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ARTICLE

What's in a Smile? Maternal Brain Responses to Infant Facial Cues

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What's Known on This Subject

How caregivers respond to infant cues plays an important role in a child's cognitive and emotional development. Other fMRI studies have suggested that the mesocorticolimbic dopamine system may be activated in response to these cues, linking cues with reward and behavior.

What This Study Adds

This study shows that infant affect modulates a mother's brain response to her own infant's face, with smiling faces specifically activating dopamine-associated reward-processing regions. The study also provides a model for better understanding the neural basis of mother–infant attachment.

ABSTRACT

OBJECTIVES. Our goal was to determine how a mother's brain responds to her own infant's facial expressions, comparing happy, neutral, and sad face affect.

METHODS. In an event-related functional MRI study, 28 first-time mothers were shown novel face images of their own 5- to 10-month-old infant and a matched unknown infant. Sixty unique stimuli from 6 categories (own-happy, own-neutral, own-sad, unknown-happy, unknown-neutral, and unknown-sad) were presented randomly for 2 seconds each, with a variable 2- to 6-second interstimulus interval.

RESULTS. Key dopamine-associated reward-processing regions of the brain were activated when mothers viewed their own infant's face compared with an unknown infant's face. These included the ventral tegmental area/substantia nigra regions, the striatum, and frontal lobe regions involved in (1) emotion processing (medial prefrontal, anterior cingulate, and insula cortex), (2) cognition (dorsolateral prefrontal cortex), and (3) motor/behavioral outputs (primary motor area). Happy, but not neutral or sad own-infant faces, activated nigrostriatal brain regions interconnected by dopaminergic neurons, including the substantia nigra and dorsal putamen. A region-of-interest analysis revealed that activation in these regions was related to positive infant affect (happy > neutral > sad) for each own–unknown infant-face contrast.

CONCLUSIONS. When first-time mothers see their own infant's face, an extensive brain network seems to be activated, wherein affective and cognitive information may be integrated and directed toward motor/behavioral outputs. Dopaminergic reward-related brain regions are activated specifically in response to happy, but not sad, infant faces. Understanding how a mother responds uniquely to her own infant, when smiling or crying, may be the first step in understanding the neural basis of mother–infant attachment. *Pediatrics* 2008;122:40–51

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Key Words
attachment, dopamine, maternal responsiveness, mother-child relations, neuroimaging

Abbreviations
fMRI—functional MRI
BDI—Beck Depression Inventory
OH—own happy
ON—own neutral
OS—own sad
UH—unknown happy
UN—unknown neutral
US—unknown sad
BOLD—blood-oxygen-level–dependent
ACPC—anterior commissure/posterior commissure
FDR—false discovery rate
BA—Brodmann area
VTA—ventral tegmental area

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STARTING FROM THE early postpartum period, mothers demonstrate a unique ability to recognize different sensory cues from their own infants, including visual,[1,2] auditory,[3] and olfactory[4] cues. These stimuli, such as a hunger cry or smiling face, are powerful motivators for a mother to respond through caregiving, physical touch, speech, or play. Animal research has suggested that infant-responsive maternal behavior is causally related to the offspring's long-term developmental outcome in a number of domains including cognitive development,[5,6] stress reactivity,[7–9] and maternal behavior in adulthood.[7,10] Factors that restrict a mother's ability to respond to her infant's cues, such as depression,[11] substance abuse,[12] or even prolonged mother–infant separation,[13] may result in adverse developmental outcomes for children.[11,12,14,15] In addition, the ability to link these sensory cues with the underlying needs of an infant, and differentially respond to such needs, is thought to be the basis for establishing secure mother–infant attachment.[15–17] Thus, a mother's behavioral and brain responses to her infant's cues may be important predictors of infant development.

Over recent years, several research groups have sought to better understand how a mother's brain responds to her child's auditory or visual cues by using functional MRI (fMRI).[18–23] One common theme that has emerged from these studies is the possible role of the mesocorticolimbic dopamine system in processing reward-based signals and

motivating maternal care, as seen in animal models (see review in ref 24). Several studies have shown that the striatum, a key projection of midbrain dopamine neurons that includes the putamen and caudate head, is activated in response to face images of a mother's own child compared with unknown (or familiar but unrelated) children,[22,23] as well as to infant-cry stimuli.[18] Similar activation patterns have been seen in response to pictures of romantic partners,[22] beautiful faces,[25] and sexual stimuli,[26] which suggests a link between brain reward circuits and attachment.

However, some maternal-response studies have failed to show striatal activation,[20,21] among other important differences. The amygdala, for example, was strongly activated in some studies[20,23] but deactivated in another.[22] Because the amygdala plays an important role in processing face affect,[27] and its response may be modulated by dopamine,[28,29] differences in infant face affect may have been a confounding factor. Although most infant-face studies sought to standardize face affect, none of them specifically controlled for variation in affect or examined response differences related to facial affect. In addition, most previous studies had a small sample size (≤10 subjects) or used a suboptimal fixed-effects analysis,[24] which prevents generalization of the results to the population from which the sample was drawn.[30]

Our study included a relatively large sample of first-time mothers and their infants and specifically compared maternal brain responses to infant-face stimuli grouped into happy, neutral, and sad affect. We predicted that "own-infant" faces compared with "unknown" faces, would activate dopamine-associated reward-processing brain regions, including the ventral striatum and prefrontal cortex, and that the contrast in these regions would be greater for smiling infant faces than for neutral or sad faces. On the basis of pilot results[31] and results from infant-cry studies,[18] we also predicted that sad faces from a mother's own infant compared with those from an unknown infant would activate the anterior cingulate cortex, which is involved in conflict monitoring,[32] and both the insula and amygdala, regions often associated with negative emotion processing.[27] Together these response patterns would help us to better define the neural basis of human mother–infant attachment.

METHODS

Subjects

This cohort is part of larger longitudinal study of mother–infant attachment, including 43 women who were enrolled during the third trimester of pregnancy. Subjects were recruited from prenatal clinics, local church groups, and poster, magazine, and Internet advertisements. Each woman was screened for recruitment by telephone or by completing an online questionnaire. Inclusion criteria included first-time singleton pregnancy, right-handedness, nonsmoking during pregnancy, not currently on psychotropic medications, and no contraindications for MRI scanning (such as metal implants or severe claustrophobia). At the time of the fMRI visit, ~1 year after enrollment, 5 women were lost to follow-up or declined further participation and 10 were unable to be scanned (9 because of a second pregnancy and 1 because of a past history of seizures), which left 28 women who received fMRI scans. During the second scanning run, data were only available for 26 women because of unacceptable head motion in 1 case and scanner failure in another.

