THE INTERPLAY OF BRAIN AND EXPERIENCE IN PARENTAL LOVE

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Three brain imaging studies were performed to understand whether past and present experience that parents have may be associated with changes in parental brain during the postpartum period.

The first study examined whether perceived quality of maternal care in childhood is associated with brain structure and functional responses to salient infant stimuli among human mothers in the first postpartum month. Mothers who reported higher maternal care in childhood showed larger grey matter volumes in the superior and middle frontal gyri, orbital gyrus, superior temporal gyrus and fusiform gyrus. Furthermore, in response to infant cries, these mothers exhibited higher activations in the middle frontal gyrus, superior temporal gyrus, and fusiform gyrus; whereas mothers reporting lower maternal care showed increased hippocampal activations. These findings suggest an association between maternal care in childhood and neurobiological substrates of parenting behavior in human mothers.

The second study investigated the associations between breastfeeding, neurological mechanisms of maternal behavior, and maternal sensitivity at 2-4 weeks postpartum and 3-4 months postpartum. At one month postpartum, when listening to their own baby cry, breastfeeding mothers showed greater activation in brain areas related to maternal behaviors (midbrain, thalamus, anterior cingulate, and superior prefrontal cortex) and emotional information processing (insula, fusiform gyrus, superior temporal gyrus) compared to the formula-feeding mothers. At 3 months postpartum,

breastfeeding mothers showed greater activation in areas implicated in maternal behavior (ventral tegmental area, and thalamus), while formula-feeding mothers exhibited increased activations in superior frontal cortex and superior temporal gyrus. Furthermore, across both groups, greater activations in reward-related circuits were associated with higher sensitivity at 3 months. Maternal brain responses at one month postpartum may predict maternal behaviors at later months postpartum and breastfeeding may further promote sensitive maternal behaviors and thus potential long-term positive outcomes for children.

The third study examined changes in grey matter volumes in mothers and fathers from 2-4 weeks postpartum to 12-16 weeks postpartum. The longitudinal study using voxel-based morphemetry analysis yielded an increase in the grey matter of prefrontal cortex, parietal lobes, and midbrain for both primiparous and multiparous mothers. Multiparous fathers showed an increase in grey matter particularly in the prefrontal cortex regions whereas primiparous fathers showed little change in brain structure. These results indicate that parenthood over the first three months postpartum is accompanied by structural changes in brain regions important for parental behaviors.

BIOGRAPHICAL SKETCH

Pilyoung Kim was born in Pusan, South Korea and grew up in Seoul, South Korea. She received her bachelor's degree from Korea University in Seoul, South Korean in 2002 majoring in English literature and Psychology. She received her master's from Harvard Graduate School of Education in 2003 majoring in Human Development and Psychology with a concentration in Mind, Brain and Education. Since 2004, she had been enrolled in the MA/PhD Developmental Psychology program in the department of Human Development at Cornell University. She received her MA in Development Psychology in 2007. Pilyoung was also an exchange scholar and graduate researcher at the Child Study Center, Yale University School of Medicine, during 2007-2009 while she was conducting her dissertation projects.

To my husband, Show

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CHAPTER 1

PERCEIVED QUALITY OF MATERNAL CARE IN CHILDHOOD AND STRUCTURE AND FUNCTION OF MOTHERS' BRAIN IN THE EARLY POSTPARTUM

Introduction

The early experience of parental care has long-term effects on a range of behaviors, including those associated with parenting. For example, women who experienced consistent and positive emotional climate in their family of origin are more likely to provide warm and sensitive parenting to their children (Belsky, Jaffee, Sligo, Woodward, & Silva, 2005). On the other hand, individuals who received less care from their mothers are at a greater risk of providing low care parenting to their own children (Kaufman & Zigler, 1987; Miller, Kramer, Warner, Wickramaratne, & Weissman, 1997; Weinfield, Sroufe, & Egeland, 2000). The intergenerational transmission of parenting has been shown across mammalian species from rodents (Fleming et al., 2002) to nonhuman primates (Maestripieri & Carroll, 1998) and humans (Belsky, 2005; Chen & Kaplan, 2001). Recent studies with rodents suggest that the species-specific repertoire of maternal behaviors may be transmitted intergenerationally through changes in the neurobiological systems related to stress reactivity or social attachment (Francis, Diorio, Liu, & Meaney, 1999; Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005). Such findings may suggest that in human mothers, adverse early experience may lead to similar neurobiological changes expressed in high stress reactivity and insecure attachment, which, in turn, may impair the mother's responsiveness to infants (Belsky, 2005; Meaney, 2001). However, the neurobiological mechanisms underlying maternal behaviors in humans have only

recently become the subject of investigation and their relationship with early experience has not yet been well-understood (Swain, Lorberbaum, Kose, & Strathearn, 2007).

The mechanisms underlying the relationship between the early environment, the developing brain, and the emergence of parenting behavior have been studied mainly in nonhumans. Rat pups who received more maternal care in the form of high levels of licking and grooming (HLG) from their mothers were more likely to exhibit HLG behaviors to their own pups. In contrast, the female offspring of mothers who provided low levels of licking and grooming (LLG) showed a similar pattern of LLG behaviors when they become mothers (Francis, Diorio, Liu, & Meaney, 1999; Francis, Young, Meaney, & Insel, 2002). It has been suggested that the intergenerational effects of early maternal care on maternal behaviors are related to stress reactivity (Kaffman & Meaney, 2007). As adults, offspring raised by LLG mothers showed greater responses to stress than did the offspring of LLG mothers and this greater neurobiological stress reactivity may make the offspring of HLG mothers less responsive to their own pups. Furthermore, increased frequency of licking and grooming provided by the rodent mother is associated with changes in glucocorticoid receptor gene expression in the hippocampus (Kaffman & Meaney, 2007). Thus, such heightened stress response has been further associated with decreased hippocampal synaptic density in the offspring of LLG mothers (Bredy, Grant, Champagne, & Meaney, 2003). In humans, women who reported low maternal care in childhood had a smaller hippocampal volume (Buss et al., 2007). However, the question of whether early experience is related to stress dysregulation as indexed by changes in the hippocampus physiology has not been examined in human mothers.

Low maternal care in childhood affects the parents' responsiveness to their infants through changes in the brain. Studies have found that children who

experienced low quality of interactions with their mothers tend to develop insecure attachment, socioemotional difficulties, and limited capacity for empathy across childhood and up to adolescence (Feldman, 2007a, b; Feldman & Eidelman, 2004). Possibly, children of less responsive mothers are less capable of processing social and emotional information efficiently which, in turn, may impact their ability to respond sensitively to their own infants when they become parents. Brain structures such as the limbic system, in particular, the amygdala, and the medial/inferior prefrontal cortex, including the orbitofrontal cortex, superior and middle temporal cortex, and insula, play important roles in emotional and social information processing (Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008; Sander, Grafman, & Zalla, 2003; Saxe, 2006). A recent study has shown that insecure attachment is associated with greater amygdala sensitivity to negative emotional stimuli (Lemche et al., 2006; Vrticka, Andersson, Grandjean, Sander, & Vuilleumier, 2008). These regions have also been shown to be sensitive to parenting-specific contexts. In several functional magnetic resonance imaging (fMRI) studies, mothers showed activation in the amygdala, medial prefrontal cortex, temporal cortex, and insula when presented with infant cries (Lorberbaum et al., 2002; Seifritz et al., 2003; Swain et al., 2004).

In light of the above, the current study aims to further understand the neurobiological mechanisms underlying the relationship between early experiences and later parenting behaviors in human mothers. We examined whether perceived quality of maternal care, as recalled by mothers in the immediate postpartum period is associated with their brain structure as well as patterns of functional activation in response to highly salient infant-cry stimuli (Swain, Lorberbaum, Kose, & Strathearn, 2007). Mothers were divided into high and low maternal care groups. We then examined whether perceived maternal care in childhood is related to grey matter volume in the brain. To determine whether perceived maternal care is further linked

with brain response in specific regions, we examined blood oxygenation level dependent (BOLD) signal response among postpartum mothers while they attended to infant cries. We hypothesize that, compared to mothers in the low maternal care group, mothers in the high maternal care group would show larger grey matter volumes and greater responses to infant stimuli in brain regions that are related to emotional information processing and stress regulation during the early postpartum period.

Methods

Participants

Twenty six biological mothers with full-term, healthy infants were recruited in postpartum hospital wards at the Yale New Haven Hospital. Mothers' age averaged 32.7 years (SD = 6.56; range = 19.58 to 47.08) and all the mothers were Caucasian. Exclusion criteria included current or past psychiatric diagnosis or taking prescription medications within 2 weeks of the brain imaging and home visit. Informed consent was obtained from each participant according to procedures approved by the Yale University School of Medicine Human Investigations Committee.

Mothers were divided into two groups based on their perceived maternal care scores on the PBI - with "high" and "low" perceived maternal care (PMC) groups determined from a cut-off score of 27, which was obtained from a large normative sample (Parker, 1979). Mothers in the higher PMC group (n=13) and lower PMC group (n=13) had no mean differences in age, handedness, nursing method, the number of children, and educational level (see Table 1.1). As expected, the maternal care score from PBI were significantly different comparing the higher and lower PMC groups, $t(24)=8.17$, $p<.0001$. The two groups showed no significant difference on their depression (BDI) and trait anxiety (STAI) scores. To confirm that these variables

were not related to the PBI scores, we conducted zero-order correlation analysis, and PBI scores were not significantly correlated with BDI and trait anxiety scores.

Table 1.1. Characteristics of higher and lower perceived quality of maternal care (PMC) groups

	High PMC group	Low PMC group
	n=13	n=13
	Mean (SE)	Mean (SE)
Age	30.87 (1.67)	34.46 (1.89)
Handedness (L/R)	2/11	1/12
# of children	1.38 (.24)	1.77 (.20)
Breastfeeding/Formula-feeding	11/2	11/2
Educational level (in years)	17.09 (.95)	16.75 (.82)
BDI	5.08 (.98)	7.69 (1.20)
Trait Anxiety	47.08 (.57)	45.23 (.73)
PBI Maternal care*	33 (.70)	21.15 (1.27)

*p<.0001

Procedures

Both home interview and brain imaging data were obtained between 2-4 weeks postpartum. A brain imaging study was conducted when participants visited the research center. Questionnaires and demographic information were completed during a home visit within a few days of the brain imaging

Measures

Parenting Bonding Instrument (PBI).

The PBI is a self-report measure for adults to rate their parents' caring behaviors during the first 16 years of the respondent's development. The measure has

two scales: parental care (12 items) and overprotection (13 items) (Parker, 1979). Items are rated on a 4-point Likert scale of 0 (very unlike), 1 (moderately unlike), 2 (moderately like), and 3 (very like). In this study, participants completed items for maternal care to assess the perceived care that they received from their own mothers when they were children. The items ranged from closeness, emotional warmth, and affection to neglect, and indifference. An example of a maternal care item is "(Mother) spoke to me with a warm and friendly voice." Scores in the current study ranged from 13 to 36. Based on a large normative sample (Parker, 1979) a cutoff score of 27 was determined to differentiate respondents with high and low experiences of maternal care.

Beck Depression Inventory (BDI).

A self-report measure was used to assess parental depressed mood (Beck, Steer, Ball, & Ranieri, 1996). BDI consists of 21 items that assess symptoms of depression. All the items were answered on a 0 to 3 scale. In the current study, scores ranged from 2 to 18 with a mean of 6.38 (SD=4.11).

Spielberger State/Trait Anxiety Inventory (STAI).

This instrument assesses the individual's current state of anxiety (state) and general anxiety proneness (trait) (Spielberger & Vagg, 1984). All items were rated on a 4-point Likert scale with one being almost never true and four almost always true and the trait anxiety score was used in the present study. In the current study, scores ranged from 40 to 51 with a mean of 46.15 (SD=2.52).

Brain Magnetic Resonance Imaging (MRI)

Image acquisition. First, high resolution T1-weighted structural magnetic resonance images (MRI) were obtained (3D MPRAGE; TR = 2530; TE = 3.66; matrix size 256 by 256) with a Siemens trio 3T full-body scanner (Erlangen, Germany). Next,

anatomical T1-weighted echo-planar images (spin-echo; TR = 300ms; TE = 4ms; matrix size 64x64; 30 axial slices; 3.125-mm in-plane resolution 5-mm thick, no skip) were acquired to be coplanar with the functional scans for spatial registration. Finally, functional MRI (fMRI) were acquired (echo planar T2*- weighted gradient-echo, TR = 2000 ms, TE = 30ms, matrix size 64 by 64, 5-mm thick, 3.125-mm in-plane resolution; 5mm thick, skip 0). Head movements were restrained throughout with foam padding and surgical tape placed across each participant's forehead.

Voxel-based morphometry (VBM) processing and analysis. VBM analyses were performed with VBM2 toolbox for Statistical Parametric Mapping 2 (SPM2) (Wellcome Department of Neurology, London, UK). All the structural images were processed according to the optimized VBM protocol (Ganzel, Kim, Glover, & Temple, 2008; Good et al., 2001). Study-specific T1 grey matter, white matter, CSF templates were first created based on the images of all participants. Next, the customized T1 grey matter templates were used for segmentation and normalization of the original images. Template creation and subsequent segmentation and normalization were performed using default options in VBM toolbox (25 mm cut off, medium regularization, medium HMRF [Hidden Markov Random Field]) weighting for segmentation) with 16 nonlinear iterations. The normalized segments of each participant's grey matter image were modulated for grey matter volume analysis. All the modulated images were smoothed with a filter of 12mm Gaussian kernel. Finally, the modulated and smoothed images were analyzed with t-test in SPM2 to test comparisons grey matter changes in higher vs. low PMC groups. All the analyses included control variables for the age and total grey matter volume of each participant. A value of $p < .001$ (uncorrected) and extent threshold of 50 voxels were used to determine statistical significance.

fMRI stimuli. Identical standard baby cry stimuli were used to activate the brains of each participant. The baby cries were collected during the first two weeks postpartum by mothers who were not included in this study using a portable digital audio recorder during the discomfort of a diaper change (Swain et al., 2008). All non-baby cry sounds, such as gurgles or grunts, were removed to generate a 30 second block of baby cry stimuli using Cool Edit Pro Version 2.0 (Syntrillium Software, Phoenix, AZ). Among eight baby cry samples, a standard baby cry was chosen as one with median emotional intensity as rated by eight investigators on a scale of 1-10. The control sound was made by replicating the baby cry sound envelope and replacing the cry with white noise, which controlled for baby cry pattern and sound volume (total root-mean-square sound intensity of -8dB). During each of two functional runs, participants heard ten sound blocks through padded headphones. Each sound block was 30 seconds long and composed of (A) baby cry, and (B) control sound. These stimulus blocks were arranged so participants heard each sound block a total of five times in the following order: ABBAB and then ABAAB. Each stimulus block was separated by a 10-sec rest period during which only background scanner noise could be heard. Before scanning, participants listened to samples of all sounds through headphones, so that the volume of the sounds could be adjusted at the level that the participants would hear the sounds clearly. This also enabled participants to become familiarized to the sounds to minimize surprise effects. During the scans, participants were asked to think about how much the stimuli reminded them of their own baby and current parenting experiences.

fMRI data analysis. Functional imaging data were preprocessed and statistical analysis was performed using Brainvoyager QX Software version 1.6 and 1.8 (Brain Innovation, Maastrict, The Netherlands). Functional runs were pre-processed using 3-dimentional head-motion correction based on trilinear interpolation by spatial

alignment of all brain volumes to the first volume. One participant exceeded the minimal movement requirements of < 3mm in x, y or z directions, and was excluded from all analyses. Slice scan-time correction was performed by sinc interpolation. After linear trend removal, a temporal high-pass filter was used to remove nonlinear drifts of 3 cycles or less per timecourse. Motion-corrected images were spatially smoothed using a Gaussian filter with a full-with half-maximum value of 6.25mm. Data from each participant were coregistered with each participant's high-resolution 3D anatomical data set, then transformed into standardized 3D Talairach coordinate space (Talairach and Tournoux, 1998) using piecewise linear warping. The functional data were resampled at 1 mm3 voxels.

