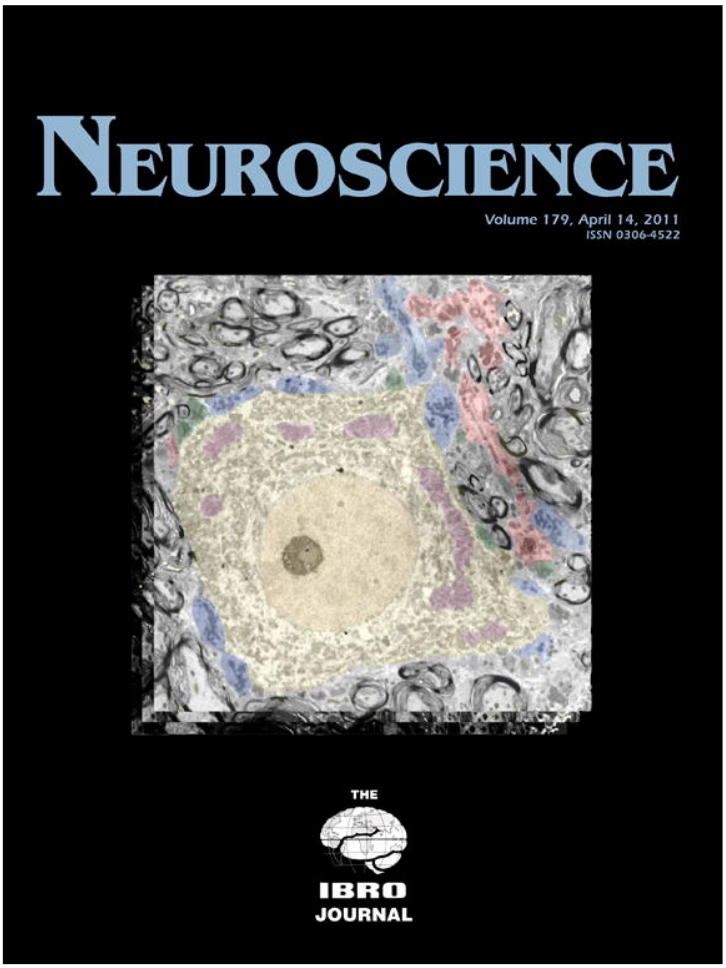

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CONTEXT–SPECIFIC SOCIAL BEHAVIOR IS ALTERED BY ORBITOFRONTAL CORTEX LESIONS IN ADULT RHESUS MACAQUES

B. A. BABINEAU,[a,b,c] E. BLISS-MOREAU,[a,b] C. J. MACHADO,[a,b] J. E. TOSCANO,[a,b] W. A. MASON[b,d] AND D. G. AMARAL[a,b,c,e,*]

[a]*Department of Psychiatry and Behavioral Sciences, University of California Davis, Davis, CA 95616, USA*

[b]*California National Primate Research Center, University of California Davis, Davis, CA 95616, USA*

[c]*Center for Neuroscience, University of California Davis, Davis, CA 95616, USA*

[d]*Department of Psychology, University of California Davis, Davis CA 95616, USA*

[e]*The M.I.N.D Institute, University of California Davis, Sacramento, CA 95817, USA*

Abstract—Although the orbitofrontal cortex has been implicated in important aspects of social behavior, few studies have evaluated semi-naturalistic social behavior in nonhuman primates after discrete lesions of this cortical area. In the present report, we evaluated the behavior of adult rhesus monkeys during dyadic social interactions with novel animals following discrete lesions of the orbitofrontal cortex. In a constrained condition, in which animals could engage in only restricted social behaviors, there were no significant differences in social behavior between the lesion group and the sham-operated control group. When the experimental animals could freely interact with partner animals, however, lesioned animals differed from control animals in terms of social interest and fear-related behaviors. These alterations were contingent on the partner with which they interacted. The lesioned animals, when compared to the control animals, had a significantly greater propensity to approach some but not all of their social partners. They also grimaced more towards the partner animal that they did not approach. Behavioral alterations were more apparent during the initial interactions between animals. We discuss these findings in relation to the role of the orbitofrontal cortex in context dependent modulation of social behavior.

Key words: macaque, behavioral regulation, social behavior, frontal lobe.

The orbitofrontal cortex is one of several brain areas that appear to play a critical role in regulating an individual's ability to interact appropriately in a social environment (Adolphs, 2003; Bauman and Amaral, 2008). Orbitofrontal cortex damage alters people's personalities such that they make risky financial decisions, alienate friends and family or act in socially inappropriate ways (Harlow, 1848; Eslinger and Damasio, 1985; Namiki et al., 2008). Individuals with orbitofrontal cortex lesions also have difficulties with emotional processing, including deficits in recognizing emotion in faces and voices (Hornak et al., 1996, 2003). Some patients report feeling few or no self-conscious emotions, such as embarrassment, even when intentionally placed in a socially uncomfortable situation (Beer et al., 2003, 2006). These findings from patients with lesions are complemented by a substantial body of functional neuroimaging findings demonstrating that the orbitofrontal cortex is activated by stimuli with emotional or social content (Bechara, 2004; Kringelbach and Rolls, 2004; O'Doherty, 2007). For example, tasks which require the subject to make a social decision, such as whether or not to cooperate with another, activate the orbitofrontal cortex (Rilling et al., 2002, 2008; Decety et al., 2004). While studies from human patients suggest that the orbitofrontal cortex is critically involved in normal social functioning, the lesions on which this conclusion is based are often quite large and do not respect boundaries of cortical fields. The socially driven activity in the orbitofrontal cortex also suggests that this area is involved in social information processing, however these findings are correlative and cannot alone determine if the orbitofrontal cortex is critical for regulating species-typical social behavior.

Animal models, particularly nonhuman primates, provide a valuable tool for determining which precise areas of the orbitofrontal cortex are most influential in the mediation of normal social behavior. Rhesus macaques are a particularly good model for human social behavior because they live in large social groups and establish dominance hierarchies both in the wild and in laboratory settings (Bernstein and Mason, 1963). Negotiating a dominance hierarchy requires animals to establish appropriate relationships with animals from different ranks, with animals of different ages or genders and with both kin and non-kin. To accomplish this, rhesus monkeys have an extensive repertoire of social behaviors which includes vocalizations, facial expressions and whole body gestures (Altmann, 1974). While the complex social world in which macaque monkeys live makes them the model of choice for human social behavior, equally important is the similarity between human and macaque neuroanatomy. Macaque cortical neuroanatomy closely resembles that of the human, both in surface morphology and cytoarchitecture (Ongur and Price, 2000). The macaque model is especially good for evaluating phylogenetically newer areas such as the or-

*Correspondence to: D. G. Amaral, The M.I.N.D. Institute, University of California Davis, 2825 50th Street, Sacramento, CA 95817, USA. Tel: +1-916-703-0225; fax: +1-916-703-0237.
E-mail address: dgamaral@ucdavis.edu (D. G. Amaral).

Abbreviations: ANOVA, analysis of variance; CNPRC, California National Primate Research Center; DL, dorsal lateral; FP, frontal pole; Ia-Pir, intermedial agranular insula and precentral opercular areas; MRI, magnetic resonance imaging; OFC, orbitofrontal cortex; ROIs, regions of interest; VL, ventral lateral; VM, ventral medial.

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bitofrontal cortex, which are poorly developed in rodents (Ongur and Price, 2000).

Most nonhuman primate studies to date support the general conclusion that the orbitofrontal cortex is critical for species-typical social behavior (Deets et al., 1970; Snyder, 1970; Franzen and Myers, 1973; Myers et al., 1973; Machado and Bachevalier, 2006). Across published studies, however, the patterns of social behavior vary depending on social setting, social rank of the subjects and size of the subjects' lesions. In a study of free ranging macaques, animals with lesions to all of the prefrontal cortex located anterior to the frontal eye fields (which included the orbitofrontal cortex) left their troops and eventually perished in isolation (Myers et al., 1973). Animals with lesions to the entire frontal lobe, observed in laboratory settings, also displayed abnormal social behavior, such as decreases in the frequency and duration of grooming (Deets et al., 1970; Franzen and Myers, 1973; Raleigh and Steklis, 1981). Mid-ranking rhesus macaques with lesions of the frontal granular cortex (which included Brodmann areas 9, 45 and 46 laterally, 9, 32, 24 and 25 medially and 10, 11, 12, 13 and 14 on the ventral surface) directed inappropriate aggression towards higher ranked animals (Brody and Rosvold, 1952). However, in another study (Snyder, 1970) animals that were the highest ranked among their group displayed less aggression following the creation of large lesions of the orbitofrontal cortex and were eventually displaced by lower ranking animals. Some studies describe increases in threats generated by lesioned animals towards conspecifics without any significant changes in physical aggression (Deets et al., 1970; Machado and Bachevalier, 2006). One study reported no changes in aggression, though this study was conducted with vervet monkeys, a less aggressive species than rhesus macaques (Raleigh et al., 1979). Taken together these previous studies clearly suggest that the orbitofrontal cortex influences aspects of normal social behavior, despite the varied lesion extents and broad range of findings.