The protocol was approved by the institutional review board at Baylor College of Medicine, and all subjects provided written informed consent.

Experimental Design

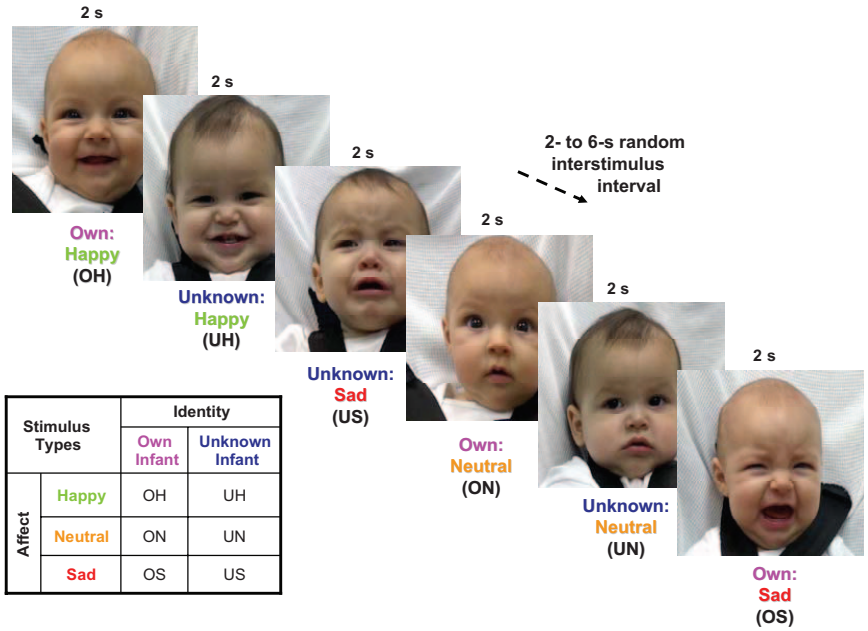
Prenatal Session

During the third trimester of pregnancy, enrolled women provided sociodemographic information from which was calculated the Hollingshead SES score (A. B. Hollingshead, PhD, *Four-Factor Index of Social Status*, working paper, 1985). They also participated in a variety of psychometric tests including the Adult Attachment Interview, the Personality Disorder Questionnaire 4+, the McLean Screening Instrument for Borderline Personality Disorder, and the Beck Depression Inventory (BDI).[33]

Videotaping Session

Approximately 7 months after delivery, each infant was videotaped in a standard setting at the Human Neuroimaging Laboratory at Baylor College of Medicine. Smiling faces were elicited by the experimenters interacting with the infants by using a variety of age-appropriate toys, and crying faces were obtained by leaving the infant alone in the room (observed from behind a 1-way mirror) with the video camera recording facial expressions. To ensure that each infant-face image was novel when presented during the subsequent scanning session, the mothers did not observe the videotaping. At this visit, the mothers also updated their demographic information and completed another BDI.

Infant-face still images encompassing various affect levels (happy, neutral, and sad) were then captured from the videotape. By using a facial affect coding scheme based on work by Cole et al,[34] these images were classified by a trained research assistant into 1 of 5 affect groups: very happy, happy, neutral, sad, or very sad. Excellent interobserver reliability was demonstrated on the basis of 466 double-coded images (Pearson correlation coefficient: 0.925; 2-tailed $P < .001$). Control infant-face images, unknown to each mother, were collected from the infants of other enrolled mothers or mothers involved in the pilot study. Each subject infant was matched to a single control infant, with an equal number of face images from each affect group. Whenever possible, the 2 infants were also matched on age and race. In cases of mixed race, the matching was based on a combination of race, complexion, and hair color. Gender was matched if there were any obvious distinguishing features such as earrings or longer hair. Each infant had been videotaped in a gender-neutral white jumpsuit. All images were standardized for size, orientation, and background by using Adobe Photoshop (Adobe Systems, San Jose, CA).



Stimulus Types		Identity	
		Own Infant	Unknown Infant
Affect	Happy	OH	UH
	Neutral	ON	UN
	Sad	OS	US

FIGURE 1
Infant-face presentation paradigm in the fMRI experiment. Ethnically matched still infant-face images were presented for 2 seconds followed by a variable 2- to 6-second period of a blank screen. The 6 stimulus types outlined were presented in random order.

Scanning Session

A minimum of 3 months after the videotaping session, each mother attended a scanning session at the Human Neuroimaging Laboratory. Immediately before scanning, the mother participated in a 1-hour-long semistructured interview, the Parent Development Interview,[35] which prompted the mother to reflect on her relationship with her child. This provided a common setting for each mother before viewing the infant-face images in the scanner.

The mother then participated in 2 fMRI runs, each time while passively viewing a series of 60 unique infant-face images, 30 of her own infant and 30 of an unknown infant's face. Each mother was informed (by the recruitment brochure) that her "brain activity will be monitored using functional MRI while she is shown pictures of her own baby and babies unknown to her." In an event-related fMRI design, randomly presented images were viewed for 2 seconds, with a random interstimulus interval of 2, 4, or 6 seconds (Fig 1). The 60 images were divided equally into 3 affect groups (happy, neutral, or sad), with the intensity of happy and sad affect balanced between the own and unknown faces. The order of the images from each of the 6 groups (own happy [OH], own neutral [ON], own sad [OS], unknown happy [UH], unknown neutral [UN], unknown sad [US]) was pseudo-randomized within and between each run but not between subjects. There were no significant differences in the timing of own and unknown infant-face images (natural log of mean presentation times, paired-samples t test: $t = -0.73$, $df = 29$, $P = .47$) or in the OH > UH, ON > UN, or OS > US comparisons ($df = 9$; happy: $t = 1.52$, $P = .16$; neutral: $t = 0.72$, $P = .49$; sad: $t = -1.69$, $P = .13$, respectively).

