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Perceived quality of maternal care in childhood and structure and function of mothers' brain

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Abstract

Animal studies indicate that early maternal care has long-term effects on brain areas related to social attachment and parenting, whereas neglectful mothering is linked with heightened stress reactivity in the hippocampus across the lifespan. The present study explores the possibility, using magnetic resonance imaging, that 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. 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 that maternal care in childhood may be associated with anatomy and functions in brain regions implicated in appropriate responsivity to infant stimuli in human mothers.

Introduction

The early experience of parental care has long-term effects on a range of behaviours, including those associated with later parenting. Women who experienced a 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 appropriate 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 behaviours 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 also lead to 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 behaviours in humans have only recently become the subject of investigation, and their relationship with early experience is not yet well characterized (Swain, Lorberbaum, Kose & Strathearn, 2007).

The mechanisms underlying the relationship between the early environment, the developing brain, and the emergence of parenting behaviour have been studied mainly in animal models. 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 behaviours 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 behaviours when they become mothers (Francis, Diorio, Liu & Meaney, 1999; Francis, Young, Meaney & Insel, 2002). Furthermore, the adult offspring of the LLG mothers showed lower levels of glucocorticoid receptor gene expression and decreased synaptic density in the hippocampus (Kaffman & Meaney, 2007). In humans, women who reported low maternal care in childhood, as measured by the Parental Bonding Instrument (PBI), had a smaller hippocampal volume (Buss *et al.*, 2007). These changes in the hippocampus were further associated with a reduced ability to regulate stress and emotions (Bredy, Grant, Champagne & Meaney, 2003; Heim & Nemeroff, 2009). It is thus possible that hippocampal functions may mediate the relationship between early experience and later maternal responsiveness to infants (Kaffman & Meaney, 2007). However, the question of whether early experience is related to hippocampal physiology has not been examined in human mothers.

Low maternal care in childhood may affect brain regions that regulate mothers' emotional responses to their infants. Studies have shown that children who experienced low quality of interactions with their mothers tend to develop insecure attachment, socio-emotional difficulties, and limited capacity for empathy across childhood and up to adolescence (Feldman, 2007a; Feldman, 2007b; Feldman & Eidelman, 2004). Possibly, children of less responsive mothers are less proficient in processing social and emotional information, which, in turn, may impact their ability to respond sensitively to their own infants when they themselves 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-related 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 explore the relationship between early experiences and the neuronal mechanisms underlying responses to infant stimuli in human mothers. We examined whether perceived quality of maternal care, as recalled by mothers in the immediate postpartum period using the PBI (Parker, 1979), is associated with their brain structure as well as with patterns of functional activation in response to highly salient infant-cry stimuli (Swain, Lorberbaum, Kose & Strathearn, 2007). It may be argued that because childhood experience was reported retrospectively, mothers' reports may have been affected

by other factors such as later life experiences (Hardt & Rutter, 2004). However, 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. We divided mothers into higher and lower maternal care groups based on the original cut-offs made on a large normative sample (Parker, 1979) and then compared grey matter volume in the brain using voxel-based morphometry (VBM) (Mechelli, Price, Friston & Ashburner, 2005). In addition, we compared functional blood oxygenation-level-dependent (BOLD) responses to infant cries between these high- and low-care groups of mothers during the first month postpartum.

Methods

Participants

Twenty-six biological mothers with full-term, healthy infants were recruited in postpartum hospital wards at the Yale New Haven Hospital. The mothers' age averaged 32.7 years ($SD = 6.56$; range = 19.58 to 47.08) and all the mothers were Caucasians. 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 'higher' and 'lower' 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). As expected, the maternal care scores from the PBI were significantly different for the higher and lower PMC groups, $t(24) = 8.17, p < .0001$. The two groups showed no significant difference in their depression (BDI) and trait anxiety (STAI) scores. To confirm that these variables were not related to the PBI scores, we conducted a zero-order correlation analysis and found that PBI scores were not significantly correlated with BDI and trait anxiety scores.

Procedures

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

Measures

Parental Bonding Instrument (PBI)—The PBI is a self-report measure for adults to rate their parents' caring behaviours 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 themselves 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 cut-off 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 participants' depressed mood (Beck, Steer, Ball & Ranieri, 1996). The BDI consists of 21 items that assess symptoms of depression. All the items were answered on a scale of 0 to 3. 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 1 being almost never true and 4 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 were obtained (3D MPRAGE; TR = 2530 ms; TE = 3.66 ms; matrix size 256×256) with a Siemens trio 3T full-body scanner (Erlangen, Germany). Next, anatomical T1-weighted echo-planar images (spin-echo; TR = 300 ms; TE = 4 ms; matrix size 64×64 ; 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) data were acquired (echo planar T2*-weighted gradient-echo; TR = 2000 ms; TE = 30 ms; matrix size 64×64 ; 3.125-mm in-plane resolution; 5-mm 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 the 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, and cerebrospinal fluid (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 the 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 a 12-mm Gaussian kernel. Finally, the modulated and smoothed images were analysed with a *t*-test in SPM2 to compare grey matter changes in high versus 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 an extent threshold of 50 voxels were used to determine statistical significance.