To date, there are no published studies in which rhesus macaques with discrete lesions of the orbitofrontal cortex were observed during dyadic interactions with conspecifics. The advantage of this paradigm is that it allows for direct comparison between the lesioned subjects and control animals as both groups interact with the same social partners. In the present study, we compared rhesus macaques with discrete orbitofrontal cortex lesions and age-matched neurologically intact controls as they interacted with conspecifics in two conditions. In the first condition, animals had restricted access to each another (one animal was behind a restraining barrier) in order to familiarize the animals to one another while reducing the possibility of dangerous bouts of aggression. In the second condition, animals were allowed to freely interact with each other in a large enclosure. In both cases, the frequency and durations of an extensive list of species-typical behaviors were recorded. We observed subtle differences between lesioned and control animals during social interactions that were dependent on the social context (i.e. which interaction partner was present).

EXPERIMENTAL PROCEDURES

All protocols were approved by the Institutional Animal Care and Use Committee of the University of California, Davis and were conducted in accordance with the National Institutes of Health guidelines for the use of animals in research.

Subjects and housing

Twelve adult (4–6 years old at the start of the study; ages 4.5–6.5 at the start of these experiments) male rhesus monkeys (*Macaca mulatta*) participated in this experiment. All were born and maternally reared in half-acre outdoor enclosures at the California National Primate Research Center (CNPRC). These enclosures house 70–120 male and female monkeys of all ages and provided each animal with a normal social environment prior to its relocation to indoor housing for the experiments described below. Animals selected for these studies were chosen from a larger sample following preliminary behavioral observations (two observations per day for 10 days) of each animal in its natal cage by trained observers. The frequency and duration of positive and negative social behaviors were recorded. The selected animals displayed moderate levels of affiliative behaviors (e.g. groom and mount, see Table 1 for descriptions), low levels of aggressive behaviors (e.g. threat and aggression), displayed no behavioral abnormalities (e.g. stereotypies) and were of middle dominance rank. Two animals were selected from each field cage to facilitate socialization once they were relocated indoors (see below).

Animals were housed indoors in standard cages for male rhesus monkeys (61 cm width×66 cm depth×81 cm height). Housing rooms had regulated lighting (12 h light/dark cycle) and temperature (75–85 °F). Animals were fed a diet of monkey chow (Ralston Purina, St. Louis, MO, USA) supplemented with fruit and vegetables. Water was available *ad libitum*. Familiar pairs (from the field cages) were housed adjacently, separated by a metal grate partition that allowed visual and tactile access, but minimized the possibility of injury from aggression. One monkey from each pair was assigned to the orbitofrontal cortex lesion group and the other animal was assigned to the sham-operated control group. Lesion group composition was balanced with respect to age and pre-surgical behavioral measures. The experimental groups were also balanced with respect to allelic variation of the serotonin transporter gene. The two variants, a short allele and a long allele, have different transcriptional activity, in that the long allele results in higher levels of the serotonin transporter (Lesch et al., 1997; Champoux et al., 2002). The presence of a short allele increases an individual's susceptibility to anxiety and mood disorders (Champoux et al., 2002). Further, in rhesus macaques exposed to early life stressors, animals with the short/short or long/short genotype show more pathologic behavior than animals with the long/long genotype (Spinelli et al., 2007). Each experimental group contained four animals with the long/long genotype, one with the long/short genotype and one with the short/short genotype. CNPRC practice does not allow selection of animal subjects based on genotype to maintain genetic diversity within the colony. The purpose of balancing the groups on multiple factors was to create two experimental groups that were as homogenous as possible.

Pre-surgical Magnetic Resonance Imaging (MRI)

Only animals assigned to the lesion group received a pre-surgical MRI. Animals were anesthetized individually with ketamine hydrochloride (10 mg/kg, i.m.) and medetomidine (25–50 μg/kg, i.m.). The animal's head was secured in an MRI compatible stereotaxic apparatus (Crist Instrument, Hagerstown, MD, USA). Monkeys were imaged using a 1.5 T Gyroscan magnet (GE Healthcare, Waukesha, WI, USA); 1.0 mm thick images were acquired in the coronal plane using a T1 weighted inversion recovery spoiled gradient pulse sequence (repetition time=22 ms; echo time=7.90 ms; flip angle=30; number of excitations=3; field of view=8 cm;

Table 1. Descriptive behavioral ethogram

Social interest behaviors	
Approach	Directed movement into arms reach of another subject
Accept approach[b]	Staying in place upon an approach from another subject
Proximity*,[c]	Staying within arm's reach of another subject for at least 3 s
Proximity zone[a,c]	Within a 1 m radius of the stimulus cage for at least 3 s
Contact*,[c]	Physical, non-aggressive touching of any body parts
Follow*,[b]	Slow, deliberate movement after another subject lasting for at least 3 s
Look	Animal looks/gazes at another
Affiliative behaviors	
Lipsmack	Rapid lip movements with pursed lips
Grunt	Deep, muffled, low-intensity vocalization
Anogenital explore	Sniffing, licking, touching or visual examining genital area of another subject
Groom*,[c]	One animal examines, picks, or licks at the other animal's fur or body part
Mount*,[b]	Double foot clasp, hands on back, thrusting
Present for groom*	Presentation of neck, belly, rump, limbs, back or flank to another for grooming
Present for mount*	Stiff, four point stance, tail up, rump toward partner
Threat solicitation	Animal looks towards the stimulus partner then threatens the observer
Mount attempt[a]	Any component of a mount that is attempted through the metal grille
Dominant/aggressive behaviors	
Cage shake*	Vigorous shaking of cage bars or body slams against the cage
Crooktail	Stiff-legged strut and tail held in stiff "?" shape
Threat*	Two or more of open mouth state, head bob, bark vocalization
Aggression*,[c]	Animal aggressively bites, grabs, slaps, or chases another animal
Displacement[b]	Scored when another subjects approaches and "takes the place" of another animal
Submissive/fearful behaviors	
Avoid*	Deviation from current path or leaving from an area due to impending approach
Fear grimace*	Exaggerated grin with teeth showing
Freeze*	Scored when an animal does not move and maintains a rigidly fixed body position
Scream	High pitch, high intensity vocalization
Bark	Short, sharp sound given as an alarm call
Exploratory behaviors	
Manual exploration	Use of hands to explore physical environment
Oral exploration	Use of mouth to explore physical environment
Anxious behaviors	
Scratch	Rapid hand movement, using fingers or toes to scratch own body
Yawn	Fully open mouth, lips retracted and teeth showing
Tooth grind	Repetitive, audible rubbing of upper and lower teeth
Self-directed behaviors	
Self groom	Grooming of one's own hair or body
Self sex	Anogenital exploration of self
Stereotypies	
Pace*	Repetitive motor pattern repeated at least three consecutive times
Head twist*	Animal twists neck in a dramatic display
Other stereo*	Repetitive motor or abnormal behavior patterns not described by above definitions
Anti-social behaviors	
Non-social active[c]	Active behavior (head up/exploring) out of proximity for at least 3 s
Non-social inactive[c]	Passive behavior (head down/not exploring) out of proximity for at least 3 s
Non-social stationary[a,c]	Out of the proximity zone and remains non-locomotive for at least 3 s
Reject approach[b]	Vacating the area when another animal moves within arms reach
Inappropriate Mount[b]	A mount or incomplete mount made to any part of the body other than the perineum
Mount refusal[b]	Refusal of a mount, either by moving away or physically pushing the animal away

Note:
[a] Behaviors which were only scored in the constrained dyad experiment.
[b] Behaviors which were only scored in the unconstrained dyad experiment.
[c] Behaviors for which a duration could be scored.
* Behaviors scored in the field cage observations.

matrix=256×256). After scan completion, the medetomidine was reversed with atipamazole (0.15 mg/kg, i.m.). Images were converted into a surface reconstruction that allowed visualization of the ventral surface of each animal's frontal lobe prior to surgery. This facilitated planning of the direct surgical approach that was used to produce the lesion of the orbitofrontal cortex.

Surgical procedures

All surgical procedures were performed aseptically at the CNPRC. Monkeys were initially anesthetized with ketamine hydrochloride (10 mg/kg, i.m.). Animals were then intubated and a stable level of anesthesia was maintained throughout surgery with a combination

of isoflurane (~1.0% inhalation; percentage varied as needed) and i.v. infusion of fentanyl (7–10 mg/kg/min, i.v.). The animal's head was immobilized in a stereotaxic apparatus with elevated ear bars (David Kopf Instruments, Tujunga, CA, USA) to allow clear access to the frontal lobe. Heart and respiration rates, blood pressure, expired CO_2 and body temperature were monitored during surgery and maintained within normal physiological levels.