The analysis of the BOLD signal changes in brains in response to the baby cry sound relative to control sound were analyzed using a random effect general linear model (GLM). The exploratory whole-brain analysis was used to contrast activities in two conditions (baby cry vs control noise) across the two groups. Significance threshold of the activities was set at $p < .01$, and was corrected for multiple comparisons using the cluster filter (Forman et al., 1995; Goebel, Esposito, & Formisano, 2006), such that only clusters larger than 833 mm3 survived the correction. The group effects (the higher vs lower perceived maternal care) X the condition effects (baby cry vs control noise) were tested by performing a conjunction of random effect GLM analysis and subsequent generation of group t maps (2-tailed, $df = 24$). The significance threshold for between-group differences was set at $p < .01$, and was also corrected for multiple comparisons using the cluster filter. Thus, all the uncorrected activated clusters smaller than 1011 mm3 were rejected. The priori regions of interest analysis performed in the hippocampus and in functionally defined regions that were convergent with the regions from the VBM analysis. Among the regions that show significantly different levels of the activations between two groups

in the fMRI analysis, the regions that were in the same anatomic structure in both hemispheres compared to the VBM results were identified as converged regions. The results of the priori regions of interest analysis were reported at $p < .05$ after correcting for multiple comparisons using a cluster filter, with activated clusters that were larger than 4482 mm3 surviving. Finally, ordinary least squares (OLS) regression was performed for each significant result to test whether the group effect would be significant after controlling for depression or anxiety levels. This was performed by extracting the data from Brain Voyager and analyzing with SPSS version 15 (Chicago: SPSS Inc). Finally, we extracted the data of the grey matter volume from the VBM analysis and the data of the BOLD signal, then correlated them and also with the PBI scores by running the zero-order correlation analysis in SPSS version 15.

Results

Voxel-based morphometry (VBM) results

As presented in Table 1.2 and Figure 1.1, optimized whole brain VBM analyses revealed that mothers in the higher PMC group had significantly larger grey matter volumes in several brain regions in frontal and temporal gyri, $p < 0.001$ (uncorrected). OLS regression results indicated that the higher levels of perceived maternal care were significantly associated with larger grey matter volumes in these regions after controlling for the BDI, and anxiety scores, $p < .005$. In contrast, the lower perceived maternal care group had significantly greater grey matter volume in left and right inferior parietal gyri, $p < 0.001$ (uncorrected). OLS regression results showed that the lower levels of perceived maternal care were significantly associated with larger grey matter volumes in these regions after controlling for the BDI, trait anxiety scores, $p < .01$. There was no significant group difference in either the right or left hippocampus.

Table 1.2. Results of the whole-brain voxel-based morphometry (VBM) analysis

Anatomical Areas	BA	Side	z score	cluster size	Tailarach coordinates x	y	z
Higher perceived maternal care (PMC) group > Lower PMC group							
Superior Frontal Gyrus	10	L	3.56	52	-21	57	8
Orbital Gyrus	47	L	3.41	114	-13	26	-23
Superior Temporal Gyrus	22	R	3.38	99	59	9	0
Middle Temporal Gyrus	20	R	3.82	1270	52	-35	-6
Fusiform Gyrus		R	3.75		46	-33	23
Cerebellum		L	4.05	1521	-31	-31	-36
		R	3.79	1036	53	-56	-30
Lower PMC group > Higher PMC group							
Parietal Cortex	7/40	L	3.83	105	-22	-48	57
Inferior Parietal Cortex	7/40	R	3.45	277	41	-69	48

$p < .001$ (uncorrected)
BA= Brodmann Area

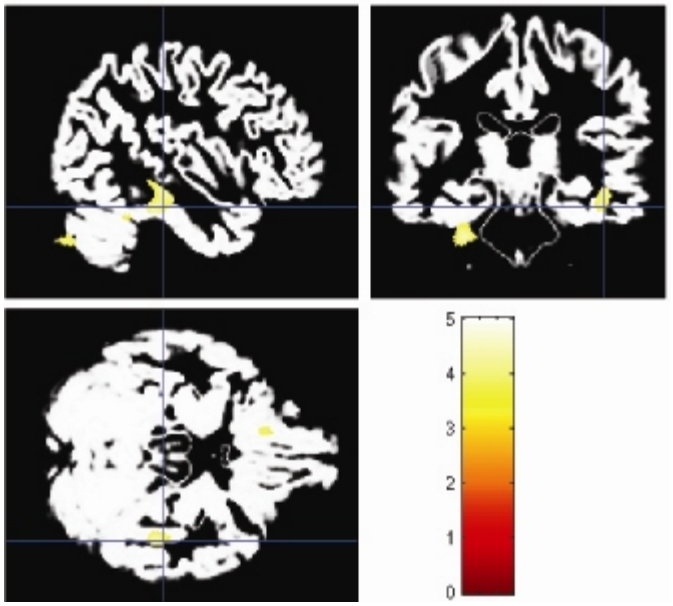


Figure 1.1. Whole-brain voxel-based morphometry (VBM) showing areas with significantly higher mean grey matter volume in higher perceived maternal care group relative to the lower perceived maternal care group, controlling for age, and total grey matter volume, p< .001 (uncorrected). Left orbital gyrus, right superior and middle temporal gyri and cerebellum are shown in yellow in this map.

Functional brain imaging results

Whole-brain fMRI results.

First, we examined maternal brain responses to baby cry compared to control noise across two groups (see Table 1.3). Baby cry activated the superior, medial and inferior frontal regions, superior and middle temporal gyrus, and insula, cuneus regions, p<.01 (corrected).

Table 1.3. Activation results of the contrast of 'infant cry' minus 'control sound' across two groups.

Area of Activation	BA	Side	t score	cluster size	Tailarach coordinates x	y	z
Superior Frontal Gyrus	8	L	3.75	1843	-4	27	48
Medial/Sueprior Frontal Gyrus	6	L	4.95	2040	-1	2	61
Superior Frontal Gyrus	6,8	R	3.72	1779	6	16	52
Precenteral Gyrus/ Inferior Frontal Gyrus	9	R	5.96	4147	42	9	32
Inferior/Middle frontal gyrus	9	L	3.91	1826	-40	11	26
Precenteral Gyrus	6,4	R	3.85	2419	43	-7	47
	4	L	4.13	871	-42	-12	54
Precenteral Gyrus/ Inferior Frontal Gyrus	44,45	L	3.75	1261	-52	12	9
Insula	13	L	5.07	3485	-29	17	12
Superior/Transverse Temporal Gyrus	41,22,13	R	8.87	8388	53	-20	8
		L	7.97	11707	-54	-18	8
Superior/Middle Temporal Gyrus	41	R	5.69	3480	46	-39	10
Posterior Cingulate Gyrus	23	R,L	4.25	977	1	-39	25
Cuneus	17,23	R	3.32	806	12	-78	9
Occipital Gyrus	18	L	3.72	1356	0	-73	-5

$p < .01$ (corrected)

Next, we examined the group effect to predict maternal brain responses to baby cry compared to control noise. Mothers in the higher PMC group showed a greater BOLD signal in several frontal areas including the dorsolateral prefrontal cortex,

middle frontal gyrus, and precentral gyrus, superior temporal gyrus including the fusiform gyrus and the lingual gyrus, p <.01, corrected (see Table 1.4). OLS regression analysis revealed that the group effects were significantly associated with greater activations in these regions after controlling for the BDI, anxiety scores, p<.01 (except right lingual gyrus, p<.05). No brain areas were found to exhibit significantly greater BOLD activations among the lower PMC group in response to baby cry (minus control noise) at this level of significance.

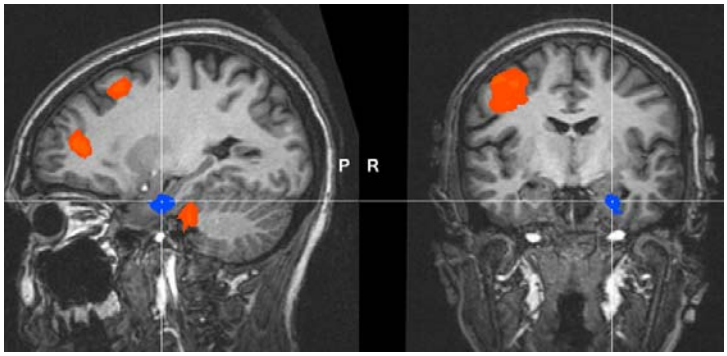
Table 1.4. Activation results of the group comparison in the contrast of 'infant cry' minus 'control sound'

Area of Activation	BA	Side	t score	cluster size	Tailarach coordinates x	y	z
High perceived maternal care (PMC) group > Low PMC group							
Dorsolateral Prefrontal Cortex	9	R	3.31	999	32	27	27
Middle Frontal Gyrus	6	R	3.69	2438	41	-2	45
Precentral Gyrus	2	R	3.97	1859	50	-24	43
	3	R	3.97	1502	42	-20	48
Superior Temporal Gyrus	22	R	3.68	518	57	-48	13
Fusiform Gyrus	19	R	3.77	271	42	-69	-12
Lingualis Gyrus	19	R	3.46	664	10	-72	1

p <.01 (corrected)

A priori regions of interest analysis. In the left hippocampus, mothers in the lower PMC group showed greater activations in hippocampus in responses to baby cry (minus control noise) while listening to baby cry, whereas activations in the same area decreased among mothers in the high perceived maternal care group, t(24)= -2.64, se=0.29, p< .05 (corrected) (see Figure 1.2). The result was consistent after controlling for BDI, state and trait anxiety scores, p<.05. The group difference was still significant after controlling for BDI and anxiety scores.

A.



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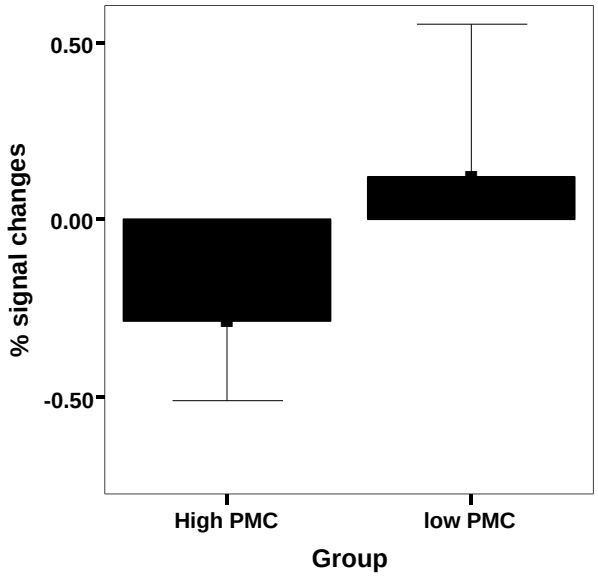

*PMC = perceived maternal care

Figure 1.2. Left hemisphere hippocampus activity (baby cry minus control sound). Panel A shows decreased activity in left hippocampus (in blue) among the higher perceived maternal care group relative to the lower perceived maternal care group ($p<.05$, corrected). Panel B compares higher and lower perceived maternal care groups' activity in left hippocampus, $t = -2.64$ ($p<.05$).

Convergence of VBM and the fMRI results

Significant activations to baby cry were found in the higher PMC group relative to the lower PMC group all of the regions that also had higher grey matter volumes from the VBM analysis except in the left superior frontal gyrus, orbital gyrus, and right cerebellum, $p<.05$ (corrected) (see Figure 1.3). Furthermore, the grey matter volume of each VBM region was significantly correlated with the BOLD responses of the matched fMRI region across two groups (see Table 1.5). The brain areas with greater grey matter volume in the higher PMC group also showed higher levels of functional brain activations relative to the mothers in the lower PMC. In addition, the regions with the smaller grey matter volumes in the higher PMC group were negatively correlated with the matched region with the greater activations in the higher PMC group (see Table 1.5). Significant correlations between the VBM and fMRI were not seen in the parietal lobe, orbital gyrus or right cerebellum. In addition, we examined the correlation between PBI score, VBM and fMRI results across two groups. PBI score was correlated most of the VBM and fMRI results. However, the only exceptions were the VBM results of right inferior parietal lobe and the fMRI results of left fusiform gyrus.

Table 1.5. Convergence of VBM and fMRI results

VBM results	fMRI data results							Correlations		
	BA	Side	t score	cluster size	Tailarach coordinates x	y	z	VBM-fMRI	PBI-VBM	PBI-fMRI
L Superior Frontal Gyrus (BA10)									.49*	
L Orbital Gyrus (BA47)									.60**	
R Superior Temporal Gyrus (BA22)	22	R	3.68	6354	57	-48	13	.48*	.56***	.51**
R Middle Temporal Gyrus (BA20)	19	R	3.77	1459	42	-69	-12	.54**	.70***	.64***
R Fusiform Gyrus	21	L	3.4	2053	-60	-32	-3	.40*		.28
L Parietal Lobe (BA 7/40)	7	R	2.55	1292	24	-72	39	-.48*	-.58**	.41*
R Inferior Parietal Lobe (BA 7/40)	40	R	3.95	1964	55	-33	41	-.49*	-.37	.48*
	40	L	2.67	181	-58	-41	45	-.52**		.36*
R Cerebellum									.53**	
L Cerebellum		L	3	1080	-24	-25	-30	.56**	.67***	.58**

For VBM results, p<.001 (uncorrected); For fMRI data results, the group comparison in the contrast of infant cry – control sound, p <.05 (corrected). ***p<.001, **p<.01, *p<.05

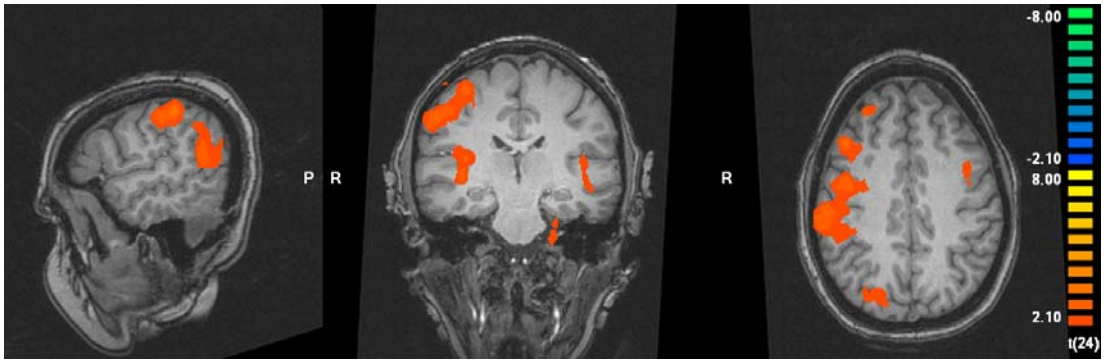

Figure 1.3. Areas of activation in the contrast (baby cry minus control sound). Areas in red shows greater activations in higher perceived maternal care group relative to lower perceived maternal care group ($p<.05$, corrected). The areas shown in this map include the left and right middle temporal gyrus, right superior temporal gyrus and right inferior parietal lobe.