fMRI stimuli: Identical standard infant-cry stimuli were used to activate the brain of each participant. The infant 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-infant-cry sounds, such as gurgles or grunts, were removed to generate a 30-second block of infant-cry stimuli using Cool Edit Pro version 2.0 (Syntrillium Software, Phoenix, AZ). Among eight infant-cry samples, a standard infant cry was chosen as the one with median emotional intensity as rated by eight investigators on a scale of 1–10. The control sound was made by replicating

the infant-cry sound envelope and replacing the cry with white noise, which controlled for infant-cry pattern and sound volume (total root-mean-square sound intensity of -8dB). During each of two functional runs, participants heard 10 sound blocks through padded headphones. Each sound block was 30 seconds long and was composed of (A) infant cry and (B) control sound. These stimulus blocks were arranged so that 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-second 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 to the level at which the participants would hear the sounds clearly. This also enabled participants to become familiarized with the sounds and thus minimize surprise effects. During the scans, participants were asked to reflect how much the stimuli remind them of their own baby and current parenting experience.

fMRI data analysis: Functional imaging data were preprocessed and statistical analysis was performed using Brainvoyager QX software versions 1.6 and 1.8 (Brain Innovation, Maastricht, the Netherlands). Functional runs were pre-processed using 3D 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 $< 3\text{mm}$ in the x -, y - or z -direction, and was excluded from all the 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 fewer per timecourse. Motion-corrected images were spatially smoothed using a Gaussian filter with a full-width half-maximum value of 6.25 mm . Data from each participant were co-registered with each participant's high-resolution 3D anatomical dataset, and then transformed into standardized 3D Talairach coordinate space (Talairach & Tournoux, 1998) using piecewise linear warping. The functional data were resampled at 1-mm^3 voxels.

The analysis of the BOLD signal changes in brains in response to the infant-cry sound relative to the control sound were analysed using a random-effect general linear model (GLM). The exploratory whole-brain analysis was used to contrast activities in two conditions (infant cry versus control noise) across the two groups. The 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 mm^3 survived the correction. The group effects (the higher versus lower perceived maternal care) $\times$ the condition effects (infant cry versus control noise) were tested by performing a conjunction of random-effect GLM analysis and subsequent generation of group t -maps (two-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 mm^3 were rejected. The a priori regions-of-interest analysis was 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 activation between the 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 mm^3 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 Brainvoyager and analysing with SPSS version 15 (SPSS Inc., Chicago). Finally, we extracted the data of the grey matter volume from the VBM analysis and the data of the BOLD signal from the fMRI analysis. Then, the data from the two analyses were correlated

with each other, and also with the PBI scores by running the zero-order correlation analysis in SPSS version 15.

Results

Voxel-based morphometry

As presented in Table 2 and Figure 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 the frontal and temporal gyri, $p < .001$ (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 PMC group had significantly larger grey matter volumes in the left and right inferior parietal gyri, $p < .001$ (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 and trait anxiety scores, $p < .01$. There was no significant group difference in either the right or left hippocampus.

Functional brain imaging

Whole-brain fMRI results—First, we examined maternal brain responses to infant cry compared with control noise across the two groups (see Table 3). Infant cry activated the superior, medial and inferior frontal regions, superior and middle temporal gyri, the insula, and cuneus regions, $p < .01$ (corrected).

Next, we examined the group effect to predict maternal brain responses to infant cry compared with 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, precentral gyrus, superior temporal gyrus, fusiform gyrus and lingual gyrus, $p < .01$ (corrected) (see Table 4). OLS regression analysis revealed that the group effects were significantly associated with greater activations in these regions after controlling for the BDI and anxiety scores, $p < .01$ (except for the right lingual gyrus, $p < .05$). No brain areas were found to exhibit significantly greater BOLD activations among the lower PMC group in response to infant cry (minus control noise) at this level of significance.

A priori regions-of-interest analysis: In the left hippocampus, mothers in the lower PMC group showed greater activations in response to infant cry (minus control noise), whereas activations in the same area decreased among mothers in the higher PMC group, $t(24) = -2.64$, $SE = 0.29$, $p < .05$ (corrected) (see Figure 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.

