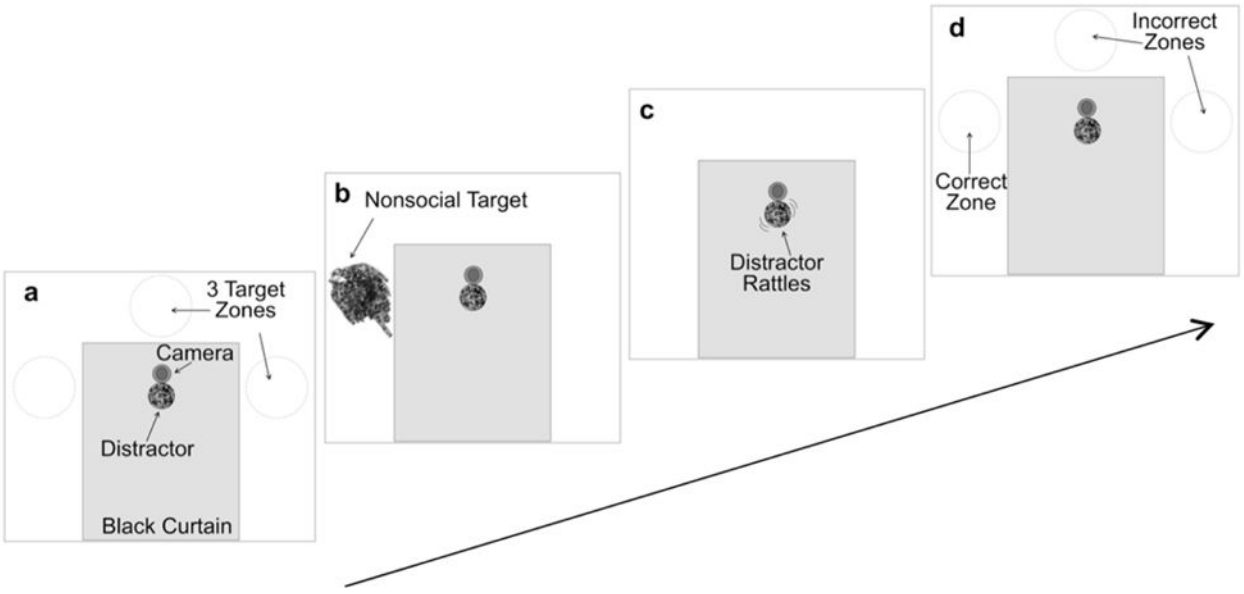

Fig. 1.

Monkey infant's view of the apparatus in the working memory task. (a) Infants viewed a black curtain surrounded by three target zones (circles). (b) At the start of a trial, a target appeared in one of the three zone locations. The target moved and produced a noise until the infant looked for 1 sec. The nonsocial target is pictured here, but there was also a social target (human lip-smacking). (c) The target moved behind the curtain out of view and an attention-getter distractor (cup filled with colorful beads) in the center of the curtain was rattled until the infant looked for 1 sec. (d) The rattle stopped and there was no stimulus for 5 sec, during which time the infant was videotaped to record the location of the first look. The correct target zone was where the stimulus previously appeared (on the left, in this case).