Discussion

Results of the present study demonstrate associations between a standard index of perceived quality of maternal care in childhood and both brain structure and function of new mothers. We found larger grey matter volumes in the brain regions of mothers who reported higher levels of perceived maternal care during their childhood. Furthermore, significantly greater brain activations in response to baby cry in similar brain regions to those with increased volume occurred among mothers with higher levels of perceived maternal care. Finally, in the left hippocampus, mothers' brain activations in response to infant cry stimuli was greater among mothers with lower levels of perceived maternal care.

The findings point to a relationship between early maternal care and brain structures and functions that may be important for maternal responsiveness to newborns. Most of the brain regions shown here to be associated with early maternal

care are those that serve an important function for the development of parenting in humans and mammals (Swain & Lorberbaum, in press; Swain, Lorberbaum, Kose, & Strathearn, 2007). Previous fMRI studies demonstrated that the prefrontal cortex, superior temporal gyrus, middle frontal gyrus, and fusiform gyrus were activated when mothers attended to baby cries (Lorberbaum et al., 2002; Swain et al., 2004) as well as when mothers saw baby pictures and video clips (Bartels & Zeki, 2004; Lenzi et al., in press; Noriuchi, Kikuchi, & Senoo, 2004; Ranote et al., 2004).

Other studies with non-parents underscored the importance of these regions for the processing of emotional stimuli more generally (Ethofer, Pourtois, & Wildgruber, 2006; Johnstone, van Reekum, Oakes, & Davidson, 2006). For example, the right posterior middle temporal cortex, superior temporal sulcus, and bilateral inferior/middle frontal cortex were activated to a greater degree when individuals were asked to respond to affective prosody as compared to the emotional contents of the vocal stimuli (Mitchell, Elliott, Barry, Cruttenden, & Woodruff, 2003). Also, the superior temporal sulcus similarly showed higher activation in response to angry speech as compared to neutral speech (Grandjean et al., 2005; Sander et al., 2005). Finally, the right anterior and posterior middle temporal gyri were more activated in response to happy voice compared to angry voice (Johnstone, van Reekum, Oakes, & Davidson, 2006). These findings are also consistent with our findings of higher grey matter volumes and greater maternal brain activations levels in the middle temporal gyrus and superior temporal sulcus among mothers who recalled higher quality of maternal care. These morphological and possessive differences may help mothers to respond more sensitively to their infant's emotional signals during the postpartum. Consistent with these results, several fMRI studies found that such regions including inferior frontal gyrus, superior temporal sulcus, insula, fusiform gyrus, inferior parietal

lobule and temporal poles were also important for understanding the emotional states of others (Iacoboni & Dapretto, 2006; Völlm et al., 2005).

The lower grey volume in the orbital gyrus in the lower PMC group may be another important indicator of the significant relationship between childhood experience and the neurological systems implicated in parenting behaviors. Particularly, the orbitalfrontal cortex (OFC), a part of the orbital gyrus, is related to evaluating and processing social and emotional information (Kringelbach, 2005). OFC activations were also reported in response to emotional vocal stimuli (Sander et al., 2005). Thus, decreased volumes in the orbital gyrus in the low perceived maternal care group may reflect subtle individual differences in responsiveness to emotionally salient information. The importance of the prefrontal cortex in parenting is supported by primate studies which show that damage to the prefrontal cortex including the orbital gyrus significantly disrupt maternal behaviors (Franzen & Myers, 1973). Furthermore, other fMRI studies on human mothers found that the orbital gyrus was activated when mothers heard infant cries compared with control sounds (Lorberbaum et al., 2002; Seifritz et al., 2003).

We also report an association of perceived maternal care and functional differences in the left hippocampus – a region well established to be part of stress response regulation. Specifically, the left hippocampus of the lower PMC group exhibited stronger activations in response to baby cry stimuli. This may be linked to differences in the mothers' level of stress reactivity to baby cries. A number of studies have found that elevated biological stress responses in the hypothalamo-pituitary-adrenocortical (HPA) axis is associated with increased activations in the hippocampus (Dunn & Orr, 1984; Herman, Ostrander, Mueller, & Figueiredo, 2005). Less responsive maternal care in childhood may be linked to a cascade of brain developmental processes that cumulate in the experience of infant cry as more

stressful. This interpretation is also consistent with the well established findings from the animal literature that early maternal care has long-term consequences for later parenting behaviors. The negative reactions to infant cry may be amplified by these mothers with difficulties in social information processing. In turn, while listening to an infant cry, mothers with negative early experience showed elevated responses in the hippocampus whereas mothers with higher experienced maternal care reacted to infant cry sounds more positively and exhibited lower stress response. Further work with actual measurements of neuroendocrine stress reactivity during parental brain responses and the connectivity between the hippocampus and brain regions for emotional information processing are required to test this interpretation. In a study of subjects diagnosed with post-traumatic stress disorder, for instance, memory of traumatic events increased activations in the hippocampus and decreased activations in the prefrontal cortex, the fusiform cortex and the medial temporal cortex (Osuch et al., 2001).

In contrast to the fMRI results, no structural differences were found in the hippocampus in the VBM analysis between the high and low maternal care groups, suggesting that the impact of perceived low quality of maternal care on the hippocampus is likely to be mainly functional and not reflected in grey matter volume. We speculate that significant structural changes in the hippocampus may be found among mothers who were exposed to additional life stressors. This hypothesis is consistent with Buss and colleagues (2007), who found that women with low maternal care scores on the PBI had a smaller hippocampal volume only if they were born at a low birth weight (Buss et al., 2007). Thus, additional risk factors for normal brain development may make the hippocampus more vulnerable to permanent structural changes in adulthood.

No significant results were found in either the left or right amygdala in response to infant cry and control noise. The VBM analysis and fMRI analysis also did not reveal the grey matter volumes or the activations in amygdala to differ by the perceived quality of maternal care in childhood. In several other fMRI studies, significant increases in amygdala in response to baby cry or pictures were not evident (Bartels & Zeki, 2004; Nitschke et al., 2004; Swain et al., 2008). Perhaps the perceived quality of maternal care is more strongly linked to changes in hippocampus, but not in the amygdala.

Significant correlations emerged between the anatomical and functional results for the two maternal care groups. This consistency underlines the importance of these regions for the mother's capacity to parent, and its links with her early experience of being cared for as a child. For example, the volumes of the superior temporal gyrus, middle temporal gyrus, and fusiform gyrus in the high perceived maternal care group were not only greater but also more activated in response to the infant's cry. However, in the parietal lobe, decreased grey matter volume was associated with greater functional activation. This is interesting as the parietal lobe has been shown to be important for sensory information processing (Rizzolatti & Craighero, 2004). Studies have found that the right inferior parietal lobe may be important for information processing of negative emotions such as anxiety (Liotti et al., 2000). Thus, the association reported in the current study between relatively lower perceived quality maternal care in childhood and increased grey matter volumes in the inferior parietal lobe may be due to elevated anxiety levels experienced over time. Additionally, fMRI studies with PTSD suggest that exposure to stressful stimuli decreases activations in the inferior parietal lobe, suggesting a dysregulation in this area (Liotti et al., 2000). Thus, when new mothers are exposed to parenting-related cues, such as infant cries,

those with more positive early maternal care experience may be better able to regulate their negative emotions, as indicated by greater parietal lobe activation.

Finally, the results should be considered in the light of the study's limitations. First, it is important to note that the findings do not imply a causal relationship between the recalled quality of early maternal care and later maternal brain responses. It is possible that both the mothers' report on their early caring experiences and their brain responses to infant stimuli are explained by a third common factor not measured in the current study. Future research using a longitudinal design including the influence of genetic factors as well as other environmental factors such as paternal care is needed to better isolate the effects of early experience on maternal behaviors in adulthood. Second, the PBI is a self-reflective instrument that is reported in retrospect (Parker, 1979). Although it may be argued that because childhood experience was reported retrospectively, such report may have been affected by other factors such as later life experience or current mental state (Hardt & Rutter, 2004), several studies have demonstrated that the maternal care scores of the PBI have long-term stability over a 20-year interval (Wilhelm, Niven, Parker, & Hadzi-Pavlovic, 2005) and correlate with adult attachment styles and risk for mood disorders (Manassis, Owens, Adam, West, & Sheldon-Keller, 1999; Parker, 1983; Wilhelm, Niven, Parker, & Hadzi-Pavlovic, 2005), suggesting that the instrument captures a stable and meaningful component of the mother's early experience. Third, although the PBI taps the entire span of childhood and adolescence, it does not include detailed information on the child's rearing environment including issues such as physical or sexual abuse. Other objective measures that tap maternal care at different time points across childhood and take into account various forms of parent-child interactions and possible neglect and abuse would strengthen the study. Fourth, despite the considerable overlap between the anatomical and functional findings of the VBM and

fMRI, the results should be interpreted with caution. The exact locations of the clusters were not identical for some of the overlaps, and this may have resulted from the difference between the two methods. Our VBM analysis results showed brain areas that were affected by exposure to low levels of perceived maternal care over time; whereas our fMRI analysis results represents the brain areas that were not only affected by low perceived maternal care but are also important for parenting-specific stimuli (i.e., infant cry). Fifth, mothers in the current study were middle-class backgrounds, well-educated and in stable relationships with healthy infants. Thus, the results may not generalize to higher risk mothers. Mothers at risk due to poverty, child abuse, and low social support may experience more striking changes in brain structure and function because of greater variability in their early life experiences. The effects of the early childhood experience on the brain may be more extensive or qualitatively different in such cases. For example, studies have found that women who experienced physical and/or sexual abuse in childhood had significantly smaller hippocampal volumes in adulthood (Vermetten, Schmahl, Lindner, Loewenstein, & Bremmner, 2006; Vythilingam et al., 2002). Abnormal patterns of activation in the amygdala and prefrontal cortex have also been reported in humans who suffer from PTSD (Damsa, Maris, & Pull, 2005). Finally, it could be interesting to examine whether the functional and structural changes in the brains of mothers with varying quality of early childhood care generalize to women who are not mothers as well as to men.

The findings point to several directions for future research. Future studies can reveal whether brain activation and structural differences among mothers who recalled having low maternal care in childhood would be associated with differences in maternal behavioral responses to their infants. These brain changes may be also critical to explain why mothers with adverse childhoods are more vulnerable to depression, anxiety and other mental health problems. It has been suggested that low

levels of perceived maternal care in childhood may be associated with depression (Mayes & Leckman, 2007) as well as with higher parental preoccupations and behaviors during the postpartum period (Leckman et al., 1999). Finally, future research may incorporate the findings of the current study to inform the construction of specific interventions for mothers with negative early experience in order to help improve the mother's well- being and attachment to the infant during the vulnerable period following childbirth and to improve the experience of the next generation.

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CHAPTER 2

MATERNAL BRAIN ACTIVATION AND MATERNAL SENSITIVITY IN THE POSTPARTUM: THE ROLE OF BREASTFEEDING

Introduction

Breastfeeding is a maternal behavior that enhances emotional bonds between mother and infant via close physical and social contact. Breastfeeding facilitates greater maternal sensitivity during interactions with infants, and reduces the risk of child maltreatment (Britton, Britton, & Gronwaldt, 2006; Feldman & Eidelman, 2003; Strathearn, Mamun, Najman, & O'Callaghan, 2009). In addition, the positive effects of breastfeeding on maternal sensitivity may further impact more positive outcomes in children. Several longitudinal studies using large samples have shown that breastfeeding predicts better neurological and cognitive competence beginning in early childhood and continuing through to adulthood (Golding, Rogers, & Emmett, 1997; Kramer et al., 2008). However, whether the neurobiological processes associated with maternal sensitivity are also linked with breastfeeding has not been studied in humans.

Nevertheless, several studies have explained potential mechanisms through which breastfeeding could impact the development of maternal sensitivity during the postpartum period. Close physical contact during breastfeeding can help mother-infant bonding. Mothers who provided skin-to-skin contact to their infants immediately after birth showed greater maternal sensitivity in during the first months of life (Klaus & Kennell, 1976). Breastfeeding mothers also exhibited more interactive behaviors, such as touching and gazing at their infants as well as more affectionate responses during feeding at one and three months postpartum in comparison to formula-feeding mothers (Dunn & Richards, 1977; Lavelli & Poli, 1998). Breastfeeding mothers were also

found to be more sensitive to infant cues during interactions at 3 month (Britton, Britton, & Gronwaldt, 2006). The higher levels of maternal sensitivity among breastfeeding mothers may help mothers to be more attuned to the infant's physical and mental needs, and greater maternal attunement in early infancy, in turn, contributes to the infant's social and emotional growth (R. Feldman, 2007b; R. Feldman & Eidelman, 2004).

Breastfeeding may influence maternal sensitivity through neurobiological mechanisms. Extensive animal research and recent human functional magnetic resonance imaging (fMRI) studies have identified several limbic and cortical areas related to maternal responsiveness to infant stimuli such as infants' cry or pictures (Lorberbaum et al., 2002; Swain, Lorberbaum, Kose, & Strathearn, 2007) In particular, the hypothalamic regions including the medial preoptic area (MPOA), located in the rostral hypothalamus, next to the bed nucleus of the stria terminalis (vBNST), are key areas for maternal motivation (Numan, & Insel, 2003). The MPOA projects to the mesolimbic dopaminergic system for reward processing and activations of the brain reward systems have been shown to play a key role in maternal motivation in both animal (Numan & Insel, 2003) and human (Bartels & Zeki, 2004) studies. These brain reward systems include the midbrain regions -- nucleus accumbens (NAcc), substantia nigra (SN), the ventral tegmental area (VTA), and periaqueductal gray (PAG). The mesocorticolimbic reward system also includes connections between the midbrain, amygdala, striatum (putamen, caudate, globus pallidus), anterior cingulate gyrus, and prefrontal cortex. Recent fMRI studies revealed that when mothers responded to parenting-related stimuli, particularly to their own baby related stimuli, increased brain activity was observed in the mesocorticolimbic dopaminergic system, including the hypothalamus, midbrain, amygdala, striatum, and prefrontal regions (Noriuchi, Kikuchi, & Senoo, 2004; Ranote et al., 2004; Strathearn, Li,

Fonagy, & Montague, 2008). Thus, activations in these regions may be be critical for a mother to perceive infant stimuli is in a more positive and rewarding manner and to develop a stronger bond with her infant.

Breastfeeding mothers may responds to their infant stimuli by increased levels of activations in the brain systems implicated in maternal motivation and reward. In an fMRI study with lactating rat mothers, greater activation in the reward-associated system, including hypothalamus, amygdala, midbrain (NA, SN, VTA, PAG), striatum (ventral pallidus, caudate, putamen), anterior cingulate, and medial and lateral prefrontal cortices were found during pup suckling (Febo, Numan, & Ferris, 2005; Ferris et al., 2005). Thus, it is possible that increased level of activation in the reward brain regions among breastfeeding mothers facilitates greater maternal sensitivity during mother-infant interactions. However, whether breastfeeding is associated with the maternal brain responses specifically related to maternal sensitivity has not been examined in human mothers.

In this study, we investigated the relationship between breastfeeding and the neural correlates of mother-infant bonding by comparing maternal brain responses to infant cry stimuli in breastfeeding and formula-feeding mothers at two time-points in the postpartum period: in the first month after birth and at 3 months postpartum. We compared the maternal brain responses of breastfeeding and formula-feeding mothers to their own baby cry is relative to control baby cry. Infant cry is highly salient stimuli that elicit maternal behaviors (Bowlby, 1969) and maternal brain responses (Swain, Lorberbaum, Kose, & Strathearn, 2007). We hypothesized that in response to their own baby-cry, mesocorticolimbic reward-associated regions would be more activated in breastfeeding mothers at one month postpartum. At 3 months postpartum, a second fMRI scan was conducted using the same own-infant vs. control infant cry stimuli, in order to explain changes in the effects of breastfeeding on the maternal

brain response across the early postpartum. Animal studies suggest that the effects of breastfeeding on the neurobiological systems during the first few weeks postpartum are most significant (Rosenblatt, 2002). Thus, we hypothesized that the differences in brain activations between breastfeeding and formula-feeding mothers would be most acute early postpartum and then decrease with time.