A midline scalp incision was made, followed by gentle reflection of the skin, fascia and temporalis muscles. A large bone flap was produced in the skull over the frontal lobes using an electric surgical drill. The bone flap was separated from the dura and kept submerged in warm, sterile saline until replacement after the bilateral lesions were completed. Two incisions were made in the dura over each hemisphere; one running parallel to the superior sagittal sinus and a second starting at the posterior limit of the first and running lateral, adjacent to the edge of the bone flap. The frontal lobes were gently elevated using Neuro Patties (Fabco, New London, CT, USA) moistened with saline. A surgical microscope (Carl Zeiss Surgical, Inc., Dublin, CA, USA) was used to aid the surgeon in visualization of the orbitofrontal surface.

Orbitofrontal lesions were intended to include Walker's areas 11, 13 and 14. Based on the pre-surgical MRI, the extent of the intended lesion was first outlined on the surface of the brain using electrocautery. The lesion extended from the rostral tip of the lateral orbital sulcus and continued caudally approximately 3 mm. The lesion extended medially approximately to the midline and approximately 3 mm up the medial wall. The lesion continued rostrally approximately 8 mm. A line of cautery was then made connecting the rostral extent of the medial portion of the lesion to the fundus of the medial orbital sulcus. To complete the anterior boundary, a line of cautery was created from the tip of the medial orbital sulcus to the tip of the lateral orbital sulcus. The cortex within these boundaries was then cauterized and removed using a fine gauge (7 French) Baron suction probe (Biomedical Research Instruments, Rockville, MD, USA). Once the lesion was complete for one hemisphere, the dura was sutured and the lesion procedures were repeated on the contralateral side. Once the lesion was completed bilaterally, the bone flap was replaced using six dog-bone shaped titanium plates (Osteomed, Addison, TX, USA). The muscle, fascia and skin were closed in anatomical layers. The six sham-operated control animals underwent the same pre-surgical preparations and then received a midline incision and skull exposure only. Their wounds were also closed in anatomical layers and they were maintained on anesthesia for the average duration of the lesion surgeries. After the surgical procedures were completed, the monkeys were monitored by a veterinarian and provided antibiotics (Cefazolin 25 mg/kg) and analgesics (Ketoprofen 2 mg/kg and Oxymorphone 0.15 mg/kg) as deemed necessary by the veterinary staff. Animals remained in the hospital for 6–8 days before returning to their home cage. Veterinary staff monitored all animals an additional 1–2 weeks following hospital discharge to ensure that all animals were fully recovered before any testing began. Recovery was indicated by normal eating patterns, alertness and lack of motor impairment. Behavioral testing began 10–12 weeks following surgery.

Post-lesion MRI

Animals received a second MRI approximately 18 months after surgery to assess the location and extent of the lesions. Procedures were identical to the pre-lesion MRIs described above.

Lesion analysis

Post-surgical T1-weighted images were compared to pre-surgical T1-weighted images to identify the location and quantify the extent of the lesions. The extent of damage was quantified using Analyze 10.0 software (Biomedical Imaging Resource, Rochester, MN, USA). On each coronal image, starting from the frontal pole and continuing back 1 mm caudal to the intended lesion area, the intended lesion area and other frontal lobe regions of interest (ROIs) were manually outlined based on a detailed set of tracing guidelines (Table 2). Two raters (C.J.M. and B.A.B.) manually traced all ROIs after establishing reliability on MRI scans from two pre-lesion cases and two post-lesion cases with an inter-rater reliability correlation of greater than 90%. The titanium plates used to re-secure the bone-flap to the skull created MRI artifact in the dorsolateral ROI. Because the boundaries of the artifact were clear, we were able to determine what missing MRI signal was due to artifact. Intact tissue which was obscured by the MRI artifact was included in the dorsolateral ROI. In one case (OFC-3) the artifact could not be distinguished from the damaged tissue and therefore all missing tissue was considered part of the lesion extent. Once the ROI tracings were completed for each animal, Analyze software was used to calculate the volume of areas of all ROIs from both the pre-surgical and post-surgical images. Percentage of damage for each ROI in each lesioned animal was calculated by subtracting the post-surgical volumes from the pre-surgical volumes, then dividing the differences by the pre-surgical volume and multiplying by 100. Both the extent of damage of the intended lesion area and the extent of extraneous damage were compared to the behavioral alterations seen in the lesioned ani-

Table 2. Lesion extent analysis boundary definitions

Region of interest	*Definition*
Orbitofrontal lesion	*The boundaries of this ROI approximated the intended lesion area. The anterior boundary was defined as the first image clearly showing the medial orbital sulcus. The lateral border was the lateral orbital sulcus and the medial boundary was approximately 2 mm up the medial wall. The posterior boundary was approximately 20 images caudal to the anterior boundary*
Frontal pole	*The anterior boundary was defined as the second image clearly showing frontal polar cortex. The posterior boundary was the last image before the first appearance of the medial orbital sulcus*
Ventromedial prefrontal cortex	*The anterior boundary of this region was the same as described above. The dorsal boundary was the fundus of the cingulate sulcus. The ventral boundary was the dorsal boundary of the orbitorfrontal cortex ROI. The posterior boundary was two images past the posterior boundary of the orbitofrontal cortex*
Dorsolateral prefrontal cortex	*The anterior and posterior boundary of this ROI is the same as described for the ventromedial prefrontal cortex above. The medial boundary was the fundus of the cingulate sulcus. The lateral boundary was the ventral lip of the principal sulcus*
Ventolateral prefrontal cortex	*The anterior and posterior boundary of this ROI is the same as described for the ventromedial prefrontal cortex above. The dorsal border was contiguous with the ventral border of the dorsolateral prefrontal cortex ROI described above. The medial boundary was the fundus of the lateral orbital sulcus*
Intermediate agranular insula areas-precentral opercular areas	*This anterior boundary of this ROI was the image following the last appearance of the orbitofrontal cortex ROI. The posterior boundary was two images past the posterior boundary of the orbitofrontal cortex. The lateral boundary was the fundus of the lateral orbital sulcus and the medial boundary was the medial wall*

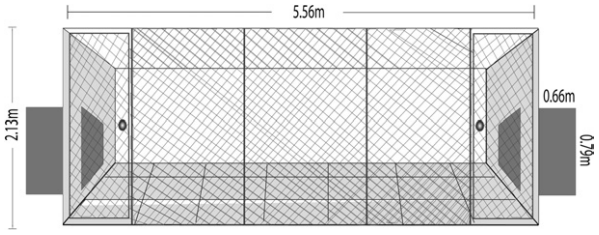

Fig. 1. Drawing of the experimental test cage. The two smaller cages on either side are the release cages used during the constrained dyad condition. These cages each connect to the middle arena via an opaque plastic door and metal grille that could be raised and lowered by the experimenter using a pulley system. During constrained dyad interactions a metal grille was lowered and locked in place to limit direct interaction between the animals.

mals to determine if there was a correlation between the extent of tissue damage and patterns of social behavior.

Behavioral testing

Testing cage. Behavioral observations occurred in a large testing enclosure (5.56×1.91×2.13 m^3) described previously by Emery and colleagues (2001). The enclosure was constructed from pipe and chain-link fencing and had a cement floor (Fig. 1). At either end of the enclosure was an aluminum release cage (0.66×0.64×0.79 m^3) with an opaque door and a metal grille. The door and the grille could be raised and lowered independently using a pulley system located outside the cage. The observers were positioned at the center of the cage, approximately 2 m away from the front of the chain-link. Prior to the start of testing, all animals were acclimated to the enclosure with observers present and were trained to enter or exit the release cage when the opaque door was raised. Each acclimation session was approximately 10 min long. Animals continued to be acclimated until they exited the main testing cage within 1 min on three consecutive days. Acclimation lasted approximately 6–8 weeks for each animal.

Social interaction partner animals. A group of four rhesus macaques served as common social partners ("stimulus animals") for the 12 experimental animals during the two conditions described below. The stimulus animals were two males (M1 and M2) and two females (F1 and F2). These animals were selected from the indoor colony and were observed in their living quarters prior to selection. Each of these animals displayed appropriate social behaviors with their pair-mates. The stimulus animals were within the age range of the experimental animals (ages at the start of testing: M1=5.5 years, M2=4.5 years, F1=5.5 years, F2=4.5 years). Although the animals were similar in age, their physical attributes were quite different. M1 was larger than M2 (13.32 kg vs. 8.89 kg) and F1 was larger than F2 (12.90 kg vs. 6.13 kg). The stimulus animals were unfamiliar to all experimental animals at the start of behavioral testing.