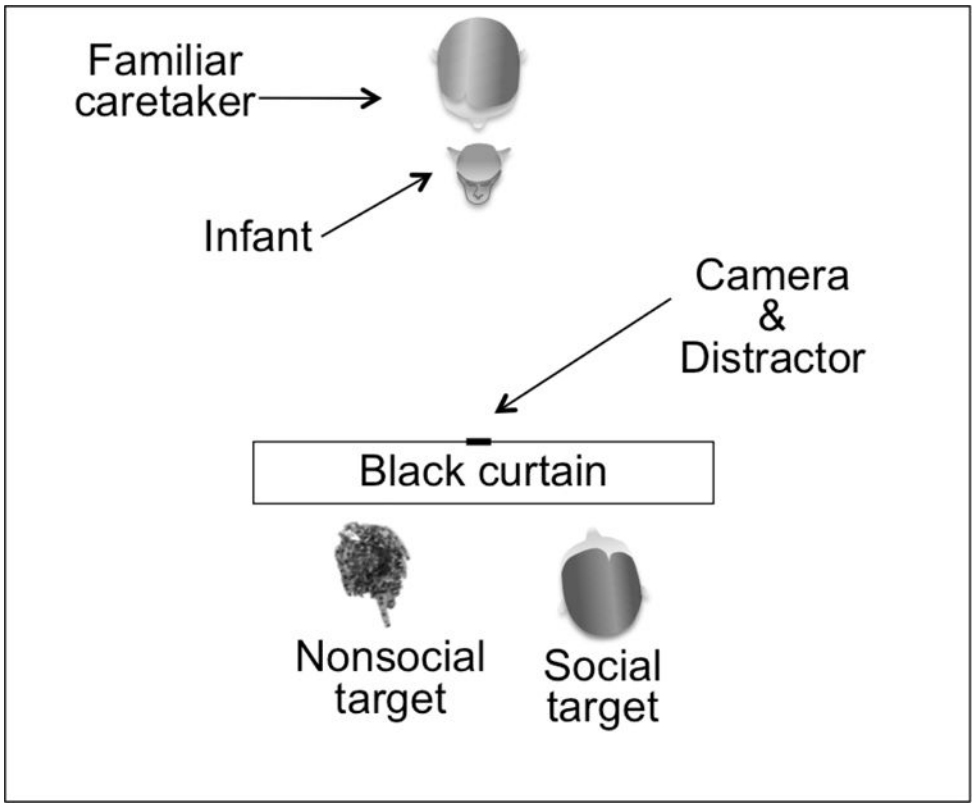

Fig 2.

Aerial view of the working memory task. A familiar caretaker held the infant monkey in front of a black curtain, through which a camera filmed the infant. Two stimulus types were hidden behind the curtain: a nonsocial target (colorful collection of bows, beads, bells) and a social target (familiar human experimenter). At the start of a trial, one stimulus—either the social or nonsocial—would appear outside the edge of the curtain, in view of the infant, in one of three locations, and would produce sound to attract the infant's attention. Once the infant looked, the stimulus would disappear behind the curtain and a distractor—a cup of colorful beads shaken—would orient the infant to the center of the black curtain. Once the infant looked to the distractor, it would stop rattling and there would be no further stimulation. At this time, we recorded the location of the infant's first look to one of the three target locations.

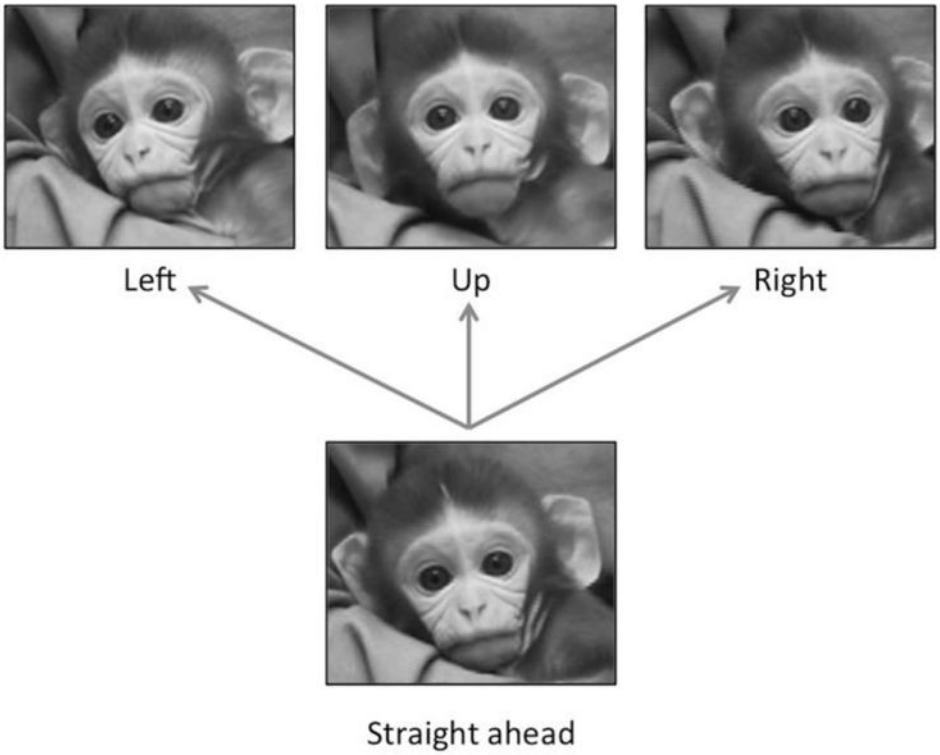

Fig. 3.