All imaging was performed by using a 3-T Siemens Allegra head-only MRI scanner (Siemens, Iselin, NJ). Visual images were generated by using a computer-controlled LCD projector and presented to the mother via an overhead mirror display. High-resolution T1-weighted structural images (192 slices; in-plane resolution: 256 × 256; field of view: 245 mm; slice thickness: 1 mm) were acquired first. Regional brain activation was assessed by measuring changes in blood-oxygen-level–dependent (BOLD) fMRI signal. Subjects underwent 2 whole-brain functional runs of ~185 scans each (gradient-recalled echo planar imaging; 37 slices; repetition time: 2000 milliseconds; echo time: 25 milliseconds; flip angle: 90°; 64 × 64 matrix [in-plane resolution]; field of view: 220 mm; slice thickness: 3 mm; gap thickness: 1 mm). Slices were positioned 30° to the anterior commissure/posterior commissure (ACPC) line in the axial plane, downward from posterior to anterior, which (along with a reduced echo time and slice thickness) has been shown to optimize visualization of the orbitofrontal cortex.[36]

After the scanning session, each mother was reshown and asked to rate each of the infant-face images on how she thought the infant was feeling, as well as her own feelings of pleasure or arousal, by using an adaptation of the Self-Assessment Manikin.[37] Each mother also completed the Wechsler Test of Adult Reading as a predictor of IQ,[38] and repeated the BDI. At ~14 months of age, all but 1 of the children were assessed for general development by using the screening test of the third-edition Bayley Scales of Infant and Toddler Development.[39] They also participated in a child assessment of attachment by using the strange-situation procedure.[40]

Data Processing and Analysis

Imaging data for each subject were preprocessed in Brain Voyager QX 1.7.9[41] and analyzed in versions 1.8.6 and 1.9.9 by using the steps described below.

Head-motion correction was performed by using trilinear/sinc interpolation by spatial alignment of all brain volumes to the first volume by rigid body transformations. One subject had >2-mm translation (2.3 mm)

during run 1, and analyses were repeated before and after excluding this subject. A single subject also had unacceptable head motion during run 2 (3.2-mm translation and 3.5-mm rotation) and was excluded from further analyses.

Slice scan-time correction was performed by using sinc interpolation on the basis of the repetition time and order of slice scanning (ascending interleaved). After linear trend removal, low-frequency nonlinear drifts of ≤3 cycles were removed by using a temporal high-pass filter. Spatial smoothing was not performed.

The anatomic data set underwent isovoxel scaling to 1 × 1 × 1-mm resolution and was transformed into sagittal orientation. It was then transformed into ACPC and Talairach standard space by using sinc interpolation.[42] Functional runs for each subject were coregistered with the anatomic three-dimensional data set, isovoxel-transformed to 3 × 3 × 3-mm resolution, and then transformed into standard ACPC and Talairach coordinate space, resulting in normalized four-dimensional volume-time course data. For presentation purposes, the final activation map was interpolated into a 1 × 1 × 1-mm resolution.

For each functional run of the event-related data, a BrainVoyager protocol file was created, representing the timing of each stimulus event. The 6 infant-face stimulus types in the design matrix included OH, ON, OS, UH, UN, and US (Fig 1). Each predictor was then convolved with a double-γ hemodynamic response function.[43] With the general linear model, group effects were evaluated by using a random-effects analysis, with a percent time-course transformation applied to each run of each subject separately. In the random-effects analysis, statistical maps were created for each individual subject before being subjected to a second level of statistical analysis, which allowed generalization to the sample population of first-time mothers. Main effects and possible interaction effects of infant "identity" and "affect" (Fig 1) were explored by using 2-factor repeated-measure analyses of variance (F test, $df = 2,54$). Group t maps (2-tailed, $df = 27$) were also generated after specifying a particular contrast in stimulus types (eg, OH > UH) and were visualized on an averaged three-dimensional anatomic image, which was created from all of the individual subject images.

The false-discovery-rate (FDR) approach[44] was used to correct for multiple comparisons at a threshold of $q < 0.05$, which accepts 5% of the discovered (suprathreshold) voxels as false-positives. A cluster threshold of 100 mm^3 (or ~4 voxels) was used except in the brainstem, for which a threshold of 30 mm^3 (or ~1 voxel) was used to reveal activation of smaller nuclei. Anatomic regions were confirmed by using the automated "Talairach Daemon" (searching for "nearest gray matter")[45] and manually by using a human brain atlas.[46] Brodmann areas (BAs) were defined by using the BrainVoyager Brain Tutor.[47]

Hemodynamic responses to event types (percentage of BOLD signal change) were averaged and standardized across subjects and plotted against time to create an event-related averaging plot for anatomic regions of interest. A random-effects general-linear-model analysis was performed on each volume individually.

TABLE 1 **Demographic Information for Study Cohort (at Time of Scanning Unless Noted)**

Variable	Value
Age of mother, y	
Mean ± SD	30.2 ± 5.0
Range	20–42
Age of infant, videotaping session, mo	
Mean ± SD	6.7 ± 1.6
Range	5–10
Age of infant, scanning session, mo	
Mean ± SD	10.7 ± 2.3
Range	7–17
Hollingshead SES score (joint with partner)[a]	
Mean ± SD	49.1 ± 12.7
Range	24–66
Maternal IQ (WTAR-predicted WAIS-III)	
Mean ± SD	108.7 ± 9.2
Range	81–120
Maternal race, *n*	
White, non-Hispanic	13
Black	7
Hispanic	4
Other	4
Maternal education, *n*	
Postgraduate degree	13
College/university degree	9
Incomplete college	6
Marital status, *n*	
Married	20
Single/never married	5
Unmarried cohabitation	3
Child development at 14 mo, *n*[a]	
Cognitive	
Competent	21
Emerging	5
At risk	1
Receptive communication	
Competent	25
Emerging	2
At risk	0
Expressive communication	
Competent	21
Emerging	6
At risk	0
Fine motor	
Competent	25
Emerging	2
At risk	0
Gross motor	
Competent	27
Emerging	0
At risk	0

WTAR indicates Wechsler Test of Adult Reading; WAIS-III, Wechsler Adult Intelligence Scale-III.
[a] Data missing for 1 subject.