Data collection. Behavioral data were collected with The Observer software package (Noldus et al., 2000) by trained observers demonstrating an inter-observer reliability ≥85% (agreements/[agreements+disagreements]×100). All observers were blind to lesion condition at the time of behavioral data collection. Using a focal sampling method, the frequency and duration of social and non-social behaviors generated by the experimental animals (or "initiated" by experimental animals) and generated by the stimulus animals towards the experimental animals (or "received" from the stimulus animals) were recorded based on a catalog of behaviors (ethogram) commonly used to assess the behaviors of adult rhesus monkeys (Capitanio, 1985) (see Table 1 for a list of behaviors and brief definitions). Individual behaviors are grouped into categories based on the type of social information conveyed by the action, facial expression or vocalization.

Condition 1: Constrained Dyads. During the "constrained dyad" experiment, one animal remained in the release cage constrained by the metal grille and the other animal was allowed to freely move about the large testing arena. The two animals had visual and tactile access to one another though the metal grille. Each daily testing session lasted for 20 min. During the first 10 min, one animal was free to move about the large, middle arena and the other remained in the release cage. During the second 10 min, the previously free animal was placed in one of the release cages and the previously constrained animal was allowed access to the main arena. All experimental animals interacted with each of the four stimulus animals on six different test days for a total of 24 10-min observations during which the experimental animal was constrained and 24 10-min observations during which the experimental animal was free. The starting position of each animal was counter-balanced across days (i.e. if the experimental animal was constrained during the first 10 min in meeting 1, the stimulus animal would be constrained during the first 10 min of meeting 2). All behaviors generated by the free animal were recorded. Behaviors generated by the constrained animal and directed towards the free animal were also recorded. Behavioral data collection began when the free animal entered the large testing cage. Experimental animals had one meeting with one stimulus animal each day. Stimulus animals participated in three meetings each day. Stimulus animals had approximately a 5-min break between each meeting. The order in which the experimental animals met the stimulus animal was balanced across days.

Condition 2: Unconstrained Dyads. In the "unconstrained dyad" experiment, both the experimental animal and the stimulus animal were allowed to freely interact in the main testing arena for the entire 20-min session. Again, all experimental animals met each of the four stimulus animals six times for a total of 24 20-min observations. As in the "constrained dyad" condition, all behaviors generated by the experimental animal were recorded. Additionally, all behaviors generated by the stimulus animal and directed toward the experimental animal were recorded. Behavioral data collection began when both animals had entered the arena. Experimental animals had one meeting with one stimulus animal each day. Stimulus animals participated in three meetings each day. Stimulus animals had approximately a 5-min break between each meeting. The order in which the experimental animals met the stimulus animal was balanced across days.

Statistical analyses

To evaluate the effect of orbitofrontal cortex lesions on social behavior, we analyzed the frequency and duration of behaviors occurring during each condition using a series of repeated measures analysis of variance (ANOVAs) with lesion condition as the between subjects factor. There was considerable variability across subjects in the total number of behaviors initiated. To control for these differences, frequency data were transformed to a percentage of total behavior (Frequency of Behavior A/Sum of all Behaviors Produced)×100). For clarity, we discuss findings as behavioral frequencies, although all data subjected to analysis and presented in figures reflect percentages of total behavior. Duration data were not transformed for analysis.

Initial analyses indicated that the behavior of the experimental animals differed based on the stimulus partner with which they were interacting. Behavior also varied across meetings with each stimulus animal. The six meetings were grouped into three time periods (two meetings each); data were averaged within each period. Therefore, frequency and duration data were evaluated based on the particular partner and meeting number using a series of 2 (lesion condition: orbitofrontal cortex-lesion vs. sham-

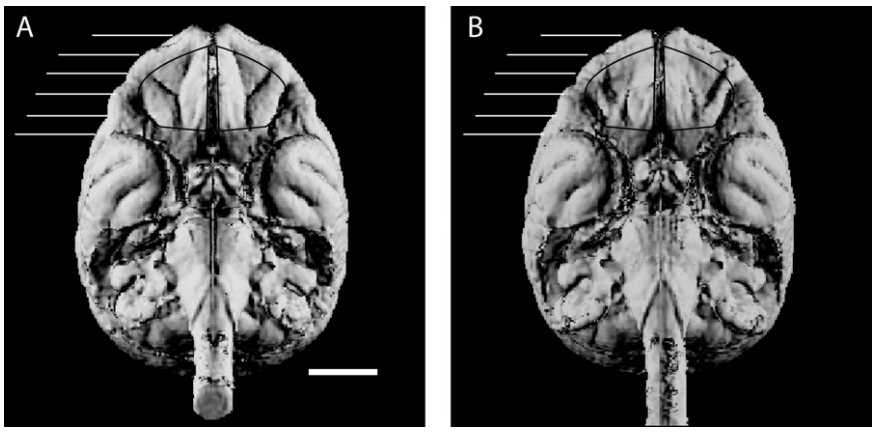

Fig. 2. Surface reconstructions of the pre-lesion (A) and post-lesion (B) brain of animal OFC-2. Surface reconstructions were created from the T1-weighted images using the Analyze software package. The intended lesion area is drawn onto both the pre-lesion and post-lesion reconstructions. The y-shaped medial orbital sulcus is prominent in the pre-lesion reconstruction (A) but less visible in the post-lesion reconstruction (B) as the surrounding cortex has been removed. Thin horizontal white lines indicate the rostro-caudal level for each of the coronal images shown in Fig. 3. Scale bar (thick white line at base of image)=1 cm.

operated control)×4 (stimulus partner: M1, M2, F1, F2)×3 (time period: P1, P2, or P3) repeated measures ANOVAs (one ANOVA for each behavior of interest). This allowed us to determine if there was an effect of lesion, of stimulus partner, of number of meetings or an interaction between these factors. Significant interactions were further evaluated using *t*-tests or univariate analysis. Only behaviors that accounted for at least 1% of total behavior were subjected to ANOVA. Significant results are discussed for individual behaviors. Behaviors initiated by the experimental animals will be discussed separately from behaviors initiated by the stimulus animals and directed towards the experimental animals. Alpha was set at $P<.05$. However, given the low number of monkeys in each experimental group and the variation of lesion extent, we occasionally report results for which *P* values fall above this threshold. Results are identified as marginally significant if their *P* value is greater the .05 but less than .1. Statistics for non-significant findings are available on request.

RESULTS

Lesion assessment

Boundary definitions for regions of interest are listed in Table 2. The intended lesion area was meant to encompass Walker's areas 11, 13 and 14 (Fig. 2). Coronal images from representative cases are depicted in Fig. 3. The extent of damage to the orbitofrontal cortex (intended lesion area) ranged from 65.64% to 87.78% (Table 3). Spared tissue typically was located in the caudal and medial portions of the intended lesion area. Unintended damage was minimal (<12%) in most of the other frontal areas. The frontal pole sustained moderate damage (35.69% on average). There was considerable distortion in the post-lesion images that was most likely caused by relaxation of remaining tissue into areas previously occupied by lesioned cortex.

Condition 1: constrained Dyads

There were no significant differences between the orbitofrontal cortex-lesioned animals and the control animals in the frequency or duration of any behaviors they initiated in the constrained dyad condition. Similarly, there were no appreciable differences in behaviors that the stimulus animals directed at the lesioned or control groups.

Condition 2: unconstrained Dyads

There were lesion-related differences in the responses generated and received by the experimental animals in the unconstrained condition.

Social interest behaviors. Approach. Animals with orbitofrontal cortex lesions tended to approach the stimulus animals more often than did the control animals, $F(1, 10)=4.540$, $P<.06$ (Fig. 4A). Orbitofrontal cortex-lesioned animals approached only some of the stimulus animals more frequently as indicated by a significant partner by lesion interaction, $F(3, 30)=4.556$, $P<.05$. Follow up *t*-tests revealed that orbitofrontal cortex-lesioned animals, when compared to control animals, approached M2, F1 and F2 more frequently (M2: $t(10)=2.066$, $P<.07$; F1: $t(10)=3.002$, $P<.05$; F2: $t(10)=2.529$, $P<.05$). By contrast, there was no difference in the number of times orbitofrontal cortex-lesioned and control animals approached M1, $t(10)=0.048$, $P>.1$. The number of approaches varied over time as indicated by a significant period by lesion interaction, $F(2, 20)=5.483$, $P<.05$. Lesioned animals approached the stimulus animals significantly more than the control animals only in the first two dyadic interactions (Period 1, $t(10)=3.263$, $P<.05$, Fig. 4C).