Convergence of VBM and the fMRI results

Significant activations to infant cry were found in the higher PMC group relative to the lower PMC group in all of the regions that also had larger grey matter volumes from the VBM analysis, except in the left superior frontal gyrus, orbital gyrus, and right cerebellum, $p < .05$ (corrected) (see Figure 3). Furthermore, the grey matter volume of each VBM region was significantly correlated with the BOLD responses of the matched fMRI region across the two groups (see Table 5). The brain areas with larger grey matter volume in the higher PMC group also showed higher levels of functional brain activations relative to the mothers in the lower PMC group. In addition, the regions with smaller grey matter volumes in the higher PMC group were negatively correlated with the matched regions with the greater activations in the higher PMC group (see Table 5). Significant correlations between the

VBM and fMRI results were not seen in the parietal lobe, orbital gyrus or right cerebellum. In addition, we examined the correlation between the PBI score, VBM and fMRI results across two groups. The PBI score was correlated with most of the VBM and fMRI results: the only exceptions were the VBM results of the right inferior parietal lobe and the fMRI results of the left fusiform gyrus.

Discussion

The results of the present study demonstrate associations between the retrospectively perceived quality of maternal care in childhood and both brain structure and function of mothers in the postpartum period. We found larger grey matter volumes in various brain regions of mothers who recalled higher levels of perceived maternal care during their childhood. Furthermore, we found that significantly greater brain activations in response to baby cry occurred in brain regions similar to those with increased volume among mothers with recalled higher levels of perceived maternal care. Finally, in the left hippocampus, mothers' brain activations in response to infant-cry stimuli were greater among mothers with recalled lower levels of perceived maternal care.

These results may be understood in the framework of brain circuits that respond to emotionally salient stimuli. For example, some of the brain regions where higher levels of perceived maternal care were associated with increased volume and greater activations have been suggested to be involved in the processing of emotional vocal stimuli (Ethofer, Pourtois & Wildgruber, 2006; Johnstone, van Reekum, Oakes & Davidson, 2006). 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 with the emotional contents of the vocal stimuli (Mitchell, Elliott, Barry, Cruttenden & Woodruff, 2003). The superior temporal sulcus similarly showed higher activation in response to angry speech than in response to neutral speech (Grandjean *et al.*, 2005; Sander *et al.*, 2005). Finally, the right anterior and posterior middle temporal gyri were activated to a greater degree in response to a happy voice than in response to an angry voice (Johnstone, van Reekum, Oakes & Davidson, 2006). Thus, the larger grey matter volumes and greater maternal brain activations in the middle temporal gyrus, superior temporal sulcus and middle frontal cortex found among mothers who recalled a higher quality of maternal care may help these mothers to respond more sensitively to their infant's emotional signals.

Many of the brain regions shown here to be associated with early maternal care may also be related to the mother's ability to understand her infant's mental and physical states. Several fMRI studies found that such regions, including the inferior frontal gyrus, superior temporal sulcus, insula, fusiform gyrus, inferior parietal lobule and temporal poles, were also important for the representation of others' intentions and mental states (Iacoboni & Dapretto, 2006; Völlm *et al.*, 2005). Thus, increased volumes and greater BOLD responses in these regions among mothers with higher-quality perceived maternal care in childhood may be linked with their enhanced ability to understand the emotional states of the infant.

Taken together, these findings may point to a relationship between early maternal care and the brain structures and functions that may be important for appropriate maternal responses to infant cries. Infant cry is an auditory stimulus that is very effective in drawing the mother's attention to her infant and inducing maternal proximity (Bowlby, 1969). The most common response to infant cries is picking up the infant for soothing (Bell & Ainsworth, 1972). Such appropriate maternal responses to infant cries are particularly critical for infant survival and the development of mother-infant emotional bonding (Feldman, 2007a,b). Therefore, the increased grey matter volumes and strong BOLD responses in the regions

involved in emotional information processing and mentalizing infant states may enhance maternal responsiveness to the infant. Previous fMRI studies also found that the prefrontal cortex, superior temporal gyrus, middle frontal gyrus and fusiform gyrus were activated when mothers attended to infant 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.*, 2009; Noriuchi, Kikuchi & Senoo, 2004; Ranote *et al.*, 2004).

The smaller 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 behaviours. 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 lower PMC group may be interpreted as reflecting subtle individual differences in responsiveness to emotionally salient information. The importance of the prefrontal cortex in parenting is supported by primate studies that show that damage to the prefrontal cortex, including the orbital gyrus, significantly disrupts maternal behaviours (Franzen & Myers, 1973). Furthermore, other fMRI studies on human mothers found that the orbital gyrus was activated when mothers heard infant stimuli compared with control stimuli (Bartels & Zeki, 2004; Lorberbaum *et al.*, 2002; Nitschke *et al.*, 2004).