Example of infant looking behavior in the working memory task. The camera in Fig. 1 filmed the infant, who was observing the working memory task. We scored from video infants' looking to three target zone locations (left, up, right) immediately following their looking at the attention-getter stimulus (straight ahead).

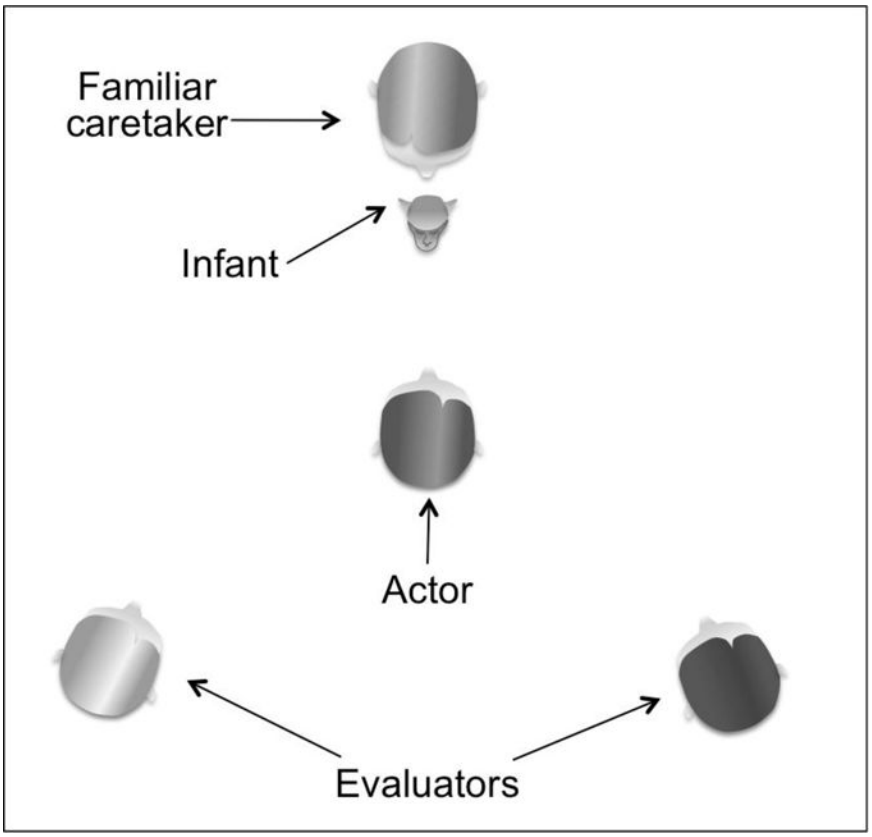

Fig. 4.

Aerial view of the gaze following task. A familiar caretaker held the infant monkey in front of an actor, facing the infant. The actor would attract the infant's attention, then turn her head 90° to look left, right, up, or down, and held this position for approximately 5 sec. Two evaluators observed the infant's behavior from each side.