Finally, we examined whether the brain responses to infant stimuli in breastfeeding and formula-feeding mothers would be associated with standardized observer ratings of maternal sensitivity during mother-infant interactions at 3 months. During the third month of life, infants enter the social world (Stern, 1985). Thus, we selected this age for the observations of mother-infant interactions. Sensitive and synchronous interactions at three months have been found to predict the development of cognitive, social, emotional, and moral abilities across childhood and up to adolescence (Feldman, 2007a; Feldman, Greenbaum, & Yirmiya, 1999; Isabella & Belsky, 1991). In the current study, we predicted that breastfeeding mothers may show greater levels of maternal sensitivity at 3 months postpartum, and that this elevated sensitivity would be associated with brain activation. Furthermore, we hypothesized that the brain activations at the early postpartum period (1 month postpartum) compared to the later postpartum period (3 months postpartum) would be more strongly associated with later maternal sensitivity at 12-16 weeks postpartum.

Methods

Participants

Twenty biological mothers with full-term, healthy infants were recruited in postpartum hospital wards at Yale New Haven Medical Center. Mothers' age averaged 32.59 years (SD = 6.07; range = 18.58 to 39.75). All mothers were Caucasian and married or cohabiting. Exclusion criteria were birth complications, current psychiatric

diagnosis, and recent history of prescription medications within 2 weeks of the experiment. Informed consent was obtained from each participant according to procedures approved by the Yale University School of Medicine Human Investigations Committee.

Ten of the mothers were categorized as breastfeeding mothers, and they were breastfeeding exclusively at 2-4 weeks postpartum. The other ten of the twenty mothers were categorized as formula-feeding mothers and they were exclusively feeding formula to their infant at 2-4 weeks postpartum. The common reasons reported by the mothers for formula-feeding were care for multiple children, problems with milk supply or previous experience of pain while trying nursing. At 12-16 weeks postpartum, six out of the ten breastfeeding mothers were still exclusively breastfeeding. Two mothers reported the use of formula supplementation less then 4 times per day and two mothers reported formula supplementation more than 7 times per day; however, the main feeding method among these mothers remained as breastfeeding. All the mothers in the formula-feeding group were feeding formula exclusively at 12-16 weeks postpartum.

In each group, all mothers participated at both time points except for one breastfeeding mother at 2-4 weeks postpartum and one formula-feeding mother at 12-16 weeks postpartum. For the two mothers, only the demographic information, questionnaires and maternal sensitivity were collected because they were not available for brain imaging scans within the time window.

Procedure

Both home interview and brain imaging data were obtained twice: first, between 2-4 weeks postpartum and second, between 12-16 weeks postpartum. At both time points, a brain imaging study was conducted when mothers visited the research

center. A home interview was conducted when a researcher visited the mothers' house. During the home interview, demographic information and questionnaires were conducted. During 12-16 weeks postpartum home visit, mothers were asked to interact with their infants in a natural way and the mother-infant interactions were videotaped for five minutes. Measures

Home Interview

Beck Depression Inventory (BDI)

A self-report measure was used to assess mothers' depressed mood during the past week (Beck, Steer, Ball, & Ranieri, 1996). BDI consists of 21 items to assess various symptoms of depression. All the items were answered on a 0 to 3 scale. In the current study, scores ranged from 1 to 26 with a mean of 7.30 (SD=5.54) at 2-4 weeks postpartum and ranged from 0 to 20 a mean of 5.26 (SD=5.07) at 12-16 weeks postpartum.

Spielberger State/Trait Anxiety Inventory (STAI).

This instrument assess the individual's current state of anxiety (state) and general anxiety proneness (trait) (Spielberger & Vagg, 1984). All items were rated on a 4-point Likert scale with one being almost never true and four almost always true and the trait anxiety score was used in the present study. In the current study, scores ranged from 40 to 51 with a mean of 45.95 (SD=2.82) and ranged from 41 to 51with a mean of 46.85 (SD=3.01) at 12-16 weeks postpartum.

Coding

Mother-infant interactions were coded using the Coding Interactive Behavior (CIB) Manual (Feldman, 1998). The CIB is a global rating system for adult-child interactions with versions for newborns, infants, children, and adolescents. It consists

of 42 adult, child, and dyadic codes, each rated on a scale of 1 (a little) to 5 (a lot). These scales are then aggregated into several composites. The CIB has been used in multiple studies and has shown sensitivity to infant age, interacting partner, cultural variations, biological and social-emotional risk conditions, and the effects of interventions (Feldman et al., 2001; 2003, 2004a; Feldman & Klein, 2003). Maternal sensitivity assessed with the CIB has shown stability in repeated assessments across the first year (Feldman et al., 2004b), from birth to five years (Feldman & Eidelman, 2009), and from 3 months to 13 years (Feldman, in press), and sensitivity measured at 3 months predicted cognitive and social-emotional outcomes across childhood and up to adolescence.

The Maternal Sensitivity construct, used in this study, includes the following (averaged) codes (alpha = .91). Mother acknowledgement of child communications, vocal clarity, positive affect, gaze, appropriate range of affect, affectionate touch, resourcefulness, consistency of style, adaptation to child signals, and supportive presence. The scales included in the sensitivity construct define the maternal sensitive-responsive style and include both the typical post-partum human maternal behavior (gaze, affect, vocalizations, touch), a predictable style (consistency) and the adaptation of maternal behavior to the infant's cues (adaptation, resourcefulness when infant is distressed, appropriate range of affect, implying that mothers increase or decrease stimulation in accordance with infant signals, and supportive presence, assessing the degree to which mother presence provides a "regulatory" context for the child).

Brain imaging study

Image acquisition. High resolution T1-weighted anatomic magnetic resonance imaging (MRI) images (3D MPRAGE; TR = 2530; TE = 3.66; matrix size 256×256; 176 slices) were obtained using a Siemens trio 3T full-body scanner (Erlangen,

Germany). Anatomical T1-weighted echo-planar images (spin-echo; TR = 300ms; TE = 4ms; matrix size 64×64; 30 axial slices; 3.125mm in-plane resolution, 5mm thick) were acquired to be coplanar with the functional scans for spatial registration. Then, functional data was acquired (echo planar T2*-weighted gradient-echo, TR = 2000 ms, TE = 30ms, flip angle=80°, matrix size 64×64, 30 axial slices, 3.125mm in-plane resolution, 5mm thick).

fMRI stimuli. During recruitment, mothers were asked to record their own baby cry within the first 2 weeks postpartum using a portable digital audio recorder provided by the researchers. For own baby cry stimuli, mothers were asked to record it during diaper change, but not while the baby is in pain or hungry. For control baby cry stimuli, among samples of baby cries from mothers who did not participate in the current study, one with an average level of emotional intensity was selected. The levels of emotional intensity were rated by 7 adults on a 1-10 scale. Both own and control baby cry sounds, non-baby-cry-sound such as gurgles or grunts were removed and blocks of 30 second baby cry stimuli was made using a sound editing software (Cool Edit Pro Version 2.0, Syntrillium Software, Phoenix, AZ). To ensure that difference in brain responses to cries between breastfeeding and formula-feeding mothers are due to their different feeding practices not due to the different levels of emotional intensity of cries, we asked 10 adults (4 males) to rate the emotional intensity of each baby cry stimuli (1=none, 2= a little, 3= moderate, 4 = maximum). There was no differences of the emotional intensity levels between baby cries of breastfeeding mothers (M = 2.58, SD=.52) and formula-feeding mothers (M=2.69, SD = .53).

In the fMRI scanning at 2-4 week (Time 1) and 12-16 week (Time 2) postpartum, mothers heard cries through headphones. During each of two functional runs, participants heard ten sound blocks through padded headphones. Each sound

block was 30 seconds long and composed of (A) own baby-cry, and (B) control baby-cry. These stimulus blocks were arranged so participants heard each sound block a total of five times in the following order: ABBAB and then ABAAB. Each stimulus block was separated by a 10-sec rest period during which only background scanner noise could be heard. Before scanning, participants listened to samples of all sounds through headphones, so that the volume of the sounds could be adjusted at the level that the participants could hear the sounds clearly and the participants were more familiarized to the sounds to minimize surprise effects. During the scans, participants were asked to rate levels of emotional responses to each cry stimuli by using a button press (1=none, 2= a little, 3= moderate, 4 = maximum emotional response).

fMRI Data Preprocessing. Functional imaging data was preprocessed and statistical analysis was performed using Brainvoyager QX Software version 1.6 and 1.8 (Brain Innovation, Maastrict, The Netherlands). Functional runs were pre-processed using 3-dimentional motion correction based on trilinear interpolation by spatial alignment of all brain volumes to the first volume. One formula-feeding mother had a far greater than 3-mm translation in both runs at 2-4 weeks postpartum, data from the mother was excluded from further fMRI analyses. Slice scan-time correction was performed by sinc interpolation. After linear trend removal, a temporal high-pass filter was used to remove nonlinear drifts of 3 cycles or less per timecourse. Motion-corrected images were spatially smoothed using a Gaussian filter with a full-with half-maximum value of 6.25mm. Data from each subject was coregistered with each subject's high-resolution 3D anatomical data set, then transformed into standardized 3D Talairach coordinate space (Talairach and Tournoux, 1998) using piecewise linear warping. The functional data was resampled at 1 mm3 voxles.

Data analysis

The analysis of the BOLD signal was based on the block design protocol in response to own baby-cry sound relative to control baby-cry sound were analyzed using a the random effect general linear model (GLM). Contrast images were computed for each condition of each participant separately. Group effects (breastfeeding vs formula-feeding) were computed using the transformed contrast images in a conjunction of random effect GLM analysis and the group t maps was generated. Two specific contrasts (a, b) were conducted in the study: brain differences activation in response to own baby-cry minus control baby-cry between breastfeeding and formula-feeding mothers at 2-4 weeks postpartum (contrast a) and at 12-16 weeks postpartum (contrast b). Significance threshold for between-group differences was set at $p < .01$, and was corrected for multiple comparisons at the cluster level false-positive rate (α) of 0.05 (Forman et al., 1995; Goebel, Esposito, & Formisano, 2006). Thus, the uncorrected activated clusters were rejected if they were smaller than 1188 mm3 (contrast a) and 1324 mm3 (contrast b). For the analysis of the mesocorticolimbic reward-associated areas as a priori regions of interest, the regions were first identified on a statistical map after the group comparison at $p <.05$ (uncorrected). In order to correct for multiple comparisons, we applied a small volume correction (SVC) method for false discovery rate (FDR) error at $q <.05$ and a cluster threshold of 162mm3 was used to all the identified regions of interest.

In order to test significant correlations of maternal sensitivity with brain activations at 2-4 weeks and 12-16 weeks postpartum across two groups, we performed a random effect analysis of covariance between brain responses to own minus control baby-cry sound and maternal sensitivity at a significance level of $p<.05$, corrected for multiple comparisons at the cluster level. The correlation analysis was limited only to the brain regions already identified to exhibit significant differences in

brain activations between the breastfeeding and formula-feeding groups. A correction for multiple testing was not employed since there is only one primary analysis based on one hypothesis (Perneger, 1998). The hypothesis is that brain activations and maternal sensitivity are positively correlated because we tested correlation only in areas which had significantly higher activations among breastfeeding mothers and the maternal sensitivity were significant higher among the breastfeeding mothers.

Results

Description of Breastfeeding and Formula-feeding groups

Mothers from the two groups were well-matched in demographic background. Mothers in the breastfeeding group and formula-feeding group had no mean differences in age, handedness, parenting experience, the number of children they have, delivery method and educational level (see Table 2.1). The mean and standard deviation of the levels of depression (BDI) and train anxiety (STAI), and maternal sensitivity are presented in Table 1. The two-way between-subjects analysis of variance was conducted to test the group effect (breastfeeding vs formula-feeding) and the time (2-4 weeks vs 12-16 weeks postpartum) on the depression, and anxiety levels among all mothers. No significant main effect for the group, and time, and no interaction between the two factors were found.

The t-test analysis revealed that at 12-16 weeks postpartum, maternal sensitivity was higher among breastfeeding mothers than formula-feeding mothers, $t(18)=2.73$, $p<.05$ (see Table 2.1). To confirm that the depression and anxiety levels were not related to the maternal sensitivity scores, we conducted the zero-order correlation analysis, and maternal sensitivity was not significantly correlated with BDI and trait anxiety scores. Among breastfeeding mothers at 12-14 weeks postpartum, a few mothers reported that they occasionally formula fed their infants. However, the

frequency of formula-feeding was not significantly associated with maternal sensitivity among the breastfeeding mothers.

Table 2.1. Comparison in Breastfeeding vs Formula-feeding mothers

	Breastfeeding		Formula-feeding	
	n=10		n=10	
	Mean (SD)		Mean (SD)	
Maternal Age	33.45 (4.09)		31.73 (7.71)	
First-born/later-born	3/7		2/8	
# of older children	1.00 (.94)		1.70 (1.77)	
Infant Gender ratio (M/F)	6/5		5/6	
Vaginal/C-section delivery	8/2		9/1	
Maternal Handedness (L/R)	1/9		1/9	
Maternal Educational level (in years)	17.90 (1.67)		15.50 (3.31)	
	2-4 weeks	12-16 weeks	2-4 weeks	12-16 weeks
BDI	5.90 (2.72)	4.89 (4.08)	8.70 (7.27)	5.60 (6.04)
Trait Anxiety	45.40 (2.37)	46.70 (2.83)	46.50 (3.24)	47.00 (3.33)
Maternal Sensitivity*	--	4.51 (0.43)	--	3.74 (0.78)

* $p < .05$

Behavioral Ratings

Mothers' subjective ratings of emotional response while listening to the cries in the scanner were analyzed using a repeated-measures ANOVA with Group (breastfeeding, formula-feeding) as a between-subjects factor; Cry Type (own baby,

control baby) as within-subjects factor, and Time (2-4 weeks, 12-16 weeks postpartum). The ANOVA analysis revealed that the main Cry effect showed a trend [$F(1,13) = 3.93$, $p<.10$, $\eta 2 = .23$]. At 2-4 weeks postpartum, formula-feeding mothers rated their own baby cry as more emotionally arousing than control baby cry, $t=2.24$, $p<.05$, whereas breastfeeding mothers did not rate the two type of cries differently (see Figure 2.1). However, at 12-14 weeks postpartum, mothers across two groups did not rate their own and control baby cries differently.