Proximity. After approaching the stimulus animals, the orbitofrontal cortex-lesioned animals maintained close proximity (stayed within arm's reach for at least 3 s) with the stimulus animals more frequently than the control animals did, $F(1, 10)=5.516$, $P<.05$ (Fig. 4D). This greater frequency of proximity was not clearly related to any particular stimulus animal, $F(3,30)=1.314$, $P>.1$ (Fig. 4E). Across meetings, the frequency of proximity differed between the lesioned and control animals as indicated by a

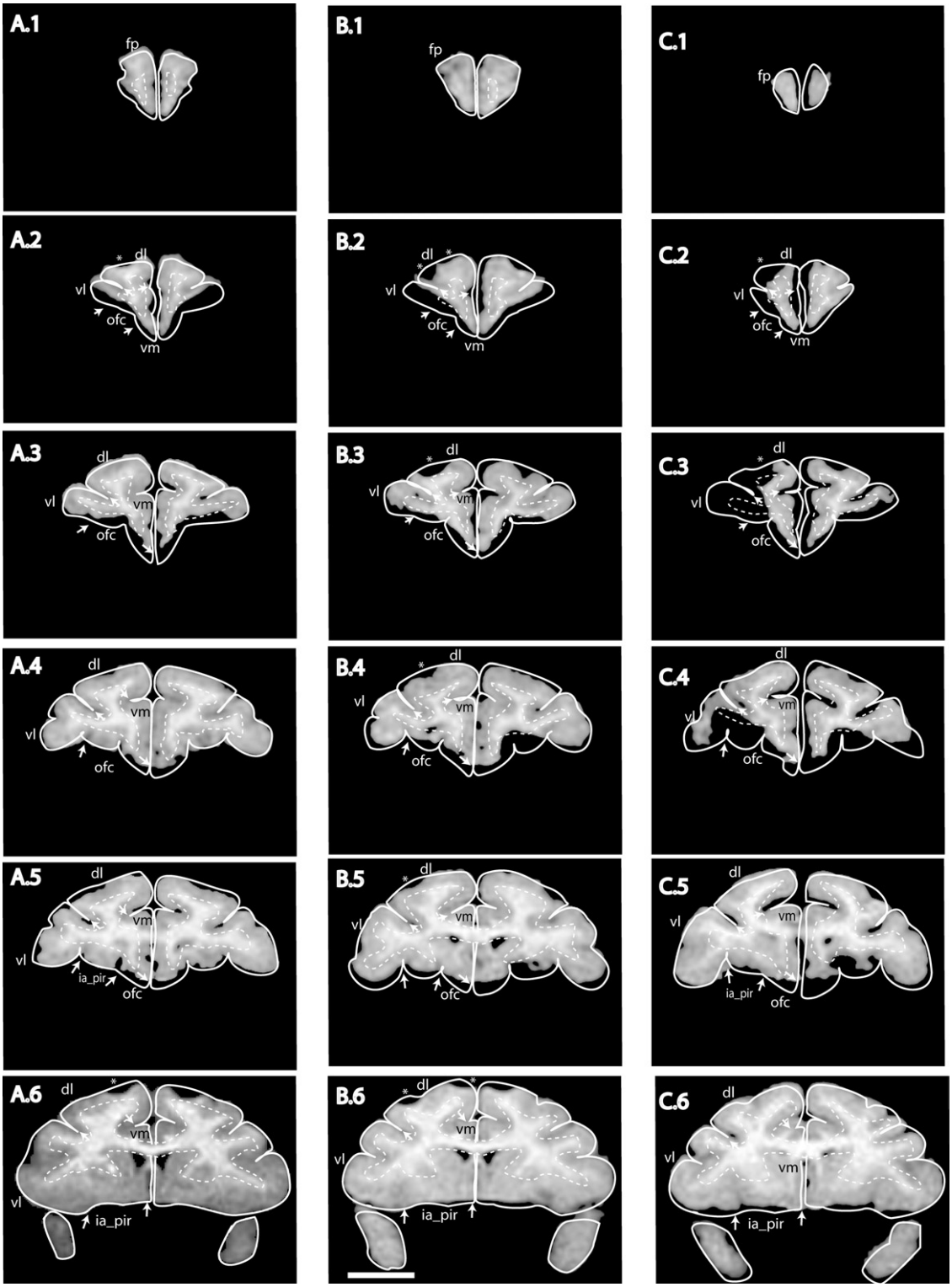

Fig. 3. T1 weighted coronal images through six levels (rostral to caudal) of the frontal lobe following surgery. All cases are represented: Subject OFC-1 (Images A.1–A.6), Subject OFC-2 (Images B.1–B.6), Subject OFC-3 (Images C.1–C.6), Subject OFC-4 (Images D.1–D.6), Subject OFC-5 (Images E.1–E.6), Subject OFC-6 (Images F.1–F.6). White lines are outlines of brain tissue from pre-lesion images at approximately the same level. Areas where the post-lesion image does not match the white outline indicate where tissue was damaged or removed. Imaging artifacts (noted by asterisks) were caused by the titanium plates used to reattach the bone flap to the skull. Image 1 (for each case) is rostral to the intended lesion area. Image 2 is near the rostral extent of the intended lesion area. Images 3 and 4 are at the middle of the intended lesion area. Image 5 is near the caudal extent of the intended lesion area. Image 6 is caudal to the intended lesion area. Distance between levels is approximately 2.5 mm. Arrows indicate the boundaries of the areas evaluated in the lesion extent analysis (for boundary definitions see Table 2). Calibration bar=5 mm.

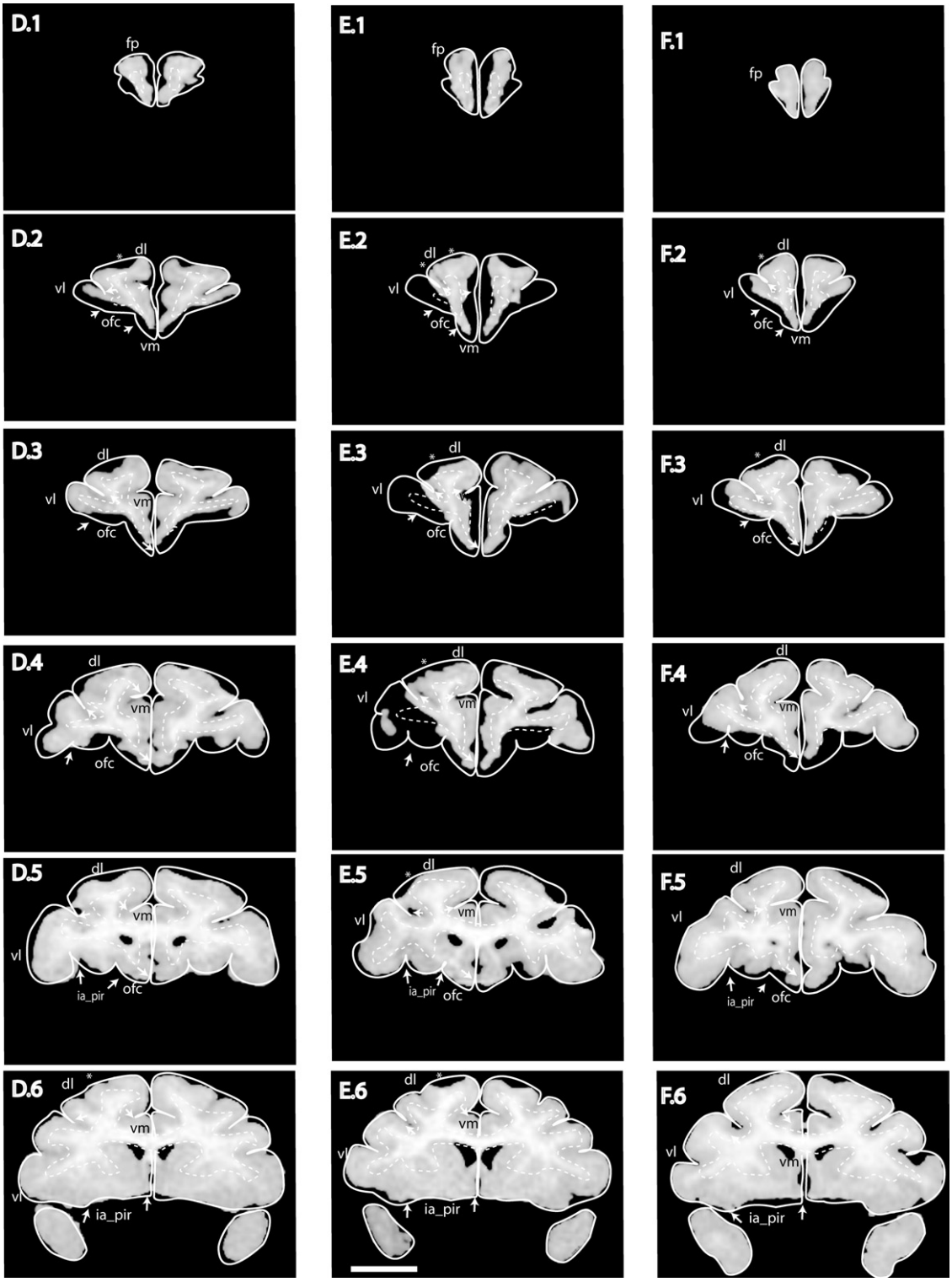

Fig. 3. (*Continued*).

significant lesion by period interaction, $F(2, 20)=8.041$, $P<.05$. Follow-up *t*-tests revealed that when compared to the control group, lesioned animals initiated proximity significantly more in Periods 1 and 2, $t(10)=2.758$, $P<.05$, $t(10)=2.973$, $P<.05$, respectively (Fig. 4F).