RESULTS

Description of Subjects

The 28 mothers who participated in this study had a mean age of 29 years, were racially diverse (representative of the Houston, Texas, population[48]), and middle to

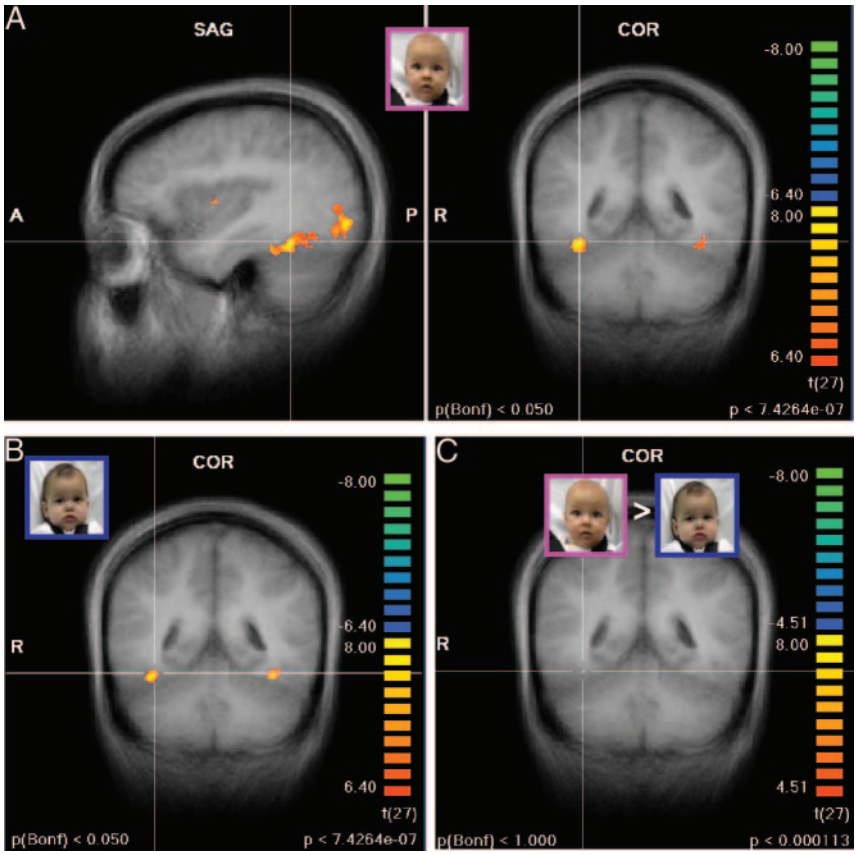


FIGURE 2
Activation of the ventral visual pathway, including the fusiform face area (Talairach coordinates 36, −46, −17) by ON and UN infant faces. A, Coronal (COR) and sagittal (SAG) views of activation from ON infant faces compared with no-face baseline. B, Coronal view of activation from UN infant faces compared with no-face baseline. C, Contrast between ON and UN (ON > UN), which shows no remaining activation of visual pathway or fusiform face area. (A and B: $P < .000001$, Bonferroni correction $P < .05$; C, $P < .0001$, uncorrected; cluster threshold = 100 mm^3).

upper class (based on the *Four-Factor Index of Social Status* [A. B. Hollingshead, PhD, working paper, 1985]), with 75% having completed higher education. Only 1 mother scored outside the reference range on Wechsler Test of Adult Reading–predicted Wechsler Adult Intelligence Scale-III IQ scores (range: 81–120; median and mode: 112) (Table 1). One other mother was classified as having "mild" depression symptoms on the basis of the Beck Depression Inventory during the videotaping session, but none of the mothers reported significant symptoms during subsequent visits. There were no self-reports of current or past alcohol or drug abuse problems or involvement in substance abuse treatment programs. However, 61% of the mothers screened positive for ≥1 personality disorder on the Personality Disorder Questionnaire 4+, including 8 mothers for obsessive-compulsive disorder and 8 for avoidant personality disorder (but none for borderline personality disorder on the McLean Screening Instrument for Borderline Personality Disorder). Although 93% of the mothers reported returning to work by the time of the scanning session, 54% were still breastfeeding, and 43% reported that they were not separated from their child for >20 hours per week. Except for 1 infant born at 36 weeks' gestation, the infants were born at term. At 14 months of age, only 1 child scored in the "at-risk" range in 1 of 5 subscales of the Bayley Scales for Infant and Toddler Development, and this score was at the upper limit of the range. For this child, 3 of the other 4 developmental scores were in the "competent" range. All other children were in the "competent" or "emerging" range for each developmental subscale, including cognition, expressive and receptive communication, and fine and gross motor development (Table 1).

Maternal Brain Responses

Before addressing the specific hypotheses of this study, we examined maternal brain responses to affect-neutral infant faces compared with the no-face baseline. As expected, face stimuli activated brain regions along the ventral visual pathway from the primary visual cortex to the temporal lobe, including the fusiform gyrus and the so-called fusiform face area (Fig 2 A and B).[49] However, after contrasting own and unknown infant faces (ON > UN), no significant activation remained, even at lowered statistical thresholds (Fig 2 C). Thus, there was no significant difference in posterior visual pathway response between the own and unknown infant-face stimuli.

Next, we tested our first hypothesis, regarding the main effect of infant identity (own > unknown) on maternal brain response. From the first scanning run, this revealed activation of forebrain regions involved in (1) emotion processing (medial prefrontal, anterior cingulate, and insula cortex), (2) cognition (dorsolateral prefrontal cortex), and (3) motor/behavioral outputs (primary motor area, BA 4) ($F = 13.6–16.0$, $df = 1,27$, $P < .001$, FDR corrected $q < 0.05$). Also activated were stri-

TABLE 2 **Areas of Significant Activation From Own Versus Unknown Infant Face Contrast (All Affect Groups Combined)**