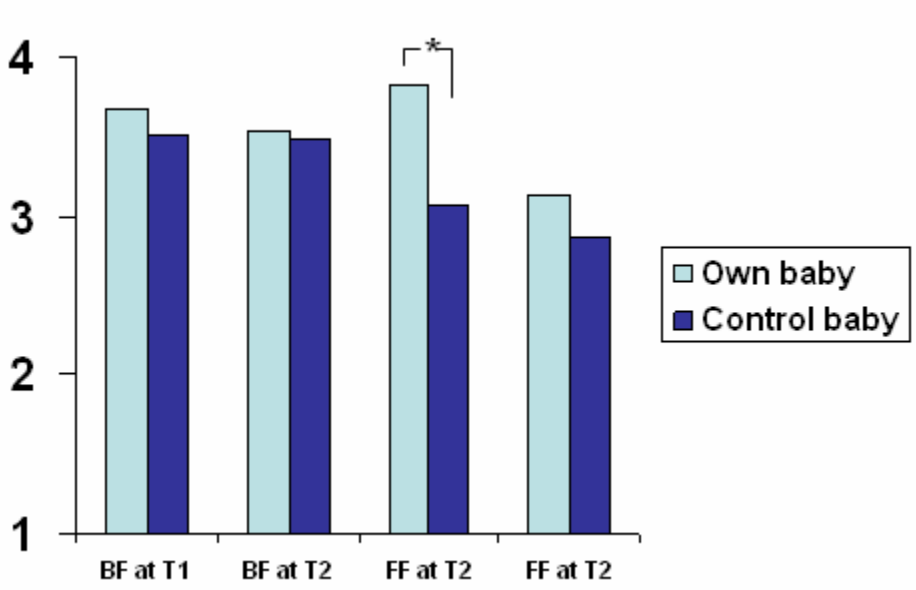


Figure 2.1. Ratings of emotional responses to own baby cry and control baby cry stimuli while in the scanner. BF = Breastfeeding Group; FF=Formula-feeding Group; T1 = 2-4 weeks postpartum; T2 = 12-16 weeks postpartum. * indicates a significant difference in the ratings for own baby cry and control baby cry among formula-feeding mothers at 2-4 weeks postpartum, $p<.05$

Brain responses to Own verse Control baby-cry at 2-4 weeks postpartum

At 2-4 weeks postpartum , the contrasts of own baby-cry versus control baby-cry between the two groups of mothers revealed that the breastfeeding mothers showed a greater BOLD signal in several brain regions in response to own baby-cry sound compared to formula-feeding mothers. Activations in the key parts of the maternal motivation systems in particular were greater among the breastfeeding mothers; the regions included bilateral thalamus, periaqueductal gray, left globus pallidus, right putamen, caudate, right amygdala, left anterior cingulated gyrus, prefrontal cortex (see Table 2.2). Bilateral Superior temporal, middle temporal gyrus, cuneus, as well as right fuiform gyrus and left precunues were more activated in response to own baby-cry among breastfeeding mothers more than among formula-feeding mothers (see Table 2.2, Figure 2.2). However, no brain areas were found to exhibit significantly greater BOLD activations among the formula-feeding mothers in response to own baby-cry (minus control baby-cry) at the level of significance, $p<.01$ (corrected) and in regions of interests at $p<.05$ (corrected).

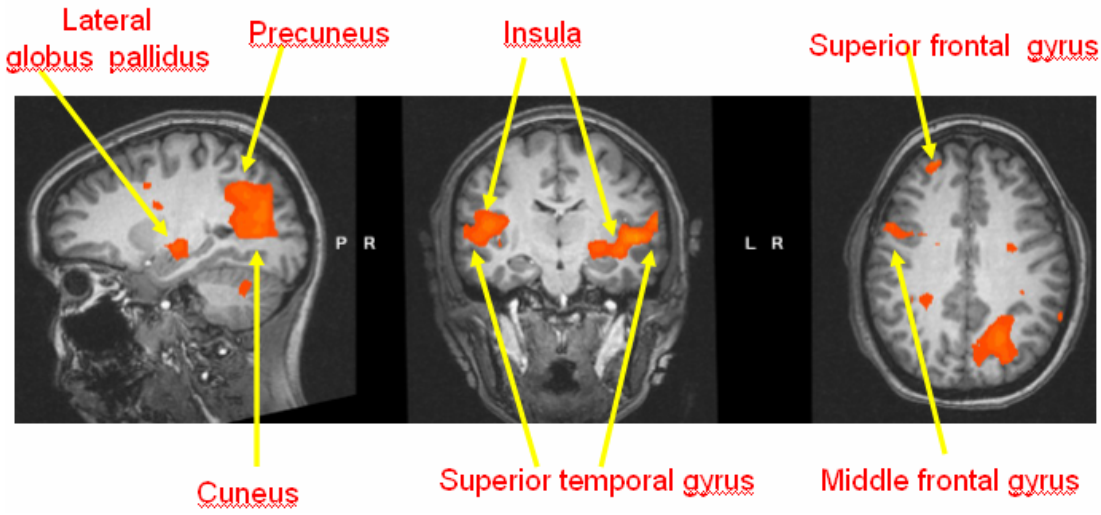


Figure 2.2. Areas of activation in the contrast (own baby cry minus control baby cry) at 2-4 weeks postpartum. Areas in red shows greater activations in breastfeeding group relative to formula-feeding group ($p<.05$ for illustration).

Table 2.2. Activation results of the group comparison in the contrast of 'Own baby-cry' minus 'Control baby-cry' at 2-4 weeks postpartum

Area of Activation	BA	Side	t score	cluster size	Tailarach coordinates x	y	z
Breastfeeding > Formula-feeding mothers							
Superior frontal gyrus	9	R	3.53	92	23	50	28
Middle frontal gyrus	10	L	3.21	56	-37	46	17
Anterior cingulate gyrus		L	4.13	104	-11	19	19
Superior temporal gyrus	13	R	3.59	403	58	-20	8
	22	L	4.24	342	-61	-40	7
Insula	43	R	3.76	145	57	-5	15
	13	R	3.43	72	33	16	17
	13	R	3.38	79	34	-68	37
	13	R	6.01	2815	44	-21	13
	13	L	5.74	2475	-43	-16	3
Middle temporal gyrus	22	R	3.86	386	50	-47	8
Fusiform gyrus	37	R	4.32	449	52	-48	-7
Precuneus	31	L	3.94	1739	-18	-60	28
Cuneus	17	R	3.82	252	13	-76	10
	18, 30	L	4.14	2831	-19	-66	16
	17	L	3.67	201	-3	-81	12
Lateral globus pallidus		L	3.32	151	-23	-15	-2
Putamen		R	4.16	810	22	0	14
Head of caudate[a]		L	2.76	575	-25	-2	29
		R	3.66	539	19	-2	21
Amygdala		R	4.84	516	21	-4	-5
Thalamus (Hypothalamus) [a]		R	2.9	119	5	-9	-1
Thalamus		L	3.07	430	-9	-5	3
PAG (Periaqueductal gray)[a]		R/L	2.4	411	1	-32	-5
Cerebellum		R	4.08	347	29	-56	-37
		L	4.56	716	-28	-57	-26

p<.01: corrected for multiple comparisons
[a] p <.05: corrected for multiple comparison

Brain responses to Own verse Control baby-cry at 12-16 weeks postpartum

At 12-16 weeks postpartum, in response to own baby-cry (minus other baby-cry), greater brain activations in the parts of the maternal motivation system such as right middle cingulate gyrus (caudate body), bilateral thalamus, right VTA, found in the breastfeeding mothers relative to formula-feeding mothers (see Table 2.3, Figure 2.3). However, formula-feeding mothers showed greater activations in cortical structures that had been more activated in the breastfeeding mothers at 2-3 weeks postpartum including bilateral superior frontal gyrus, left precuneus, cuneus, fusiform gyrus, and putamen. Left middle and inferior occipital gyrus were also more activated among formula-feeding mothers in response to own baby-cry (see Table 2.3, Figure 2.3).

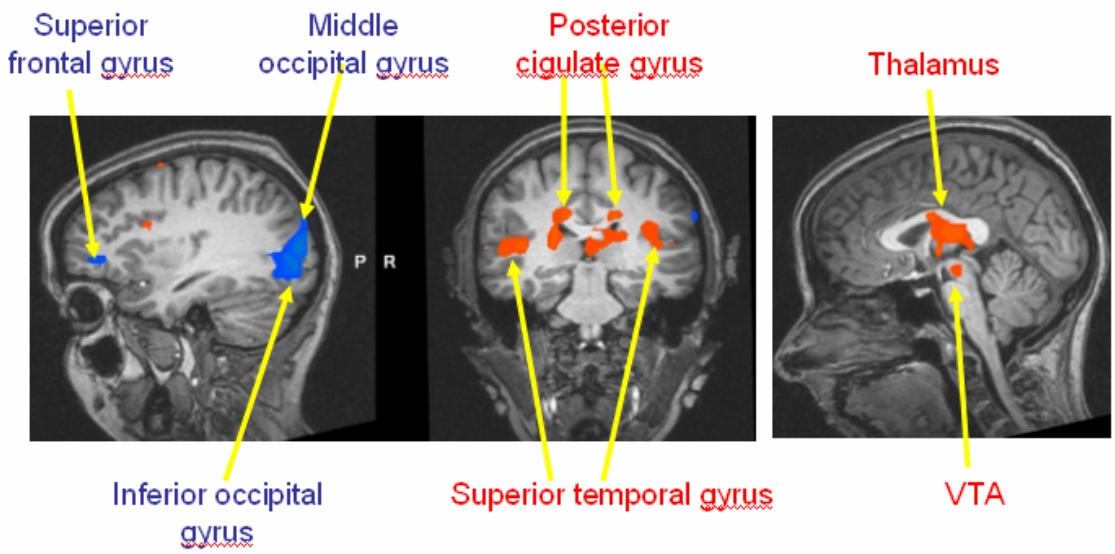


Figure 2.3. Areas of activation in the contrast (own baby cry minus control baby cry) at 12-16 weeks postpartum. Areas in red shows greater activations in breastfeeding group relative to formula-feeding group; Areas in blue shows greater activations in formula-feeding group relative to breastfeeding group ($p<.05$ for illustration).

Table 2.3. Activation results of the group comparison in the contrast of 'Own baby cry' minus 'Control baby cry' at 12-16 weeks postpartum

Area of Activation	BA	Side	t score	cluster size	Tailarach coordinates x	y	z
Breastfeeding > Formula-feeding mothers							
Superior temporal gyrus	22	R	4.78	1653	49	-17	8
	22	L	3.96	707	-56	-12	5
Insula	13	L	3.78	82	-36	-22	20
Middle cingulate cortex (caudate body)		R	4.42	1421	20	-3	24
Posterior cingulate gyrus	23	L	3.75	67	-15	-27	29
	23	R	3.49	86	15	-26	29
Thalamus		R	4.04	1030	7	-16	13
		R	4.76	1463	20	-18	17
		L	4.08	1331	-7	-19	14
VTA[a]		R	3.22	430	3	-18	-10
Formula-Feeding > Breastfeeding mothers							
Superior frontal gyrus	8	R	3.58	133	12	52	37
	10	L	3.6	68	-15	54	10
Cuneus	19	L	3.25	164	-11	-87	28
Precuneus	7	L	3.91	218	-14	-60	55
Fusiform gyrus	37	L	3.18	93	-41	-66	3
Middle occipital gyrus (V3)	19	R	5.51	1443	36	-79	9
Inferior occipital gyrus (V3)	19	R	4.75	891	37	-76	-4
Putamen[a]		L	3.17	443	-14	9	-1
Cerebellum		L	3.52	59	-8	-60	-34
		R	4.06	385	15	-54	-41

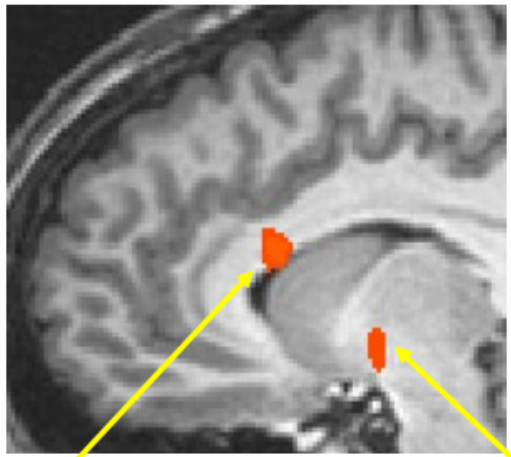
p<.01: corrected for multiple comparisons
[a] p <.05: corrected for multiple comparison

Relationships between neuroimaging and maternal sensitivity

The random effect analysis of covariance revealed that the differences in maternal sensitivity in two groups were correlated with maternal brain responses to their baby-cry stimuli. First, many of the brain areas that showed greater activations

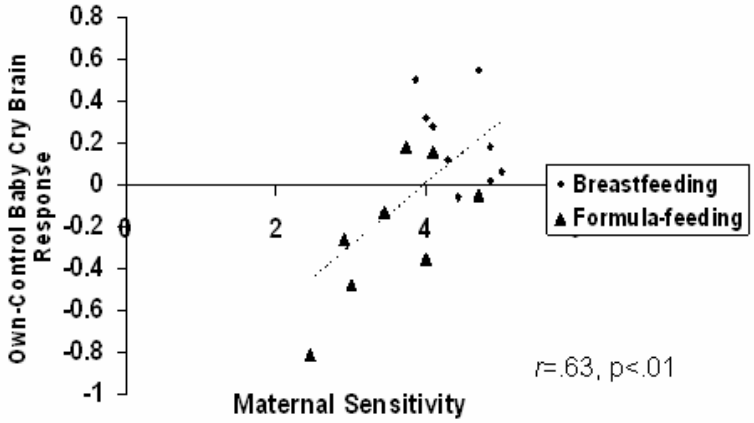
among breastfeeding mothers at 2-4 weeks postpartum was significantly correlated with maternal sensitivity at 12-14 weeks postpartum. Particularly, maternal sensitivity was positively correlated with activations in the left hypothalamus ($r=.61$, $p<.01$), the right amygdala ($r=.56$, $p<.05$); the left anterior cingulate ($r=.63$, $p<.01$), the insula, bilaterally, (right: $r=.61$, $p<.01$; left: $r=.61$, $p<.01$), and the right superior frontal gyrus ($r=.62$, $p<.01$). Activations in the right middle temporal gyrus ($r=.66$, $p<.005$), the left precuneus ($r=.68$, $p<.005$), and the cuneus (right: $r=.51$, $p<.05$; left: $r=.57$, $p<.05$) the PAG ($r=.54$, $p<.05$) as well as, the cerebellum (right: $r=.57$, $p<.05$; left: $r=.66$, $p<.005$) at 2-4 weeks postpartum were also positively correlated with greater maternal sensitivity among all mothers (see Figure 2.4), when mothers were responding to own baby-cry. However, at 12-16 weeks post partum activations of a fewer brain regions were significantly correlated with maternal sensitivity levels. Maternal sensitivity levels were positively correlated with activations only in the superior temporal gyrus (right:$r=.62$, $p<.005$; left: $r=.53$, $p<.05$).

Figure 2.4. Scatter plots showing the strong positive relationship between brain responses to own baby cry (minus control baby cry) at 1 month postpartum and maternal sensitivity at 3 months postpartum. (a) right superior frontal gyrus (x,y,z = 23, 50, 28; r=.62, p<.01), (b) left anterior cingulate gyrus (x,y,z = -11, 19, 19; r=.63, p<.01), (c) PAG (x,y,z = 1, -32, -5; r=.54, p<.05)



(x,y,z=-8,-7,-3)

a.


Own-Control Baby Cry Brain Response
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
0
2
4
Maternal Sensitivity
Breastfeeding
Formula-feeding
r=.63, p<.01

b.