Follow. The heightened social interest of the orbitofrontal cortex-lesioned animals was also evident in their elevated tendency (as compared to controls) to follow the stimulus animals around the testing cage, $F(1, 10)=3.500$, $P\leq.09$ (Fig. 4G). Orbitofrontal cortex-lesioned and control

Table 3. Lesion extent (percent damaged)

ID	OFC	FP	Ia-Pir	VL	DL	VM
Y1	87.78	41.55	13.25	13.70	19.77	8.96
Y2	74.57	45.76	36.39	22.03	9.07	9.70
Y3	70.39	50.26	20.04	6.36	7.86	9.73
Y4	79.39	37.23	11.22	1.67	2.89	8.57
Y5	83.06	23.32	3.41	10.88	12.48	8.67
Y6	85.64	15.99	26.92	13.97	10.14	7.33
AVE	76.80	35.69	18.54	11.44	10.37	8.83

Abbreviations: ID, animal identification number; AVE, average extent of damage across all regions.

animals differentially followed individual stimulus animals as indicated by a significant partner by lesion effect, $F(3, 30)=6.785$, $P<.05$. Orbitofrontal cortex-lesioned animals displayed an increase in the frequency of following F1, $t(10)=2.682$, $P<.05$, (Fig. 4H). The experimental groups also tended to differ in how much they followed the stimulus animals across meetings as indicated by a marginally significant period by lesion effect, $F(2, 20)=3.039$, $P\leq.09$, but follow-up *t*-test failed to reveal a significant group difference during any individual Period (Fig. 4I).

In summary, the orbitofrontal cortex-lesioned animals initiated more interactions with the stimulus animals than their control counterparts. This heightened interest was specific to stimulus partners M2, F1 and F2 and most prevalent during early and middle interaction sessions.

Submissive/fear-related behaviors. Fear grimace. Overall, orbitofrontal cortex-lesioned animals tended to fear grimace more than control animals, $F(1, 10)=4.513$, $P\leq .06$ (Fig. 5A). Fear grimaces were not initiated towards all stimulus animals equally as indicated by a marginally significant partner by lesion interaction, $F(3,30)=3.227$, $P\leq.06$. Post-hoc follow up tests indicated that lesioned animals had a tendency to fear grimace at M1 more than the control animals did, $t(10)=2.668$, $P\leq.06$. There were no lesion group differences with any of the other stimulus animals (Fig. 5B). Lesioned animals' grimacing also differed across periods as indicated by a marginally significant period by lesion effect, $F(2, 20)=2.588$, $P\leq.09$, but follow-up *t*-test failed to reveal a significant group difference during any individual Period (Fig. 5C). No other behaviors in the submissive/fearful behavior category revealed any significant differences between the lesion and control groups.

Behaviors generated by stimulus animals. Accepting approach. One behavior that the partner animals displayed differentially between the lesioned and control

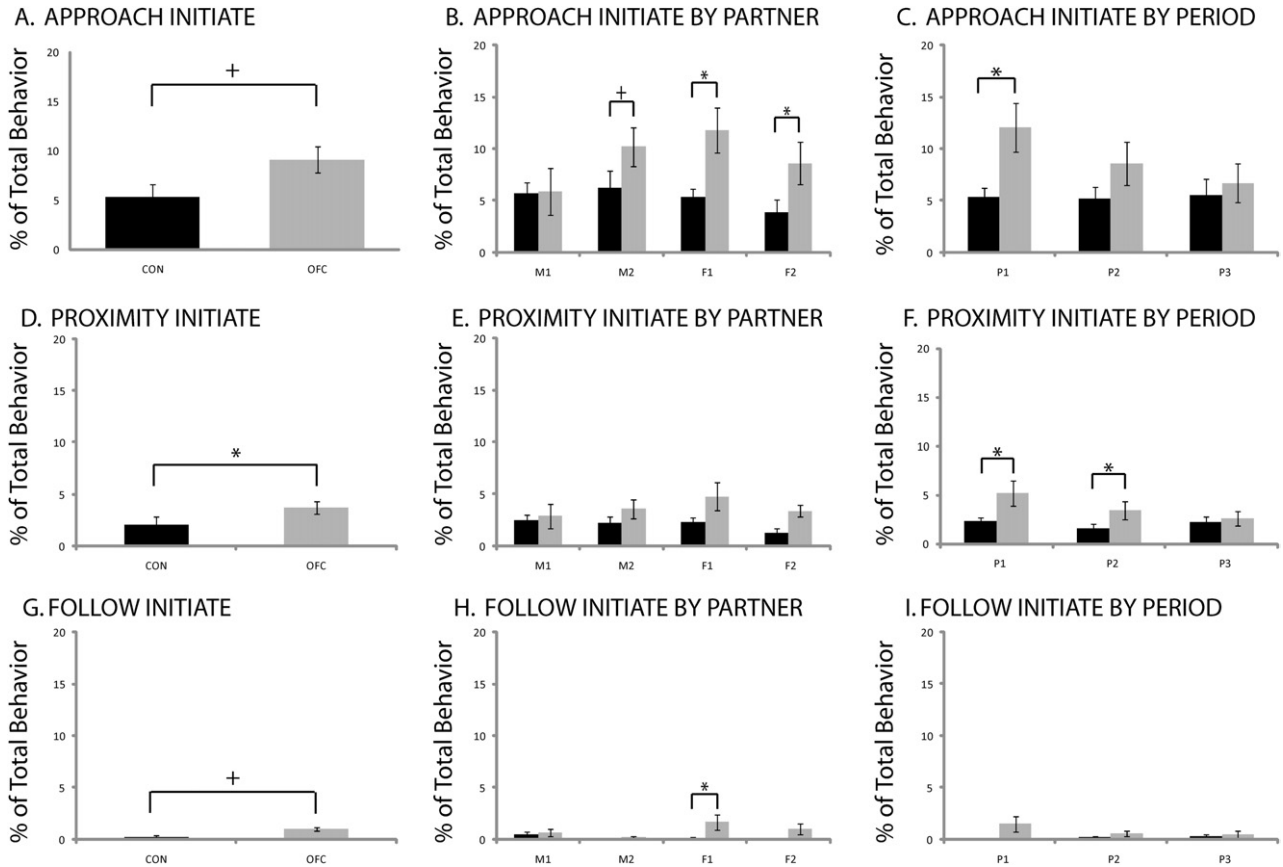

Fig. 4. Social interest behaviors (as a percent of all behaviors generated) initiated overall (A, D, G), with individual stimulus partners (B, E, H) or across periods (C, F, I). Each bar represents the average percent of approach (A, B, C), proximity (D, E, F), or follow (G, H, I) initiated by each group during the 20-min unconstrained dyadic interaction (±SEM). Plus sign denotes a trend level significance ($P\leq.1$) and an asterisk denotes a significant effect ($P\leq.05$).

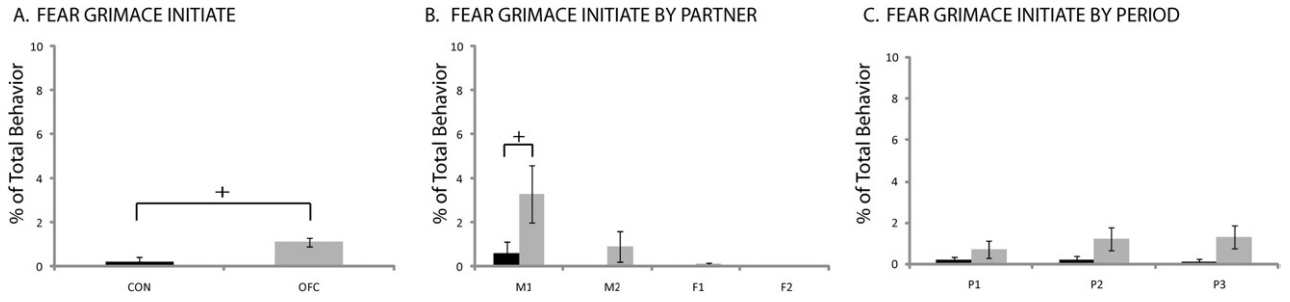

Fig. 5. Percent of fear grimaces initiated overall (A), with individual stimulus partners (B) or across periods (C). Each bar represents the average percent of fear grimaces initiated by each group during the 20-min unconstrained dyadic interaction (±SEM). Plus sign denotes a trend level significance ($P \leq .1$) and an asterisk denotes a significant effect ($P \leq .05$).

group was the number of approaches that the stimulus animals "accepted" from the experimental animals. "Accepting" an approach means that when the experimental animal approached the stimulus animal, that animal did not move away from the experimental animal. The stimulus animals differed in the frequency of approaches accepted from the experimental groups across periods as indicated by a significant period by lesion interaction, $F(2, 20) = 7.653$, $P < .05$. Follow-up *t*-tests revealed that the stimulus animals accepted more approaches from the lesioned group during Period 1, $t(10) = 3.263$, $p < .05$ (Fig. 6C). The higher number of approaches accepted from the orbitofrontal lesioned animals by the stimulus animals corresponds with the increased number of approaches and proximity states generated by the orbitofrontal cortex-lesioned animals during Period 1. Individual stimulus animals accepted similar amounts of approaches from the lesion and control group, $F(3,30) = 1.369$, $P > .1$ (Fig. 6B).