Region of Interest/Cluster (BA)	Right Hemisphere		Left Hemisphere	
	x, y, z	*z* Score O > U	*x, y, z*	*z* Score O > U
Frontal lobe				
Medial prefrontal cortex				
Superior frontal gyrus, medial (BA 6/9)	1, −2, 60	4.55	−7, 39, 25	4.41
Superior frontal gyrus (BA 9/10)	3, 59, 29	4.97	—	—
Lateral orbitofrontal cortex				
Inferior frontal gyrus (BA 47)	—	—	−43, 23, 1	5.09
Dorsolateral prefrontal cortex				
Inferior frontal gyrus (BA 44)	48, 8, 28	4.74	—	—
Middle frontal gyrus (BA 9)	—	—	−24, 48, 32	4.17
Primary motor area/somatosensory cortex				
Precentral/postcentral gyrus (BA 4)	45, −17, 37	4.86	—	—
Parietal/occipital lobe				
Postcentral gyrus (BA 3/40)	20, −27, 51	4.54	−46, −17, 37	4.69
Lingual gyrus (BA 18/19)	—	—	−15, −56, −2	4.48
Temporal lobe (lateral)				
Middle temporal gyrus (BA 21)	—	—	−56, −38, −5	4.57
Middle temporal gyrus/temporal pole (BA 38)	48, 3, −13	5.36	−47, 3, −12	4.97
Superior temporal gyrus (BA 22/21)	39, −41, 12	4.84	−39, −28, 4	5.14
Inferior temporal/fusiform gyrus (BA 37)	38, −53, −7	4.30	−41, −44, −17	5.09
Limbic lobe/sublobar regions				
Basal ganglia				
Ventral striatum (precommissural)	—	—	−13, 6, 4	4.88
Dorsal putamen (precommissural)	22, 5, 4	4.03	−23, 2, 4	4.74
Putamen (postcommissural)	24, −17, 9	4.83	−29, −12, 0	5.10
Putamen (postcommissural), superior	—	—	−26, −10, 10	4.80
Dorsal caudate (precommissural)	9, 5, 11	4.15	−14, 2, 16	4.98
Thalamus/hypothalamus				
Medial dorsal/centromedial thalamus	7, −20, 2	5.39	—	—
Ventral anterior/lateral thalamus	4, −7, 4	5.52	−9, −9, 4	5.20
Ventral anterior/lateral thalamus	14, −10, 8	4.87	−11, −16, 4	4.75
Hypothalamus	3, −8, −6	4.80	−5, −8, −7	4.59
Medial temporal lobe				
Lateral superior amygdala	—	—	−27, −6, −13	5.62
Parahippocampal gyrus (BA 36)	42, −37, −9	5.77	—	—
Insula cortex				
Insula (ventral)	32, −3, −7	5.69	—	—
Insula	40, 3, 4	4.77	−31, −5, 2	5.23
Insula (posterior)/planum polare	42, −19, −6	5.10	—	—
Cingulate cortex				
Anterior cingulate cortex, pregenual (BA 24/32)	—	—	−2, 37, 13	4.97
Anterior cingulate cortex, pregenual (BA 24)	—	—	−3, 13, 32	4.62
Middle cingulate cortex (BA 24)	1, −2, 42	4.92	—	—
Posterior cingulate cortex, retrospenial (BA 31)	—	—	−5, −53, 17	4.48
Posterior cingulate cortex, retrospenial/cuneus (BA 17)	—	—	−8, −64, 10	4.75
Midbrain (cluster threshold = 30 mm^3)				
VTA vicinity (midline)	1, −16, −15	5.56	—	—
Substantia nigra vicinity	—	—	−8, −23, −9	4.93
Red nucleus vicinity	3, −21, −7	5.23	−3, −21, −8	5.46
Cerebellum				
Cerebellum	38, −48, −25	4.78	−34, −38, −28	4.97
Anterior cerebellum	—	—	−2, −45, −39	4.69

OH + ON + OS > UH + UN + US *t* test, $df = 27$, $P < .001$, FDR corrected $q < 0.05$; all cluster thresholds = 100 mm^3, except midbrain regions. $P < .0001$ for all regions of interest. Talairach coordinates (*x*, *y*, *z*) represent center-of-gravity mean values for each region of interest. A large area of activation involving the lentiform nuclei was divided manually according to anatomical regions.

atal and midbrain regions including the ventral striatum, head of caudate, putamen, ventral tegmental area (VTA), and substantia nigra. Other significant areas included regions of the inferior, middle, and superior temporal gyri (including the fusiform gyrus and temporal pole), the lateral amygdala, thalamic nuclei, and the hypothalamus (Table 2, Fig 3). No brain region was significantly activated by infant affect as a main effect ($F > 15.66$, $df = 2,54$, using a random-effects model, FDR corrected $q < 0.05$), nor was an "identity × affect" interaction effect seen with or without FDR correction. No significant activation was seen for any contrast dur-

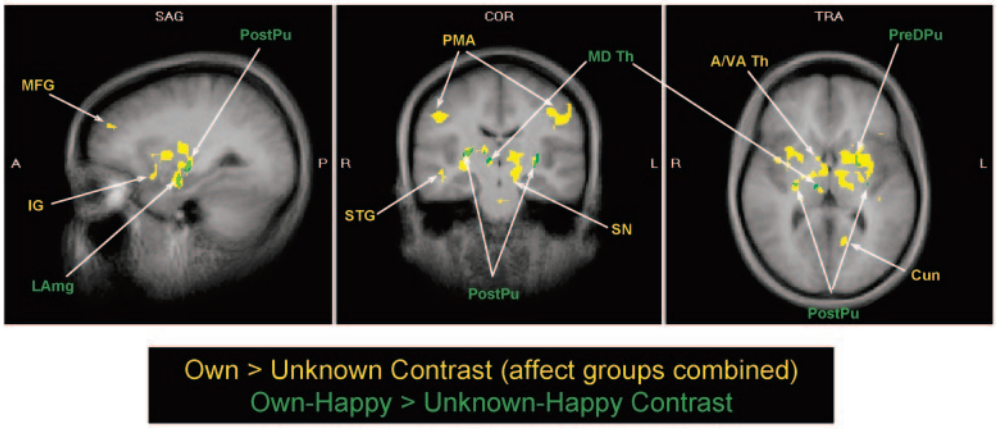


FIGURE 3

Maternal brain activation in response to OH infant versus UH infant faces (green regions and labels: *t* test, $df = 27$, $P < .0001$, FDR corrected $q < 0.05$, cluster threshold = 100 mm³) and all affect states combined (yellow regions and labels: F test, $df = 1,27$, $P < .001$, FDR corrected $q < 0.05$). The Talairach coordinates are −27, −16, and 6. LAmg indicates lateral amygdala; PostPu, postcommissural putamen; MD Th, mediodorsal thalamus; PreDPu, precommissural dorsal putamen; MFG, middle frontal gyrus; IG, insula gyrus; STG, superior temporal gyrus; PMA, primary motor area; SN, substantia nigra; A/VA Th, anterior/ventroanterior thalamus; Cun, cuneus.

ing the second scanning run, in which the infant-face stimuli from run 1 were repeated and data from 2 subjects were missing.