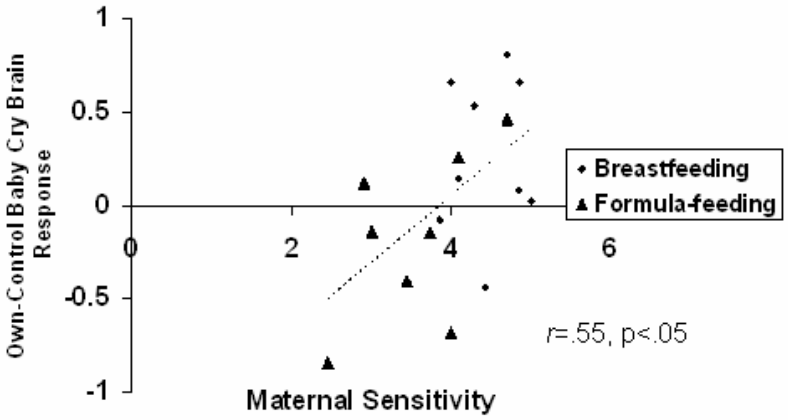
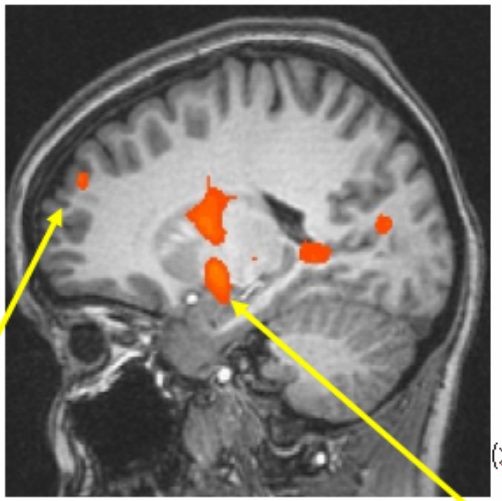
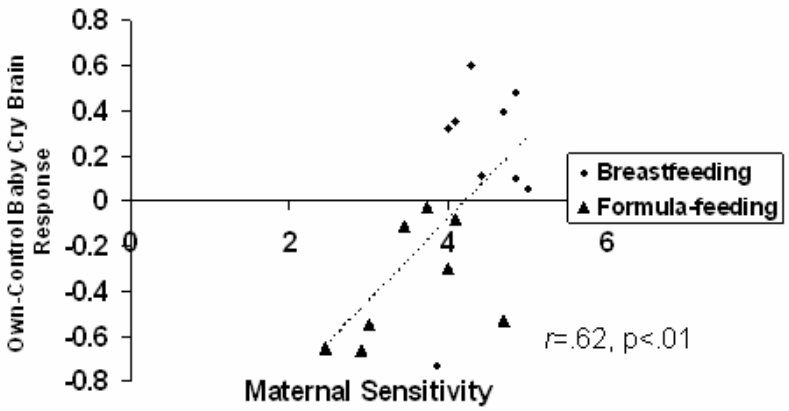

Own-Control Baby Cry Brain Response
1
0.5
0
-0.5
-1
0
2
4
6
Maternal Sensitivity
Breastfeeding
Formula-feeding
r=.55, p<.05

Figure 2.4. (Continued)



(x,y,z=-19,-42,4)

c.



d.

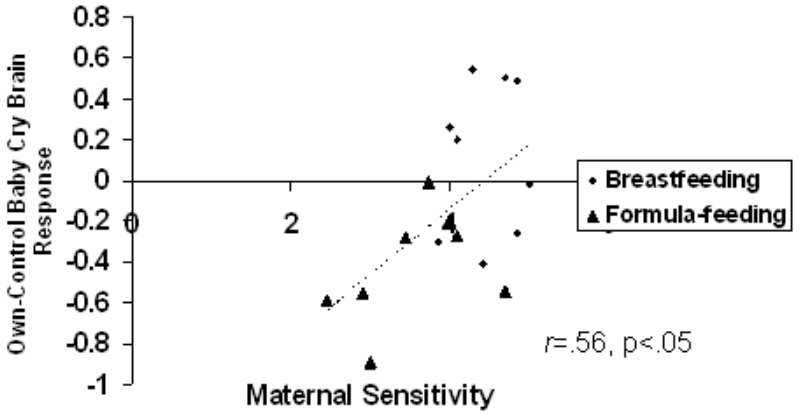
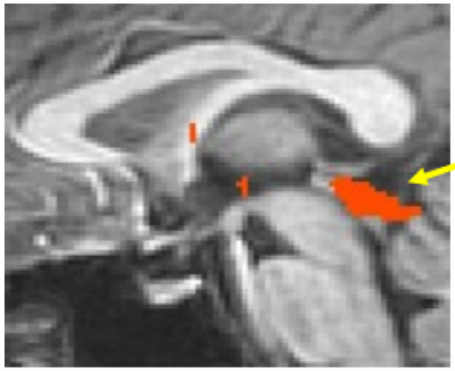
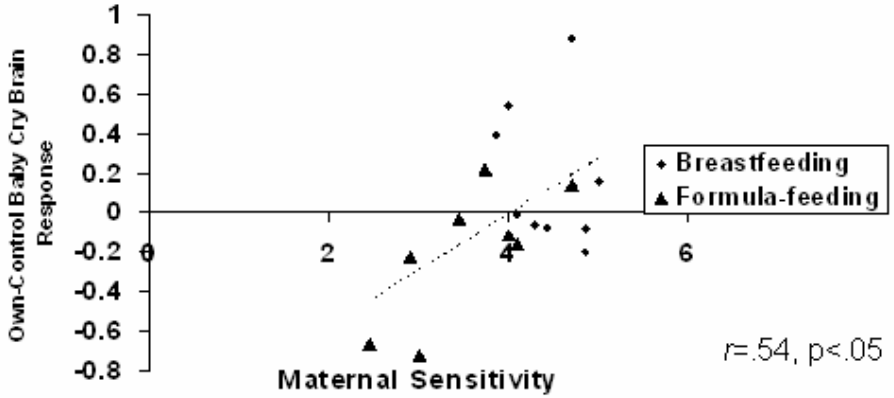


Figure 2.4. (Continued)

e.



(x,y,z=-1,32,-5)



Discussion

The present longitudinal study demonstrates the relationship between breastfeeding and maternal brain responses to own baby stimuli at two time-points across the postpartum period. During the first postpartum month, several limbic and cortical brain regions, particularly the mesocorticolimbic dopaminergic circuits for reward and maternal motivation, were more active among breastfeeding mothers as compared to formula-feeding mothers when they listened to their own baby versus a control baby cry. At 3 months postpartum, although brain regions such as superior temporal gyrus insula, thalamus, and VTA were more activated among breastfeeding mothers, several brain areas, including precuneus, superior frontal gyrus, fusiform gyrus, putamen, and occipital gyrus, were more activated among formula-feeding mothers in response to their own baby cry. Furthermore, among the brain regions that showed more activation in breastfeedfeeding mothers, the levels of brain activations in responses to own baby cry at the first month postpartum were correlated with greater maternal sensitivity observed during mother-infant interactions at the three to four months postpartum among all the mothers. These findings may provide understanding of the dynamic relationships between breastfeeding, maternal brain response, and maternal behaviors as they unfold across the early postpartum period.

As predicted, brain areas that showed differences between breastfeeding mothers were regions that have previously been found as important for maternal love and parenting behaviors. The mesocorticolimbic areas, which are the brain systems for motivation and reward, were especially more active among breastfeeding mothers when responding to their own infant cry stimuli. These regions included hypothalamus, PAG, putamen, caudate, globus pallidus, anterior cingulate gyrus, superior/middle frontal gyrus in the first month after childbirth and the VTA, PAG, caudate body, cingulate cortex at 3 months postpartum. Rodent studies have pointed

to the medial preoptic area (MPOA) located in the rostral hypothalamus and the reward circuits along the mesolimbic dopaminergic pathways as central for the emergence of maternal behavior (Mello & Villares, 1997). Lesions in these pathways severely impair the expression of maternal behaviors (Numan, 2007; Numan & Smith, 1984). Several recent fMRI studies in human mothers also suggest the importance of these reward areas in response to infant stimuli. At one-to-two months postpartum, mothers showed higher activation in the MPOA and NAcc in response to infant cry sounds compared to other emotionally neutral vocal sounds (Lorberbaum et al., 2002). Other fMRI studies investigating maternal brain responses to visual stimuli of own baby versus control baby also found greater activations in reward circuits. The activation of midbrain areas was higher when mothers saw pictures of their own children as compared to control children who were 9 months to 6 years of age (Bartels and Zeki, 2004). At 4-8 months postpartum, striatum, globus pallidus, and midbrain were more active to own baby videos (Ranote et al., 2004); at 5-10 months postpartum, prefrontal cortex, striatum, hypothalamus, and cingulate cortex, and midbrain were more active in response to own versus control baby pictures (Strathearn, Li, Fonagy, & Montague, 2008); and at 16 months postpartum, prefrontal cortex, putamen, and hypothalamus were more active when mothers watched own baby videos (Noriuchi, Kikuchi, & Senoo, 2004). Thus, increased activations of the mesocorticolimbic reward areas among breastfeeding as compared to formula-feeding mothers may be associated with the mother's affectionate attachment to her infant and her warmth and positive feelings toward the child.

In addition to the hypothalamus and the other parts of the reward circuit, amygdala activations were also greater at 2-4 weeks postpartum among breastfeeding mothers in response to own baby cry. Amygdala activations has been found to be important for maternal behaviors in rodents and nonhuman primates (Kling & Steklis,

1976; Sheehan, Paul, Amaral, Numan, & Numan, 2001). It should be noted that activations of the amygdala, particularly the medial amygdala (MeA), inhibits maternal responses to pup in virgin rats. However, animal studies suggest that once mothers are primed by postpartum hormones or are exposed to pup stimuli, the projections from the amygdala for the avoidant responses to pups is inhibited and the direct output of the amygdala to MPOA may promote approach maternal behaviors (Mayes, 2006). Thus, once mothers learned maternal behaviors and the positive and reward values of infant stimuli, the amygdala activation may become more important to activate the learned reward values. In fact, human studies show that amygdala is related to the processing of positive stimuli such as happy facial expressions (Zald, 2003). Mothers' greater amygdalar activations in response to own baby stimuli vs control baby stimuli during the postpartum period have also been found in other fMRI studies (Lorberbaum et al., 2002; Noriuchi, Kikuchi, & Senoo, 2004; Strathearn, Li, Fonagy, & Montague, 2008).

In the first postpartum month, breastfeeding mothers showed greater activations in several cortical regions in responses to own baby cry. These brain areas serve an important function for the development of parenting in humans and mammals (Swain & Lorberbaum, In Press; Swain, Lorberbaum, Kose, & Strathearn, 2007). Previous fMRI studies demonstrated that the prefrontal cortex, superior temporal gyrus, middle frontal gyrus, and fusiform gyrus were activated when mothers attended to baby cries (Lorberbaum et al., 2002; Swain et al., 2004) or saw baby pictures and video clips (Bartels & Zeki, 2004; Lenzi et al., in press; Noriuchi, Kikuchi, & Senoo, 2004; Ranote et al., 2004). In several fMRI studies, mothers showed activation in superior temporal sulcus, insula, and anterior cingulate gyrus when presented with own versus control baby stimuli (Nitschke et al., 2004; Noriuchi, Kikuchi, & Senoo, 2004; Ranote et al., 2004; Strathearn, Li, Fonagy, & Montague, 2008). Insula, medial

frontal gyrus, anterior cingulate gyrus and superior and middle temporal gyrus are involved in the processing of both vocal emotional stimuli of others (Ethofer, Pourtois, & Wildgruber, 2006; Johnstone, van Reekum, Oakes, & Davidson, 2006). These regions including the inferior frontal gyrus, superior temporal sulcus, insula, fusiform gyrus, inferior parietal lobule and temporal poles also appear important for understanding the emotional states of others (Iacoboni & Dapretto, 2006; Völlm et al., 2005). Thus, higher activation in these brain regions among breastfeeding mothers may assist them to understand their infants' emotional state and guide more appropriate reactions to the infants' needs at 2-4 weeks postpartum.

By 3 months postpartum, the patterns of brain activations of breastfeeding and formula-feeding mothers changed significantly relative to the 1 month postpartum. In response to own versus control baby cry, while most of the reward associated regions such as VTA and caudate body remained more active among breastfeeding mothers, superior frontal gyrus (an area for higher levels of cognition), precuneus and fusiform gyrus (an area for social information processing) and middle occipital gyrus (areas for processing vocal emotional stimuli) became more active among formula-feeding mothers (Johnstone, van Reekum, Oakes, & Davidson, 2006). Perhaps the shift across time was related to the increased amount of interactions with their infants mothers gained during this period. Around 1 month postpartum, infants showed limited responses to social stimuli. However, by the third to forth month postpartum, the infant becomes a social partner and interactions include smiling, eye-contact, cooing vocalizations, and body movements (Papousek & Papousek, 2002). As a result, the mother's attachment with and feeling about her infant may dramatically increase as the infant becomes a more socially responsive organism (Mercer, 1985). Thus, as both formula-feeding and breastfeeding mothers spend more time with their infants, the

mother's emotional bond with the infants increase and the maternal brain activations in response to infant stimuli became less affected by the mode of feeding.

The idea that the greater maternal brain activations among breastfeeding mothers may facilitate a greater sensitivity to the infant earlier on is also supported by the findings of the significant correlation between brain activations and observed maternal sensitivity in the current study. As predicted, breastfeeding mothers exhibited higher maternal sensitivity during interactions at 3 months compared to formula-feeding mothers. In most brain regions that showed greater activations in breastfeeding mothers in the first postpartum month, the BOLD responses to own baby cry (minus control baby cry) were correlated with higher maternal sensitivity at 3 months both in breastfeeding and formula-feeding mothers. In particular, maternal sensitivity correlated with activations in parts of the mesocorticolimbic systems for maternal motivation and reward including right superior frontal gyrus, left anterior cingulate gyrus, left amygdala, and right hypothalamus, and PAG. The brain regions for emotional and self-relevant information processing such as right middle temporal gyrus, precuneus, and cuneus at 2-4 weeks postpartum were also positively correlated with maternal sensitivity. On the other hand, only a few brain regions which showed greater activations in breastfeeding mothers at 12-16 weeks postpartum were significantly correlated with maternal sensitivity across two groups. Given the positive correlations between maternal brain activations and sensitivity among mothers of both groups, maternal brain activities at the first postpartum month may play an especially important role in predicting the mother's sensitive response to her infant at 3-4 months postpartum among both breastfeeding and formula-feeding mothers.

The relationships between breastfeeding, greater activations in hypothalamus and the mesocorticolimbic reward-associated pathways, and later sensitive maternal

behaviors may be mediated by hormones that are involved in nursing, such as oxytocin and prolactin. Oxytocin not only aids in the release of milk (Rosenblatt, 2002) but also facilitates maternal brain responses by enhancing the learning and maintenance of pup stimuli as positive stimuli through the activation of the brain reward circuits. Oxytocin receptors are highly concentrated in the mesocorticolimbic pathways, areas related to reward and maternal motivation both in animals and humans (Gimpl & Fahrenholz, 2001). Febo, Numan and Ferris (2005) found that injecting oxytocin into a rat mother's brain resulted in increased responses in the mesocorticolimbic pathyways such as MPOA, caudate-putamen, VTA, cingulated cortex, temporal cortex, and prefrontal cortex. Thus, higher activations in the hypothalamus and the reward circuits at 2-4 weeks postpartum among breastfeeding mothers may be associated with increased oxytocin levels in response to infant stimuli. Furthermore, higher levels of oxytocin across pregnancy and during the postpartum month were associated with sensitive maternal behaviors (Levine, Zagoory-Sharon, Feldman, & Weller, 2007). Thus, oxytocin may play a key role in facilitating maternal care and mother-infant bonding by increasing maternal brain responses to infant stimuli. However, the effects of maternal brain activations that are linked to oxytocin release on maternal behaviors may be reduced from the first month to later months of the postpartum period. Animal studies suggest that oxytocin may play a more critical role for the initiation of the bonding (Numan & Insel, 2003; Rosenblatt, 2002); however, the effects of hormones on maternal behaviors may decrease over time and the continuous experience of interacting with pups become important for the maintenance of maternal motivation (Fleming, O'Day, & Kraemer, 1999). Thus, it is possible that brain responses and maternal behaviors may be increasingly affected by strong emotional bonds with infants developed through interactions. In contrast, the

mother's experience of the first few weeks under the greater influence of hormones may be critical to shape the basis of mother-infant bonding and maternal sensitivity.