Mount solicitation. Overall, there were no differences in the frequency that stimulus animals solicited mounting from the orbitofrontal cortex-lesioned animals as compared to the controls, $F(1,10) = 0.162$, $P > .1$ (Fig. 6D). However, one of the stimulus animals did differentiate between the lesioned and control groups, $F(3, 30) = 4.838$, $P < .05$. Follow-up *t*-tests revealed that lesioned animals, when compared to control animals, tended to receive more presents for mount from stimulus animal F2 $t(10) = 2.094$, $P < .07$ (Fig. 6E). There was no difference in the frequency of mount solicitations initiated to the experimental groups across periods, $F(2,20) = 1.202$, $P > .1$ (Fig. 6F).

The lack of significant lesion effects for behaviors initiated by the stimulus animals suggests they did not differentiate between the experimental groups. There were, however, individual differences in the behavior displayed by the stimulus animals as indicated by significant partner effects for many behaviors. Stimulus animals M1 and F2 were distinguished from the other stimulus animals by several behaviors. Stimulus animal M1, compared to the other stimulus animals, initiated more aggression towards the experimental animals, $F(3,30) = 5.338$, $P < .05$ (M1>M2, F1, F2; pair-wise comparisons $P < .05$) (Fig. 7A). Further, M1 mounted the

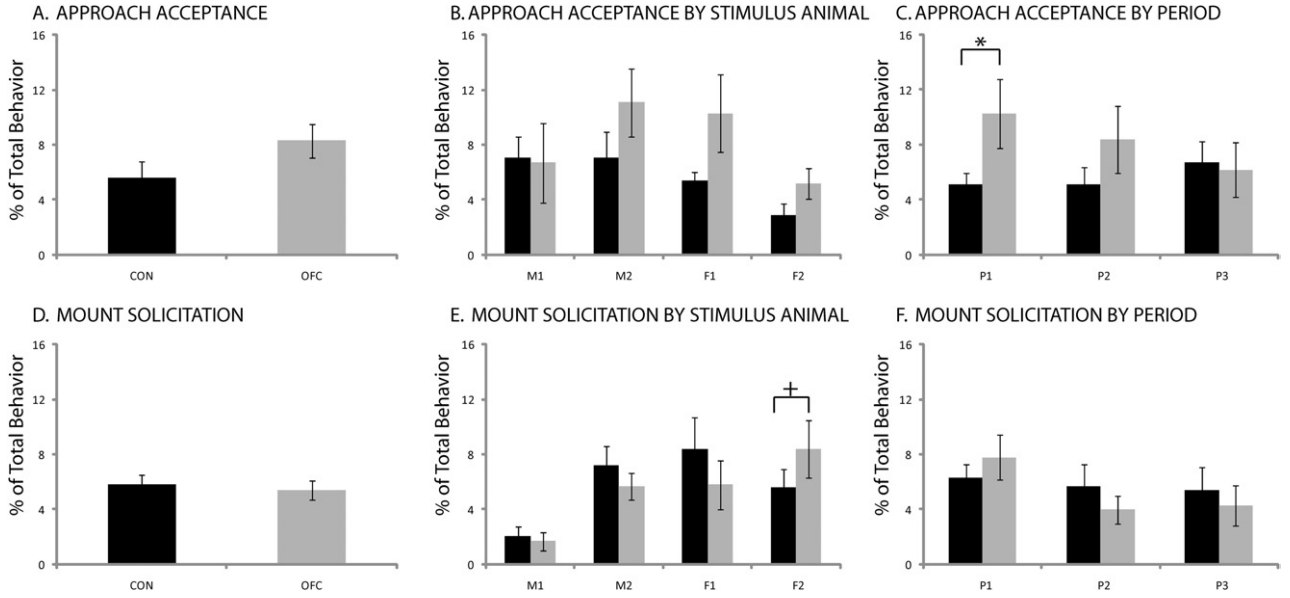

Fig. 6. Percent of behaviors generated by the stimulus animals towards the experimental animals overall (A, D), by individual stimulus animal (B, E) and across periods (C, F). Each bar represents the mean percent of approach acceptance (A, B, C) or mount solicitations (D, E, F) (±SEM). Plus sign denotes a trend level significance ($P \leq .1$) and an asterisk denotes a significant effect ($P \leq .05$).

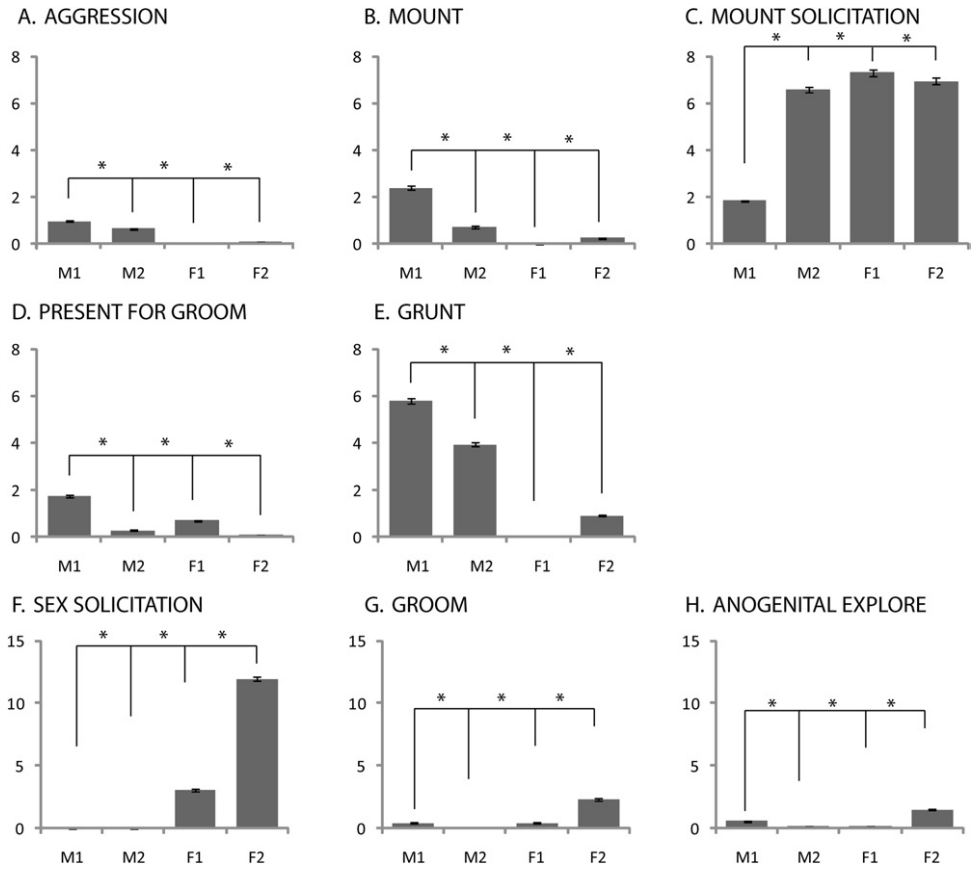

Fig. 7. Behaviors which differentiate individual stimulus animals. Stimulus animal M1 generated more aggression (A), mounted the experimental animals more (B), solicited less mounts (C), presented for groom more (D), and grunted more at the experimental animals (E) as compared to the other stimulus animals. Stimulus animal F2 solicited the experimental animals for sex more often (F), groomed the experimental animals more often (G) and contacted the experimental animal's genitals more often (H) than any of the other stimulus animals. Each bar represents the mean percent of behavior across the six meetings with the 12 experimental animals (±SEM). Asterisk denotes a significant effect ($P \leq .05$).

experimental animals more, $F(3,30)=8.964$, $P<.05$ (M1>M2, F1, F2; pair-wise comparisons $P<.05$) (Fig. 7B), but solicited mounts less $F(3,30)=22.338$, $P<.001$ (M1<M2, F1, F2; pair-wise comparisons $P<.05$) (Fig. 7C) than the other stimulus animals. Taken together, these findings suggest that stimulus animal M1 was the most dominant of the stimulus animals. M1 did, however, present for groom more, $F(3,30)=9.436$, $P<.05$ (M1>M2, F1, F2; pair-wise comparisons $P<.05$) (Fig. 7D) and grunt more $F(3,30)=26.152$, $P<.001$ (M1>M2, F1, F2; pair-wise comparison $P<.05$) (Fig. 7E) than the other stimulus animals, suggesting he made attempts to affiliate after establishing dominance.