As hypothesized, significant areas of activation were seen when the mothers were shown happy faces of their own infant compared with an unknown infant (OH > UH) ($P < .0005$, FDR corrected $q < 0.05$). Five specific regions of activation were seen in the limbic area (with a cluster threshold of 100 mm³), and 1 was seen in the midbrain (cluster threshold = 30 mm³), including bilateral putamen, left substantia nigra region, right thalamus, and the left lateral superior amygdala (Table 3). These regions essentially overlapped regions of significance in the main-effects "identity" analysis for own > unknown (Fig 3).

A region-of-interest random-effects analysis was then performed in each of the 6 OH > UH regions separately (all $P < .0001$; Table 3). To explore how these results varied with infant affect and ensure that they were not a result of infant-face familiarity differences alone, the analyses were repeated for neutral- and sad-affect faces. Significant activation was seen in 4 of the 6 regions when using the ON versus UN (ON > UN) contrast, although, as predicted, at much lower levels of statistical significance ($P < .01$). No region showed significant activation when contrasting own versus unknown sad faces (OS > US). In all 6 regions, there seemed to be a progressive decrease in the percentage signal-change differences across happy, neutral, and sad affect (Fig 4). The response to sad affect was significantly less than that for happy affect in each region (paired-sample *t* tests, 2-tailed, $df = 27$, $P < .005$, except amygdala [$P < .05$]). A significant difference was also seen between happy and neutral affect in 1 region and between neutral and sad affect in another (both $P < .05$).

When the BOLD signal change was examined over time in each of these regions, the change from baseline fMRI response coincided precisely with the presentation onset of the infant-face stimuli, and significant differences between the OH and UH stimuli responses were seen. As an example, in Fig 5 the left dorsal putamen and substantia nigra area, 2 key interconnecting dopaminer-

TABLE 3 **Areas of Significant Activation From OH Versus UH Infant-Face Contrast**

Region-of-Interest/Cluster		*z* Score		
Anatomical Region	Talairach Coordinates (*x*, *y*, *z*)	OH > UH	ON > UN	OS > US
Cerebrum (cluster threshold = 100 mm³)				
Right putamen (postcommissural)	24, −17, 9	5.60[a]	2.70[b]	1.43
Right medial dorsal/ventrolateral thalamic nucleus	9, −18, 4	5.60[a]	2.64[b]	0.09
Left dorsal putamen (precommissural)	−21, 2, 4	5.27[a]	2.88[c]	2.25
Left putamen (postcommissural)/claustrum	−27, −14, −1	5.35[a]	2.38	0.78
Left lateral amygdala (superior)	−30, −6, −12	5.56[a]	2.44	2.28
Midbrain (cluster threshold = 30 mm³)				
Left substantia nigra (vicinity)	−9, −22, −12	5.76[a]	2.65[b]	0.94

t test, $df = 27$, $P < .0001$, FDR corrected $q < 0.05$. These regions of interest were analyzed with respect to neutral and sad infant-face contrasts. Talairach coordinates represent center-of-gravity mean values for each region of interest.

[a] $P < .0001$.

[b] $P < .01$.

[c] $P < .005$.

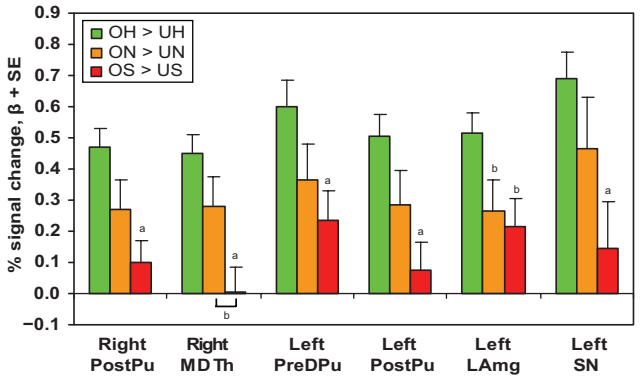


FIGURE 4

Progressive decrease in activation depending on infant affect (happy > neutral > sad) in specified regions of interest. Shown are paired sample *t* tests (2-tailed, *df* = 27) comparing happy affect with neutral or sad affect, except as noted. PostPu, postcommissural putamen; MD Th, medial dorsal thalamus; PreDPu, precommissural dorsal putamen; PostPu, postcommissural putamen; LAmg, lateral amygdala; SN, substantia nigra. [a] $P < .005$; [b] $P < .05$.

gic brain regions, showed a significant BOLD-fMRI response to OH faces but much less to neutral faces, and no response difference was seen in the sad face contrast.

Thus, although no significant affect × identity interaction effect was seen, these findings suggest that infant affect has a moderating effect in each of these 6 dopamine-associated brain regions and that familiarity does not fully explain the results of the OH > UH contrast analysis.

Finally, we examined differences in maternal brain response to sad-affect infant faces. Compared with the no-face baseline, both OS and US faces produced widespread brain activation, including the specifically hypothesized regions anterior cingulate, insula, and amygdala (*t* test, $df = 27$, $P < .001$, FDR corrected $q < 0.01$). However, as with the ON > UN contrast, no significant regions of activation remained after contrasting OS with US (at $P < .001$, cluster threshold = 30 mm², uncorrected).

Behavioral Rating of Infant Faces

From ratings of infant-face images viewed outside the scanner, the mothers' own feelings were highly correlated with how they imagined the infant to be feeling ($r = 0.82$, $P < .001$). Crying infant faces, regardless of identity, resulted in more negative affective responses from the mothers, but the mothers' emotional responses were more tightly correlated with their own infant's affect than for unknown infant faces (own: $r = 0.87$; unknown: $r = 0.80$). That is, the mothers were more sensitive to their own infants' emotional states than to unknown infant faces (slope own = 0.84, slope unknown = 0.49; $P < .05$, 2-sample *t* test, 2-tailed). The mothers also rated their feelings as being more "aroused" or intense for their own infant compared with those for unknown infant faces ($P < .01$, 2-sample *t* test, 2-tailed).