The higher levels of hormones such as oxytocin and prolactin among breastfeeding mothers may promote greater brain responses to infant stimuli and sensitive maternal behaviors by reducing stress responses. This may also be related to the finding that at 2-4 weeks postpartum, formula-feeding mothers rated their baby cries as more emotionally arousing compared to control baby cry whereas breastfeeding mothers did not. Thus, formula-feeding mothers may feel more anxious in response to their infant cry and this may be further associated with lower levels of brain activations relative to breastfeeding mothers. Animals studies suggest that lactating rats have higher oxytocin levels and show reduced stress responses (Neumann, Torner, & Wigger, 2000). Brain prolactin receptors also mediate anxiolytic effects in lactating female rats (Neumann, Torner, & Wigger, 2000). Breastfeeding mothers showed increased levels of plasma oxytocin after holding their baby, and the mothers with the increased oxytocin levels had attenuated physiological stress reactivity (Light et al., 2000). Thus, higher levels of oxytocin and prolactin among breastfeeding mothers may reduce negative responses to infant stimuli and decrease parenting-related anxiety and stress during the early postpartum period. However, because we did not measure oxytocin and prolactin directly, these hypotheses are only tentative and future studies measuring oxytocin levels or the effects of intranasal administration of oxytocin in mothers are needed to test these effects.

There are several factors that limit the interpretation of the findings and should be examined in future research. First, in the present study, breastfeeding and formula-feeding mothers were matched for similar race, age, family and socio-economic background. However, studies showed that breastfeeding mothers tend to be older, more educated, with higher socioeconomic status, and often have more social supports

(Feldman & Eidelman, 2003). Also our sample included some first-time mothers. Although their maternal sensitivity was not significantly different from ones of the experienced mothers in the current study, there is evidence for the relationships between parenting experience and maternal behaviors (Thoman, Turner, Leiderman, & Barnett, 1970). Thus, a larger, more diverse, more representative sample would enable us to more readily generalize our findings. Another factor, personality, may affect choice of feeding styles, and thus contribute to differences observed between breastfeeding and bottle-feeding mothers. Mothers who received better quality maternal care in their early childhood may respond differently to their newborns.

The dynamic relationship between mother's brain activations, parenting behaviors, and breastfeeding requires much further research. Our findings raise the intriguing possibility that greater maternal brain responses to own baby stimuli at the first few weeks of a child's life may promote maternal sensitivity via rewards associated with infant stimuli throughout the early postpartum. Breastfeeding at the first month postpartum enhances both maternal brain responses to infant stimuli and maternal sensitivity. The findings may shed light on the development of the interventions for mothers to develop close emotional bonds with their infants by promoting breastfeeding during the first few weeks postpartum. Future research needs to examine whether the differences in brain response and parenting behaviors between breastfeeding and formula-feeding mothers bear long-term consequences as were for the development of infants and children.

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CHAPTER 3

THE PLASTICITY OF PARENTAL BRAIN: LONGITUDINAL BRAIN CHANGES IN MOTHERS AND FATHERS DURING THE POSTPARTUM PERIOD

Introduction

Maternal care during the first year provides the foundation for the infant's neurobiological, socioemotional and cognitive development (Bornstein, 2002; Champagne et al., 2004). Animal studies identified several brain areas as important for the initiation and maintenance of maternal pup-directed behaviors. For example, lesion studies have shown that the medial preoptic areas (MPOA), located in the rostral hypothalamus, and its connections with the mesolimbic dopamine system for reward processing play a critical role in maternal motivation (Numan & Insel, 2003; Swain et al., 2004). Similarly, the thalamus, the parietal cortex, and brainstem serve an important functions for the processing of infant-related sometosensory information such as smell, touch, and vocalization (Xerri, Stern, & Merzenich, 1994); and the prefrontal cortex is also involved in integrating these information and monitoring parental behaviors (Afonso, Sison, Lovic, & Fleming, 2007). Recent functional magnetic resonance imaging (fMRI) brain studies in human mothers report greater activations in many of these brain regions in response to infant-related stimuli, supporting the role of these brain areas for the development and expression of parenting behaviors (reviewed in Swain, Lorberbaum, Kose, & Strathearn, 2007).

The increased activations of these brain regions during the early postpartum period may be further accompanied by structural changes in the brain. Animal studies have shown that increased interactions with pups over time during the early postpartum period lead to structural changes in the brain. For rat mothers, the amount

of experience interacting with their pups correlated with the neuronal development of the hypothalamus (MPOA), basolateral amygdala, parietal cortex and prefrontal cortex (Featherstone, Fleming, & Ivy, 2000; Fleming & Korsmit, 1996; Kinsley et al., 1999; Lonstein, Simmons, Swann, & Stern, 1998; Xerri, Stern, & Merzenich, 1994). In fathers, although the brain systems that regulate paternal behaviors is less well investigated , in a study on marmoset males, fatherhood was associated with higher density of the prefrontal cortex (Kozorovitskiy, Hughes, Lee, & Gould, 2006). Based on these animal studies, it is reasonable to expect that similar structural changes would occur in the brain of human parents during the postpartum period. However, this hypothesis has not been studied in human mothers or fathers.

In search for understanding the neuroplasticity related to parental behaviors during the early postpartum period, this longitudinal MRI study examined structural changes in human parents' brain from 2-4 weeks to 3-4 months postpartum. We employed the voxel-based morphometry (VBM) method to identify subtle and regionally specific changes in grey matter volumes over the first postpartum months (Mechelli, J, Friston, & Ashburner, 2005). To obtain a comprehensive understanding of the plasticity of parental brain, we compared the changes in grey matter volumes in primiparous and multiparous mothers and in primiparous and multiparous fathers.

Methods

Participants

Thirty-four biological parents of full-term and healthy infants were recruited in postpartum hospital wards at Yale New Haven Medical Center. These parents fell into four groups: primiparous mothers (n=11), primiparous fathers (n=6), multiparous mothers (n=8), and multiparous fathers (n=9). All parents were right handed, Caucasian, and either married or cohabiting. All mothers were breastfeeding.

Exclusion criteria included birth complications, current psychiatric diagnosis, and recent history of prescription medications within 2 weeks of the experiment. Based on the Beck Depression Inventory (BDI), all the parents had a score ranged 0-13 which indicated minimal levels of depression at both 2-4 weeks and 3-4 months postpartum (Beck, Steer, Ball, & Ranieri, 1996). Informed consent was obtained from each participant according to the procedure approved by the Yale University School of Medicine Human Investigations Committee. Demographic information of the four groups of the parents is presented in Table 3.1.

Table 3.1. Demographic characteristics of parent groups

	Mothers		Fathers	
	Primiparous (n=11) mean (SD)	Multiparous (n=8) mean (SD)	Primiparous (n=6) mean (SD)	Multiparuos (n=9) mean (SD)
Age	32.51 (7.37)	34.32(3.87)	35.69 (5.03)	35.71 (3.65)
Infant gender ratio (M/F)	7/4	3/5	4/2	4/5
# of older children	--	1.25 (.46)	--	1.22 (.44)
Educational level (in years)	17.6 (2.37)	19.63 (4.27)	17.33 (3.01)	18.54 (3.50)

Image acquisition

Brain imaging data were obtained twice: first, between 2-4 weeks postpartum (time 1) and second, between 3-4 months postpartum (time 2) at the Yale Magnetic Resonance Research Center. High resolution T1-weighted structural magnetic resonance images (MRI) were obtained (3D MPRAGE; TR = 2530; TE = 3.66; matrix size 256 by 256) with a Siemens trio 3T full-body scanner (Erlangen, Germany). Head

movements were restrained throughout the session with foam padding and surgical tape placed across each participant's forehead.

Voxel-based morphometry (VBM) longitudinal analysis.

VBM analyses were performed with VBM2 toolbox for Statistical Parametric Mapping 2 (SPM2) (Wellcome Department of Neurology, London, UK). All the structural images were processed according to the optimized VBM protocol (Ganzel, Kim, Glover, & Temple, 2008; Good et al., 2001). Study-specific T1 grey matter, white matter, CSF templates were first created based on the images of all participants in one group from both Time 1 and 2. Next, the customized T1 grey matter templates were used for segmentation and normalization of the original images. Template creation and subsequent segmentation and normalization were performed using default options in the VBM toolbox (25 mm cut off, medium regularization, medium HMRF [Hidden Markov Random Field]) weighting for segmentation) with 16 nonlinear iterations. The normalized segments of each participant's grey matter image were modulated for grey matter volume analysis. All the modulated images were smoothed with a filter of 12mm Gaussian kernel.

Finally, the modulated and smoothed images were analyzed with a paired t-test (available in the VBM2 toolbox for the longitudinal analysis) to test grey matter changes between time 1 and time 2. For the exploratory whole-brain analysis, statistical significance were determined by a value of $p < .001$ (uncorrected) and an extent threshold of 150 voxels. This statistical significance threshold used in many other VBM studies (e.g. Ganzel, Kim, Glover, & Temple, 2008, Hölzel et al., 2008; Rüsch et al., 2003). To analyze midbrain regions as small brain structures, the regions were first identified on a statistical map at $p < .001$ (uncorrected). Then, to correct for

multiple comparisons, we applied a family wise error (FWE) at p<.005 with a small volume correction (SVC) method using a sphere of 5 mm diameter.

Results

Optimized whole brain VBM analyses revealed that from time 1 (2-4 weeks postpartum) to time 2 (3-4 months postpartum), primiparous mothers showed an increase in grey matter volumes in several brain regions including prefrontal cortex, precuneus, superior parietal lobe and thalamus, p< 0.001 (uncorrected) (see Table 3.2 and Figure 3.1a). In the midbrain regions, a small volume correction analysis revealed that grey matter in right substantia nigra increased over time, p<.005, FWE corrected (Figure 3.2a). No brain region showed a decrease in grey matter volumes from time 1 to time 2 except right cingulate gyrus, p<.001 (uncorrected).

From time 1 to time 2, multiparous mothers showed changes in grey matter volumes in patterns similar to those of primiparous mothers. They also showed an increase in grey matter volumes in prefrontal cortex, precuneus, superial parietal lobe and thalamus, p< 0.001 (uncorrected) (see Table 3.2 and Figure 3.1b). In addition, an increase in grey matter volumes were found in left precentral/postcentral gyrus, and anterior cingulate gyrus, and midbrain regions including bilateral hypothalamus, globus pallidus, and brainstem (see Figure 3.2b). Only in right cerebellum were grey matter volumes found to decrease from time 1 to time 2.

Table 3.2. Grey matter volumes changes between two time points among primiparous and multiparous mothers

Regions	Location of peak voxels	BA	Side	z values	Tailarach coordinates			BA	Side	z values	Tailarach coordinates		
					x	y	z				x	y	z
		Primiparous mothers (T2>T1)						Multiparous mothers (T2>T1)					
Frontal lobe	Superior frontal gyrus	9	L	4.00	-21	42	39	9	L	3.51	-17	49	30
								10	L	4.61	-24	55	3
	Middle frontal gyrus	9	R	3.91	44	14	33	9,10	R	3.85	29	43	18
		9	L	3.94	-48	9	33	9	L	4.48	-28	38	27
		10	L	3.66	-42	47	18						
	Medial frontal gyrus	8	L	3.68	-12	37	46	10	L	4.25	-23	55	3
								9	L	4.65	-19	40	26
	Inferior frontal gyrus	46	L	3.43	-49	40	5						
	Precentral gyrus	4, 6	L	3.39	-44	-14	57						
Temporal Lobe	Superior temporal gyrus/ Insula							22	R	4.41	49	5	-6
	Middle temporal gyrus							19	L	3.96	-41	-81	23
Parietal Lobe	Postcentral gyrus	5	L	3.46	-31	-44	64						
	Precunues	7	R/L	4.14	5	-49	60	7	R	3.44	2	-71	36
								7	R	4.40	5	-55	39
								7	R	3.45	22	-75	46
								19	L	3.52	-27	-75	38
	Superior parietal lobe	7	R	3.98	29	-58	56	7	L	3.87	-23	-70	46
	Inferior parietal lobe	40	R	4.13	42	-38	50						
		40	L	4.85	-43	-48	49						
Limbic Lobe	Anterior cingulate gyrus							10	L	3.84	-21	48	11

Table 3.2 (Continued)

	Cingulate gyrus							31	R	3.69	3	-47	42
Midbrain	Thalamus		R	4	4	-15	9		R	3.52	12	-21	21
	Hypothalamus								R/L	4.15	10	-5	-17
	Globus pallidus								R/L	4.71	9	5	-2
	Substania nigra*		R	3.56	16	-11	-14						
	Brainstem (Pons)								R/L	4.73	-6	-18	-32
		Primiparous mothers (T1>T2)						Multiparous mothers (T1>T2)					
	Cingulate Gyrus	32	R	3.81	17	15	33						
	Cerebellum								R	3.40	14	-77	-39

p<.001, > 150 voxels (uncorrected); *SVC p<.005 (FEW)

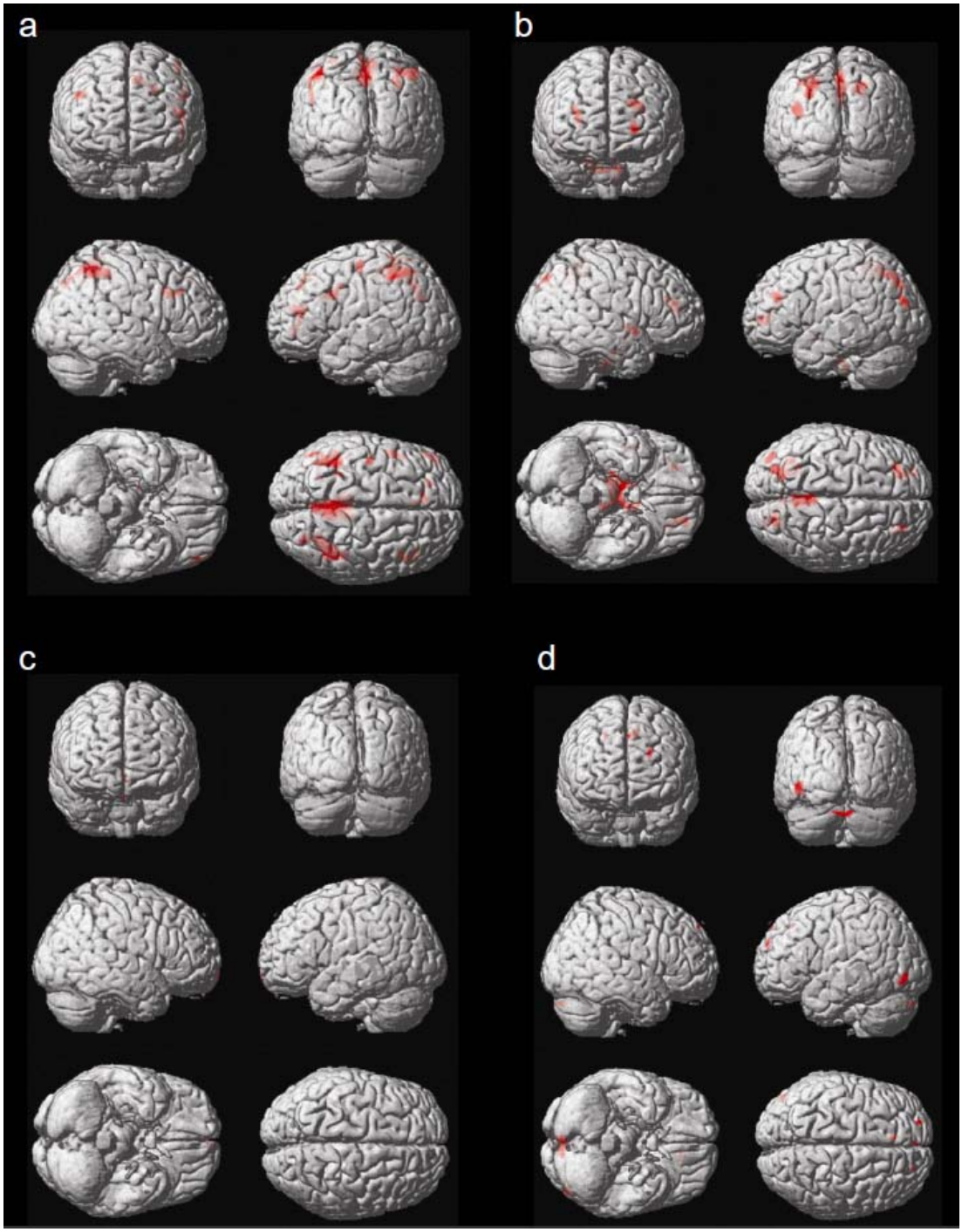
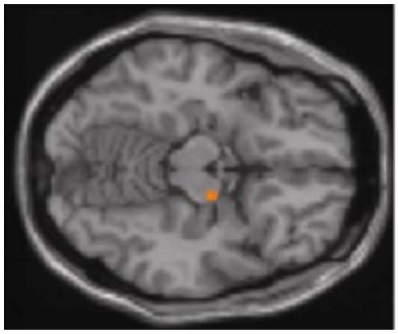
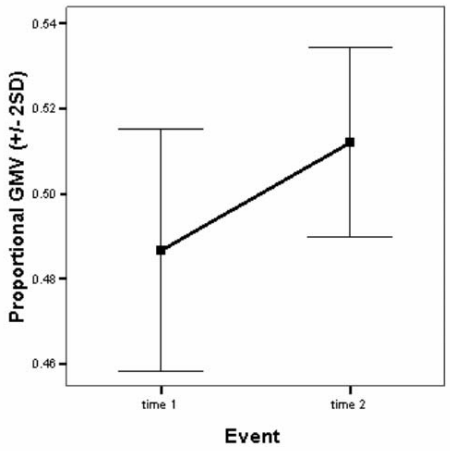