Stimulus animal F2 appeared to be the most affiliative of all the stimulus animals. Compared to the other stimulus animals, F2 solicited experimental animals for sex more often, $F(3,30)=67.035$, $P<.001$ (F2>M1, M2, F1; pair-wise comparisons $P<.05$) (Fig. 7F). She also groomed the experimental animals more, $F(3,30)=9.436$, $P<.05$ (F2> M1, M2, F1; pair-wise comparisons $P<.05$) (Fig. 7G), and touched their genitals more frequently, $F(3,30)=6.982$, $P<.05$ (F2>M1, M2, F1; pair-wise comparisons $P<.05$) (Fig. 7H).

Overall frequencies of behavior in constrained versus unconstrained dyads

We evaluated the total frequency of behavior initiated by the experimental animals in each condition (constrained, unconstrained) in order to determine if there was a significant difference between the two conditions. There were significantly less behaviors initiated by the experimental animals in the constrained condition as compared to the unconstrained condition (Constrained: $M=77.81$ $SE=1.01$, Unconstrained: $M=105.15$ $SE=1.26$; $t(22)=8.781$, $P<.001$). However, the number of specific behaviors (e.g. Approach) did not necessarily differ between conditions (e.g. Approach in Constrained Condition: $M=9.95$ $SE=4.31$, Approach in Unconstrained Condition: $M=7.84$ $SE=4.60$, $t(22)=1.11$, $P>.10$).

Correlations between lesion extent and behavioral alterations

None of the behavioral alterations described above was correlated with the extent of damage to the intended lesion area or with unintended damage to any of the other frontal areas.

DISCUSSION

In the present study, adult male rhesus monkeys with lesions to the orbitofrontal cortex and sham-operated controls were introduced to novel social partners in two conditions. In the first condition, when animals had only restricted access to one another, there were no detectable behavioral differences between lesioned and sham-operated control animals. The lack of statistically significant differences between the lesion and control animals may have been due to the low number of behaviors generated in this condition. An alternative explanation for the lack of lesion group difference may be that the constrained condition was less socially challenging than the unconstrained condition and might not have engaged social regulatory mechanisms mediated by the orbitofrontal cortex.

In the second condition, when animals could freely interact, the lesioned animals, as compared to sham-operated controls, had heightened social interest with three of the four social partners. When paired with the fourth animal, lesioned animals generated more fear-related facial expressions than control animals. The heightened social interest and overproduction of fearful behaviors by the lesioned animals suggest that the orbitofrontal cortex is involved in regulating some aspects of social behavior. Further, it appears that the behavioral alterations resulting from orbitofrontal cortex lesions may be dependent on the social context established by the temperament of the social partner.

What is unique about the findings from this experiment is that the orbitofrontal cortex-lesioned animals' social interest was not heightened with all of the stimulus animals. The lesioned animals did not approach stimulus animal M1 more than the control animals did. This finding is of interest because of the unique properties of this particular stimulus animal. M1 was larger and older than the second stimulus male. He also displayed more threats and aggression than any of the other stimulus animals, male or female. The other three stimulus animals generated mostly positive or affiliative behaviors towards the experimental animals. M1 was presumably seen as establishing a more threatening or negative context for social interactions while the other stimulus animals established a more neutral (or even positive) context for social interactions. We propose that this variation in social context led to the differing patterns of behavior demonstrated by the lesioned animals. In this view, the orbitofrontal cortex-lesioned animals were socially uninhibited in the presence of affiliative or submissive animals but regulated their social behavior more appropriately during interactions with a more threatening partner.

Since the orbitofrontal cortex-lesioned animals were able to appropriately regulate social approach behaviors in the presence of a large dominant male, it is likely that other, intact brain areas were responsible for modulating their behavior appropriately in that social context. One area of the nonhuman primate brain known to be robustly activated by threatening social stimuli is the amygdala (Gothard et al., 2007; Hoffman et al., 2007). We have previously demonstrated that the amygdala is involved in evaluating threat and preventing the organism from engaging in potentially dangerous behaviors (Emery et al., 2001; Machado et al., 2008). It is conceivable, therefore, that the orbitofrontal cortex-lesioned animals interacted appropriately with stimulus animal M1 because the amygdala was more active during social interactions with this monkey since it was perceived to be potentially dangerous. Consistent with this notion was the finding that the orbitofrontal-lesioned animals had a somewhat higher frequency of grimacing, compared to that of the control animals, in the presence of stimulus animal M1. There is now substantial evidence that the orbitofrontal cortex has an inhibitory influence on fear generated by the amygdala (for review see: Milad and Rauch, 2007). Thus, the heightened fear demonstrated by the orbitofrontal cortex-lesioned animals may reflect an active fear-generating process mediated by the amygdala that is unchecked by context dependent mechanisms mediated by the orbitofrontal cortex. With the stimulus animals not perceived as threatening, the amygdala was not engaged and the pre-potent response for social engagement (mediated by other brain regions) took over. We propose that the orbitofrontal cortex may regulate the species-specific "rules" or mores of social interaction. The lesioned animals did not have the benefit of orbitofrontal regulatory mechanisms and thus interacted more than would be socially appropriate.

Another possible explanation for the observed pattern of results is that the orbitofrontal cortex lesioned animals were unable to inhibit their pre-potent response in the specific social contexts. In other words, in a positive context, the lack of inhibition led to more approaches to the stimulus partner; in the threatening context the lack of inhibition lead to a heightened fear response. While a lack of appropriate inhibition explains many of the findings seen in human and non-human primates after damage to the orbitofrontal cortex, this explanation is not sufficient to explain all the behavioral alterations that result from orbitofrontal cortex lesion or injury (Schoenbaum et al., 2009). Testing whether the pattern of behavior in the present experiment is the result of a failure of appropriate behavioral inhibition or a failure to appropriately evaluate social stimuli (and then select an appropriate response) is a potentially fruitful avenue for future research.

It is important to note that the findings from this study seem to contrast with the findings from earlier work suggesting that lesions to the orbitofrontal cortex in nonhuman primates lead to decreased interest in social partners. Variation in experimental design may be responsible for the inconsistencies. Earlier studies that involved very large lesions of the entire frontal cortex reported robust alterations in social behavior, including decreases in time spent in proximity, grooming and body contact and increases in inter-animal distances (Franzen and Myers, 1973; Myers et al., 1973). Most of these earlier studies were conducted in group settings (i.e. more than one other interaction partner) (Brody and Rosvold, 1952; Franzen and Myers, 1973; Myers et al., 1973; Raleigh et al., 1979; Raleigh and Steklis, 1981; Machado and Bachevalier, 2006) which are socially more challenging than dyadic interactions. There-

fore, both the lesion extent and the complexity of the social interactions preclude direct comparison between these earlier studies and the work reported here.

In more recent studies, monkeys with discrete lesions to the orbitofrontal cortex revealed no alterations in grooming or social interest behaviors during small group observations (Machado and Bachevalier, 2006). The behavioral alterations of these animals were dependent on their own dominance rank within the small group and the lesion condition of the social partner with which they were interacting. Subordinate, but not dominant, animals with lesions to the orbitofrontal cortex were significantly more active after surgery as compared to before surgery. Dominant animals threatened group members more frequently following surgery. Also, dominant animals responded with more affiliative behaviors to threats from some but not all members of the tetrad group in the post-lesion condition (Machado and Bachevalier, 2006). These findings share similarities with the context-dependent results we report here.

Our results also share some similarities with findings in human patients with damage to the orbitofrontal cortex. Patients with such damage have been shown to be unusually forward with strangers during structured interaction tasks (Beer et al., 2003, 2006). Patients disclosed more personal information or teased a novel person (i.e. a stranger) more aggressively than control participants who did not have orbitofrontal cortex damage. This forwardness may be similar to the increased approach behavior seen in the lesioned animals of this study. Additionally, in a study which evaluated patients with damage mostly restricted to the orbitofrontal cortex, the behavioral alterations, as reported by close friends and family, were less severe than in patients with extensive damage to the ventromedial prefrontal cortex (Hornak et al., 2003).

In sum, discrete lesions to the orbitofrontal cortex (Walkers areas 11, 13, 14) lead to context specific alterations in social behavior during dyadic interactions between adult rhesus macaques. The context dependent nature of our findings suggests that the neural mechanism of behavioral regulation in social interactions may be dependent on the qualities of the interaction partner. Understanding the underlying neurobiology involved in the appropriate production of species-typical social behavior is critical to uncovering the possible pathology in psychiatric disorders such as autism and schizophrenia. Continued evaluation of animals with discrete lesions to the orbitofrontal cortex in more controlled settings where specific components of social behavior (e.g. social motivation) can be evaluated will contribute to better definition of the role of the orbitofrontal cortex in mediating social behavior.

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