DISCUSSION

As almost any mother will attest, seeing one's own infant smile is a uniquely pleasurable and rewarding ex-

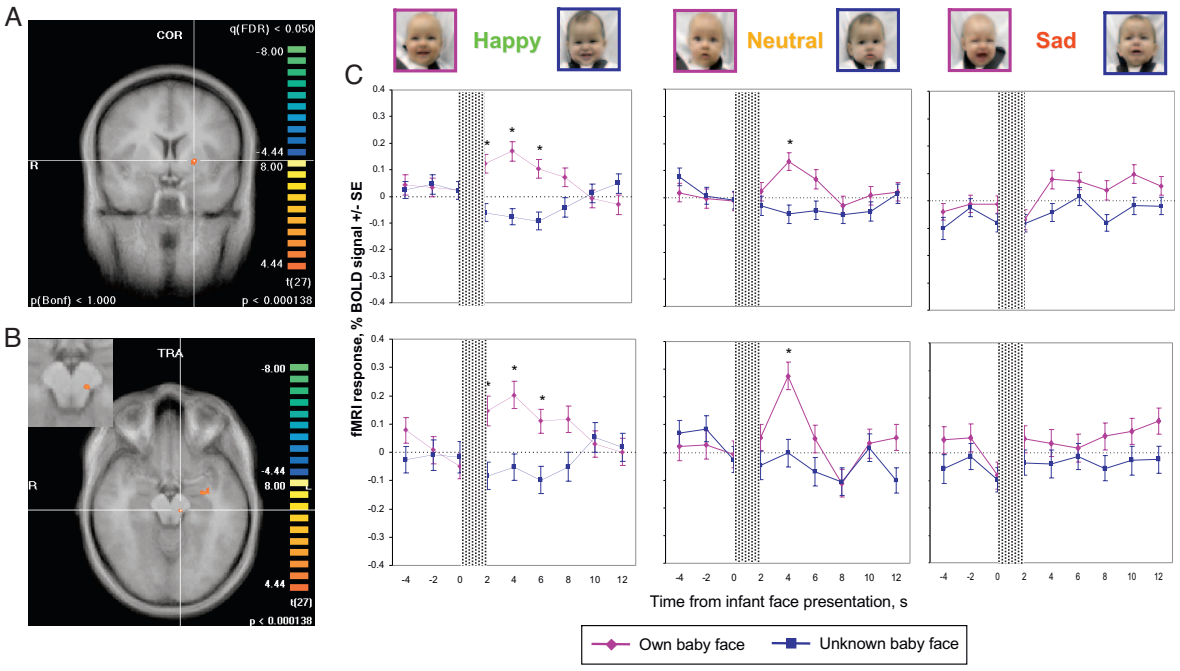


FIGURE 5

Hemodynamic brain response of mothers viewing their own infant's face compared with an unknown infant's face in the left dorsal putamen (A) and the left substantia nigra (B; enlarged view is shown in the inset) ($P < .0001$, FDR corrected $q < 0.05$). C, Event-related averaging graphs for each region separated according to affect group.

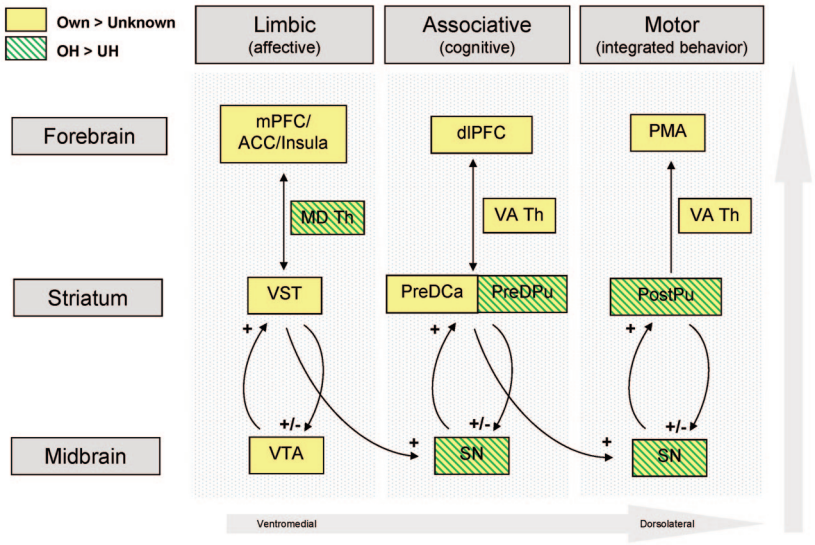


FIGURE 6
Own versus unknown infant faces activate prominent dopaminergic brain regions involved in cognitive, affective, and motor information processing. Shown are OH > UH contrast (green cross hatched boxes) and own > unknown contrast (all affect states combined; yellow boxes). MD Th, medial dorsal thalamus; PreDPu, precommissural dorsal putamen; PostPu, postcommissural putamen; SN, substantia nigra; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; PMA, primary motor area; VA Th, ventral anterior thalamus; VST, ventral striatum; PreDCa, precommissural dorsal caudate.

perience. But, what's in a smile when we consider a mother's brain response? Also, how is seeing one's own infant linked to motivated behavior? This study shows that when first-time mothers observe their own infant's face, all of the key dopamine-associated reward-processing regions of the brain are activated, including the midbrain VTA/substantia nigra regions, the striatum, and the prefrontal cortex, as well as the primary motor area. Smiling, but not neutral or sad, faces specifically activate nigrostriatal brain regions interconnected by dopaminergic neurons,[50] with a graded response that depends on infant affect (happy > neutral > sad).

Two other studies have also shown maternal brain activation in the VTA/substantia nigra and the striatum in response to child-related stimuli (see ref 22 for face stimuli of older children and ref 18 for infant-cry stimuli). In primates, Haber et al[50] demonstrated important anatomic feed-forward loops between the striatum and the VTA/substantia nigra region, suggesting that these striatonigrostriatal circuits funnel information between ventromedial (limbic), central (associative), and dorsolateral (motor) striatal regions (Fig 6). Each striatal region is integrally connected to a corresponding region of the midbrain's VTA and substantia nigra via ascending and descending dopaminergic neurons. Likewise, there are corresponding connections between the striatum and the forebrain, including those involved in emotion processing (medial prefrontal, anterior cingulate, insula), cognition (dorsolateral prefrontal), and motor/behavioral outputs (primary motor area).[50] Thus, the striatum is believed to be an important relay station between the limbic and motor systems, integrating affective information from limbic regions with cognitive information from the prefrontal cortex, in shaping motor/behavioral responses.