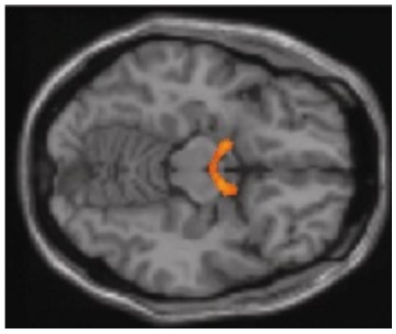
Figure 3.1. Grey matter increase from 2-4 weeks to 3-4 months postpartum, p<.001 (uncorreacted) (a) primiparous mothers (b) multiparous mothers (c) primiparous fathers (d) multiparous fathers.

a.





b.



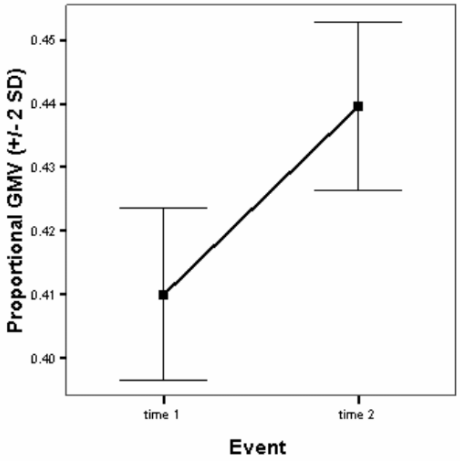


Figure 3.2. (a) grey matter increase in right substania nigra among primiparous mothers from 2-4 weeks (time 1) to 3-4 months postpartum (time 2), p<.005, FEW corrected (b) grey matter increase in bilateral hypothalamus among multiparous mothers from 2-4 weeks (time 1) to 3-4 months postpartum (time 2), p<.001, > 150 voxels, uncorrected.

Primiparous fathers showed no changes in grey matter volumes in any brain region from time 1 to time 2, p<.001 (uncorrected) (see Figure 3.1c). In contrast, multiparous fathers showed increased grey matter volumes particularly in prefrontal regions including superior and medial frontal gyrus, p< 0.001 (uncorrected) (see Table 3.3 and Figure 3.1d). There were several brain regions showing decreased grey matter volumes from time 1 to time 2 among multiparous fathers, p< 0.001 (uncorrected) (see Table 3.3).

Table 3.3. Grey matter volumes changes between two time points among multiparous fathers.

Regions	Location of peak voxels	BA	Side	z values	Tailarach coordinates		
					x	y	z
		Multiparous fathers (T2>T1)					
Frontal Lobe	Superior frontal gyrus	9	R	3.65	29	49	52
		9	L	3.62	-22	59	25
		8	L	4.04	-8	35	45
	Medial frontal gyrus	9	L	3.53	0	55	44
		10	L	3.52	-18	34	-6
Limbic Lobe	Anterior cintulate gyrus	32	L	3.44	-7	34	-10
Occipital Lobe	Middle occipital gyrus	19	L	3.56	-48	-75	-9
	Inferior occipital gyrus	19	L	3.54	-44	-81	-5
Midbrain	Cerebellum		R/L	3.52	6	-85	-29
		Multiparous fathers (T1>T2)					
Frontal Lobe	Superior frontal gyrus	8	R	3.94	11	29	49
Parietal Lobe	Precuneus	7	L	4.09	-5	-48	34
Occipital Lobe	Lingual gyrus	18	L	4.09	-6	-68	4
Limbic Lobe	Cingulate gyrus	31	L	3.9	-2	-42	29
	Anterior Entorhinal Cortex/ Amgydala	34	L	3.86	-4	-4	-24
Midbrain	Brainstem (Medulla)		R	3.87	9	-44	-57
	Cerebellum		L	3.7	-18	-66	-48

p<.001, > 150 voxels (uncorrected)

Discussion

Rodent studies have indicated that the expression of parental behaviors is associated with structural changes in brain regions including the MPOA, the somatosensory cortex, and the prefrontal cortex (Fleming & Korsmit, 1996; Xerri, Stern, & Merzenich, 1994). The current study identified structural changes in similar brain regions among human parents during the early postpartum period. Mothers showed more dramatic changes in terms of brain structures over time as compared to fathers. Increased grey matter volumes in large regions of prefrontal cortex, parietal lobe, and midbrain were found among both primiparous and multiparous mothers. Particularly, among primiparous mothers, an increase in grey matter volumes was found in substania nigra (SN), a key region of the mesolimbic dopaminergic system responsible for processing reward signals (Schultz, Dayan, & Montague, 1997). During the postpartum period, SN serves an important function in activating positive responses to pup stimuli through dopamine (DA) neurons. Thus, the increased levels of grey matter in SN may facilitate the mother's growing familiarity with the rewarding value of infant-related stimuli. fMRI studies with human mothers have similarly shown that greater SN responses to infant stimuli were correlated with the mother's self-reported positive emotional reactions to the infant stimuli (Noriuchi, Kikuchi, & Senoo, 2004).

As key regions for the expression of maternal behaviors, the bilateral hypothalamus and globus pallidus were found to show an increase in grey matter volumes by 3-4 months postpartum among multiparous mothers. Animal studies revealed that lesions in the hypothalamus including MPOA impairs maternal motivation, and the MPOA regions increased the likelihood of infanticide (Flannelly, Kemble, Blanchard, & Blanchard, 1986; Novakova, Sterc, Kuchar, & Mozes, 1993). Structural reorganization in the MPOA was also found to be sensitive to postpartum

experience; the increased amount of interactions with pups were associated with greater density in MPOA in rat mothers (Featherstone, Fleming, & Ivy, 2000; Fleming & Korsmit, 1996; Lonstein, Simmons, Swann, & Stern, 1998). The ventral pallidum (VP), a part of the globus pallidus, receives inputs from SN and regulate motor activities and behavioral reactivity (Nestler, 2001). Hypothalamus and globus pallidus has been implicated in maternal behaviors in humans (Bartels & Zeki, 2004; Lorberbaum et al., 2002). Thus, interactions with infants during the first few postpartum months may be associated with the increased grey matter volumes in the hypothalamus and globus pallidus among multiparous mothers and help the mother's to respond sensitively to their infants.

In the current study, several brain regions implicated in somatosensory information processing also showed an increase in grey matter over time among mothers. These findings may provide evidence that changes in the parent's brain structure are associated with exposure to infant-related stimuli. For maternal behaviors in rodents, the thalamus receives infant-related information from the VP and projects the information to prefrontal/cingulate cortices (Insel, 2003). In addition, human neuroimaging studies have shown that parietal lobes send a robust visual and somatosensory input to premortor and somatosensory cortex areas (Iacoboni & Dapretto, 2006). The precentral and postcentral gyrus include the primary motor cortex (BA4), secondary motor cortex (BA6) and the somatosensory association cortex (BA5 &7). Several VBM studies found gray matter changes in the parietal cortex due to experience and learning in humans (Draganski et al., 2004; Draganski et al., 2006). Together these findings suggest that the plasticity of the parietal cortex is sensitive to experience-based short-term changes. In rats, a rich amount of olfactory, auditory, somatosensorial and visual information during the physical interactions with pups and suckling stimuli during nursing were also associated with the reorganization

of the thalamus, parietal lobe, and someosensory cortex in lactating mothers (Kinsley et al., 2008; Lonstein, Simmons, Swann, & Stern, 1998; Xerri, Stern, & Merzenich, 1994). Moreover, these changes in the parietal cortex only occurred when mothers actually interacted with their pups but not when they were only exposed to the pups' smells or sounds (Fleming & Korsmit, 1996). It is interesting to speculate if the increased grey matter volumes that we report in thalamus, precentral and postcentral gyrus, and superior parietal lobe among both primiparous and multiparous mothers from the first to three-to-four months postpartum may be related to actual frequency and quality of interactions with their infants. Future experiments to test this may inform the importance of optimizing such interactions for clinical purposes to enhance maternal capacities to learn and be attuned to their infant's signals.

Another large area that showed an increase in grey matter volumes among both primiparous and multiparous mothers was the prefrontal cortex (PFC) area including superior, middle and medial frontal cortices. The prefrontal cortex plays an important role in parental behaviors in humans. Based on a large animal and human literature, the PFC is a part of the mesolimbic dopamine system in humans (O'Doherty, 2004) and the NA-PFC connections are responsible for the integration of both the emotional and motivational information and for the complex decision processes involved in parental behaviors (Numan & Insel, 2003). Afonso and colleagues (2007) found that mother rats with medial prefrontal cortex lesions exhibited deficits in a certain maternal behaviors such as pup retrievals and licking behavior, but not in nest building or pup mouthing. This is interesting because pup retrieval and licking require more complex maternal behaviors since they involve more interaction with pups compared to nest building or mouthing (Afonso, Sison, Lovic, & Fleming, 2007). Thus, it may be possible that an increase in grey matter volumes in the PFC that we report may be associated with mothers' greater capacities and skills particularly for the complex

interactive behaviors with infants during the postpartum period. Neuroimaging data highlights the importance of the PFC in parenting behaviors; greater activations in frontal regions including superior and middle frontal gyrus (BA 9, 10) and medial frontal guys (BA8) were found in almost every fMRI study of human mothers' responses to infant stimuli (reviewed in Swain, Lorberbaum, Kose, & Strathearn, 2007).

While primiparous and multiparous mothers showed very similar changes, primiparous and multiparous fathers showed very different patterns of structural changes in their brains from the first to the third and fourth month postpartum. Primiparous fathers exhibited nearly no change over time. On the other hand, multiparous fathers exhibited an increase in grey matter volumes primarily in the prefrontal cortex areas (BA8, 9, 10), the same regions where similar increases were found in the mothers. Very little work has been done on the neural circuitry of paternal care in both animals and humans. However, a previous study with biparental primates found that parenting experience was associated with higher density of pyramidal cells in the dendritic spines of the prefrontal cortex of marmoset in both primiparous and multiparous fathers as compared to non-fathers (Kozorovitskiy, Hughes, Lee, & Gould, 2006). Perhaps we did not find any structural changes in our sample of primiparous fathers because any such changes may take longer than 3-4 months postpartum to occur in primiparous human fathers. On the other hand, previous parenting experience in the multiparous fathers may set the PFC regions more sensitive to structural changes. Among fathers, the increased grey matter volumes in the PFC may serve an important function of learning and monitoring responsive parental behaviors. However, it should be also noted that no significant change may be due to a smaller sample size in the primiparous father group.

Furthermore, there was less structural changes found among fathers relative to mothers over time. The greater neuroplasticity of maternal brain may be related to several factors. One, mothers experience greater changes in several hormones including estrogen, oxytocin, and prolactin during the early postpartum period. The hormones are induced by stimuli from the infant, such as vocalization, odor, visual characteristics, behaviors, and tactile contacts (Fleming & Li, 2002). The release of the hormones activates neural sites in several key brain areas responsible for parenting elicits parental behaviors including the MPOA, and the mesolimbic reward-associated systems. On the other hand, the hormonal effects on brain sites may be more limited among fathers. Second, during the first few months postpartum, mothers tend to spend a significantly greater amount of time interacting with their infants compared to fathers (Yeung, Sandberg, Davis-Kean, & Hofferth, 2001). As results, maternal brain structure may be likely to be affected by the parenting experience than paternal brain structure.

Several regions showed a decrease in grey matter volumes over time. Particularly, the cingulate gyrus showed a decrease over time in multiparous mothers and fathers whereas the similar areas of the cingulate gyrus increase. Several studies have pointed to the role of the cingulate gyrus in parenting behaviors (Slotnick, 1967; Swain, Lorberbaum, Kose, & Strathearn, 2007); however, other studies failed to find a significant relationship between cingulate lesions and impairment in parental behaviors (Lonstein, Simmons, Swann, & Stern, 1998). Thus, it is not yet clear what effects the particular changes in the cingulate gyrus may have on parenting behaviors. In the current study, we found longitudinal changes in gray matter over the first 4 months postpartum. This postpartum period marks a critical period for parents to develop parental sensitivity to their infants. This early parental sensitivity becomes the basis of mother-infant attachment which has long-lasting impact on neurobiological

changes related to stress reactivity and social attachment (Francis, Diorio, Liu, & Meaney, 1999; Swain et al., 2004). Our finding may suggest that the experience with infants during the first few months may be associated with structural development in brain areas that are important for parental motivation and behaviors. However, it should be noted that the relationship between experience and the neuroplasticity for parental brain may be bidirectional. It may be possible that structural neurodevelopment based on the release of hormones may enhance parental motivation and capacities to interact with infants during the early postpartum period. Furthermore, rodent research suggests that multiparity is associated with an increase in volumes in the hippocampus (Kinsley et al., 2008). In addition, animal studies suggest that parental brain goes through changes during pregnancy largely based on changes in hormonal systems in females and biparental males in order to prime brain areas to inhibit avoidant response to pups (Numan & Insel, 2003). A follow-up of the parents' structural brain change from pregnancy to the later postpartum period or up until the birth of their second child would be needed to address these questions.

Our findings on the plasticity of the parental brain demonstrate normative changes among human parents since the sample of our study included healthy mothers and fathers of healthy infants who were in supportive environments. However, parents with genetic and environmental risk factors such as early traumatic experiences or postpartum depression may show different patterns of structural changes in brain regions that are important for the expression of parenting behaviors. Such abnormal brain structures may be further associated with low parental sensitivity among these parents. Further research and is thus required to identify distinctive changes in the parental brain among at-risk parents in order to devise more specific and early interventions and treatments.

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