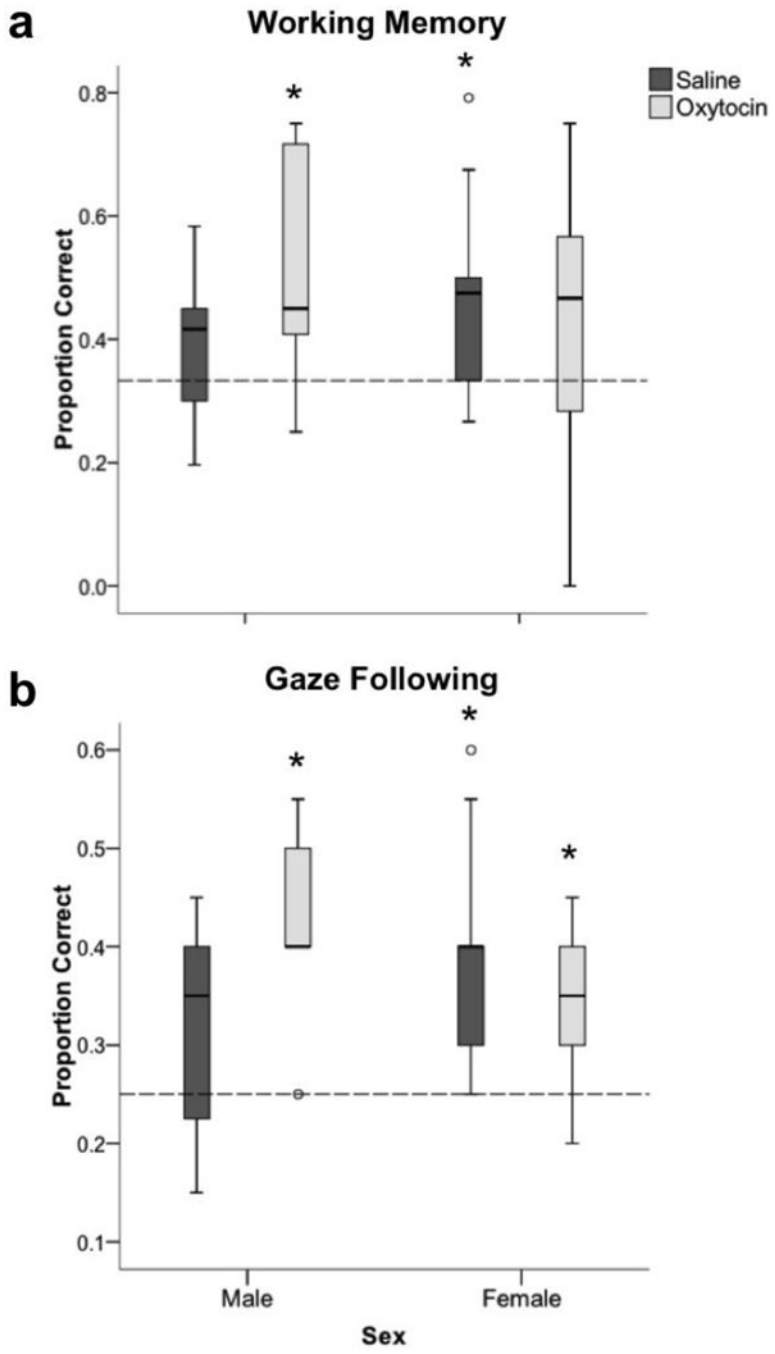

Fig. 5.

(a) Working memory and (b) gaze following performance across saline (dark bars) and oxytocin (light bars) conditions, for males (left) and females (right). Solid horizontal lines indicate medians, the bottom and top of the boxes indicates 25th and 75th percentiles, respectively, and whiskers indicate 95% confidence intervals. The horizontal dashed lines indicate chance. One-sample *t* tests compared each sex and condition to chance, *ps < .05. Exclusion of outliers (open circles) did not alter results, so we retained all individuals.

Table 1

The proportion of correct responses in the working memory task: means (*M*) and standard deviations (*SD*) across infant Sex, Condition (saline, oxytocin), and Stimulus type (social, non-social). There were no main effects or interaction effects for stimulus type in a 2 (Sex) × 2 (Condition) × 2 (Stimulus type) ANOVA ($F(1,21) < 2.0$, ps > .05), or in any follow-up paired *t* tests (shown). Paired samples *t* tests comparing social to non-social stimuli within each sex revealed that males' oxytocin-advantage was primarily driven by performance in the non-social condition ($t(10) = 2.74$, $p = .021$, $d = .83$), and that oxytocin did not significantly improve performance in the social condition, ($t(10) = .93$, $p = .376$). In contrast, females performed similarly in saline and oxytocin conditions across both social ($t(12) = .075$, $p = .941$) and non-social stimuli ($t(11) = 1.09$, $p = .299$).

		Social		Non-Social					
Sex	**Condition**	***M***	***SD***	***M***	***SD***	***df***	***t***	***p***	***d***
Males	Saline	0.41	0.17	0.36	0.11	10	1.10	0.30	.33
(*n* = 11)	Oxytocin	0.51	0.33	0.54	0.16	10	0.25	0.81	.07
Females	Saline	0.45	0.19	0.47	0.21	12	0.27	0.79	.07
(*n* = 13)	Oxytocin	0.45	0.25	0.41	0.22	11	1.19	0.26	.33