In responding to infant social cues, whether positive or negative, mothers need to integrate both affective and cognitive information about their infant, and evaluate competing demands, before choosing the most appropriate behavioral response.[51,52] For example, a distressed infant usually evokes an empathic emotional response from a mother, as well as cognitive processes to determine, on the basis of past experience and knowledge, possible causes and remedies for her infant's distress. Likewise, a smiling infant's face usually leads to positive affective arousal in a mother, associations with other rewarding experiences, and contingent behavioral responses such as smiling, caressing, or playing.

The difference in striatal and midbrain responses seen in this study between happy, neutral, and sad affect (Table 3, Figs 4 and 5) is consistent with results from other studies that showed preferential activation for more appetitive or rewarding stimuli,[53] including faces rated as more beautiful[25] or monetary reward.[54] Nonhuman primate studies have shown that the firing rate of dopaminergic neurons is increased in response to "positive prediction errors," meaning unexpected natural or conditioned rewards.[55] Perhaps a mother's own infant's unexpected smile, for example, may activate dopamine circuits via a similar mechanism. In rat dams, extracellular dopamine release in the ventral striatum is associated with an increase in maternal behaviors, with the dopamine signal preceding the onset of the behavior.[56] Although fMRI only measures BOLD changes in brain activity, together these studies suggest that positive sensory cues from infants, such as a smiling facial expression, may stimulate dopamine release in the striatum and promote responsive maternal care.

In this population of mothers, OH infant faces tended to activate associative and motor regions of the striatum rather than the more affect-related regions of the ventral striatum and the VTA[50] (Fig 6). However, these regions were activated when all affect groups were combined in the own > unknown contrast (Table 2). Given that the OH > UH contrast used only one third the number of images used in the own > unknown contrast (20 vs 60), this result may simply reflect insufficient statistical power. In fact, when statistical thresholds were lowered in the OH > UH contrast, a similar activation pattern was seen (data not shown). However, additional re-

search should explore whether this pattern varies with maternal characteristics such as adult attachment classification, in which affective and cognitive brain responses have been hypothesized to be key distinguishing features.[51]

The fact that the mothers did not have a stronger response to their own infant's crying face compared with that of an unknown infant was also surprising. It seems that, at least in this sample of mothers, the brain responds equally to own and unknown infant faces in distress. This was evident from the contrast between sad faces and baseline, which revealed widespread activation in response to both OS and US infant faces, although with a similar pattern for each. Thus, in the contrast between OS and US, no significant activation remained. However, it is possible that differences in timing of the 2 conditions could have biased the results, with earlier images expected to produce a stronger hemodynamic response. Although the timing difference between OS and US images was not statistically significant ($t = -1.69$, $P = .13$), OS images were seen somewhat earlier in the run than the US images. This would, however, have biased the results in favor of OS rather than US images. Another possible explanation is that individual mothers respond differently to their own infant's sad face, some feeling distress themselves, others inhibiting their own negative affect. Future work to explore adult attachment strategies may reveal important individual differences in maternal brain response to sad infant affect.

One limitation of this study is that the mothers were scanned at varying times postpartum (between 7 and 17 months), viewing infant faces that ranged from 5 to 10 months of age (Table 1). Although there have been no published fMRI data on the question, mothers may respond differently to their infant at differing ages, which may have influenced our results. Also, some key maternal brain regions identified in animal studies, such as the medial preoptic area[10] and ventral bed nucleus of the stria terminalis, were not activated in this study. However, other fMRI studies have only demonstrated activation of these areas in mothers of younger infants, during the first few months of life,[18,24] which suggests that these regions may be more important during the early postpartum period.

Although individual variation seen within this population (such as breastfeeding duration, mother–infant separation, and psychopathology risk) is another limitation in interpreting study findings, it also presents an opportunity for additional research into the significance of these individual differences. In addition to understanding how previous experience may influence maternal brain responses, the present paradigm might also enable investigators to explore how these response patterns relate to current maternal behavior. For example, the difference in response between OH and UH faces in these dopamine-associated regions may be an index of the reward value or salience of the infant's face to the mother, which may in turn relate to maternal sensitivity or conversely, child neglect. This may further our understanding of brain processes that mediate the effect of previous experience on current maternal behavior in humans.

Individual differences in affective and cognitive brain responses are fascinating topics for ongoing and future research. In some mothers, for example, a crying infant may trigger an angry response, or even physical abuse,[57] rather than empathic caregiving. Likewise, in cases of maternal depression[11] or substance abuse,[12] a smiling face may repeatedly fail to illicit positive caregiving. Depressed individuals show a decreased emotional response to happy faces, decreased accuracy in recognizing facial expressions, and increased memory for negative faces.[58] Cocaine, a common drug of abuse among women of childbearing age and which activates both mesocorticolimbic and nigrostriatal dopamine systems,[59–61] seems to compete with natural infant-related reward signals,[62] which may relate to relatively high rates of child neglect in cocaine-exposed mothers.[63]

Important questions that are currently being examined include: What are the effects of maternal depression or substance abuse on brain responses to infant cues? How do brain responses predict differences in maternal sensitivity or attachment? What effect may these response differences have on a child's subsequent development or attachment security?

CONCLUSIONS

How a mother responds to her infant's behavioral cues may have an important role in shaping future child development. Our study takes us one step closer to understanding the underlying brain processes and pathways involved in this important dyadic relationship.

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AIR COMBAT BY REMOTE CONTROL

"The sniper never knew what hit him. The Marines patrolling the street below were taking fire, but did not have a clear shot at the third-story window that the sniper was shooting from. They were pinned down and called for reinforcements. Help came from a Predator drone circling the skies 20 miles away. As the unmanned plane closed in, the infrared camera underneath its nose picked up the muzzle flashes from the window. The sniper was still firing when the Predator's 100-pound Hellfire missile came through the window and eliminated the threat. The airman who fired that missile was 8,000 miles away, here at Creech Air Force Base, home of the 432nd air wing. The 432nd officially 'stood up,' in the jargon of the Air Force, on May 1, 2007. One year later, two dozen of its drones patrol the skies over Iraq and Afghanistan every hour of every day. And almost all of them are flown by two-man crews sitting in the air-conditioned comfort of a 'ground control station' (GCS) in the Nevada desert."

Carney BM. *Wall Street Journal.* May 12, 2008
Noted by JFL, MD