Individual differences in perceived maternal care were also related to functional differences in the left hippocampus. The left hippocampus of the lower PMC group exhibited stronger activations in response to infant-cry stimuli. This may be considered as a manifestation of differences in the mothers' level of stress reactivity to infant cries. The hippocampus plays an important role in assessing stressor intensity and inhibiting the biological stress responses of the hypothalamo-pituitary-adrenocortical (HPA) axis (Dedovic, D'Aguiar & Pruessner, 2009). Increased activations in the left hippocampus were observed when individuals were seeing emotionally distressing pictures in the scanner (Sinha, Lacadie, Skudlarski & Wexler, 2004). A number of studies have found that chronic stress such as adverse early experience is associated with volumetric reductions and increased activations in the hippocampus (Heim & Nemeroff, 2009; Lupien, McEwen, Gunnar & Heim, 2009). Furthermore, elevated HPA-axis activity is associated with increased activations in the hippocampus (Dunn & Orr, 1984; Herman, Ostrander, Mueller & Figueiredo, 2005). Gonzalez and colleagues (2009) found that human mothers with early-life adversity such as parental loss and childhood maltreatment exhibited higher levels of morning cortisol and heightened diurnal cortisol levels during the postpartum period compared with mothers without early adversity (Gonzalez, Jenkins, Steiner & Fleming, 2009). Thus, it may be possible that less responsive maternal care in childhood may be linked to heightened stress reactivity in the hippocampus and the HPA axis during the postpartum period. The difficulties in regulating stress may be further associated with maternal responsiveness to infants (Martorell & Bugental, 2006).

In contrast to the fMRI results, no structural differences were found in the hippocampus in the VBM analysis between the higher and lower PMC 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 results from 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.

Despite reports of activations in response to infant cry in the amygdala (Sander, Frome & Scheich, 2007; Seifritz *et al.*, 2003), no significant results were found in either the left or right amygdala in response to infant cry and control noise across groups. The VBM analysis and the fMRI analysis also did not reveal grey matter volume differences or activation differences in the amygdala according to the perceived quality of maternal care in childhood. These results may be because our report is a contrast across groups rather than across experimental versus control stimuli within a group. It may also be that the amygdala habituates too quickly in response to infant stimuli, as other brain-imaging studies using infant cries or pictures have also failed to report significant amygdala activations (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 the hippocampus than 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 these regions' 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 higher PMC group were not only larger 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). Several studies have found that the right inferior parietal lobe may be important for the information processing of negative emotions such as anxiety (Liotti *et al.*, 2000). Thus, the association reported in the current study between relatively lower quality perceived maternal care in childhood and increased grey matter volumes in the inferior parietal lobe may be the result of elevated anxiety levels experienced over time. In addition, fMRI studies with post-traumatic stress disorder 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 experience may be better able to regulate their negative emotions, as indicated by greater parietal lobe activations. Future studies with behavioural measures of parenting are required to address these questions.

Finally, the results should be considered in 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' reports 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 behaviours in adulthood. Second, the PBI is a self-reflective instrument that is reported in retrospect (Parker, 1979), and a mother's rating on the PBI may be affected by her current mental state or by recent life experiences. On the other hand, a number of studies have shown that current mood states do not bias responses of the PBI (Parker, 1979), and a recent test-retest study of the PBI indicated long-term stability over a 20-year interval that was not affected by gender, depression, life events, or neuroticism (Wilhelm, Niven, Parker & Hadzi-Pavlovic, 2005). Third, although the PBI taps the entire span of childhood and adolescence, it does not include detailed information on the child's rearing environment or 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 future studies. 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, possibly because of 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 represent brain areas that not only were affected by low perceived maternal care but also are important for parenting-specific stimuli (i.e. infant cry). Fifth, mothers in the current study were of 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 because of 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 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 & Bremner, 2006; Vythilingam *et al.*, 2002). Abnormal patterns of activation in the amygdala and prefrontal cortex have also been reported in humans who suffer from post-traumatic stress disorder (Damsa, Maris & Pull, 2005). Finally, it would be interesting in the future 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, and to men.

The findings point to several directions for future research. Future studies could reveal whether brain activation and structural differences among mothers who recalled having low maternal care in childhood are associated with differences in maternal behavioural responses to their infants. These brain changes may be also critical to explaining 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 behaviours during the postpartum period (Leckman *et al.*, 1999). Finally, future research may incorporate the findings of the current study in the construction of specific interventions for mothers with negative early experiences in order to help to 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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Figure 1.

Whole-brain voxel-based morphometry (VBM) showing areas with significantly larger mean grey matter volume in the 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.

Figure 2.

Left hemisphere hippocampus activity (infant cry minus control sound). (a) shows decreased activity in the left hippocampus (in blue) among the higher perceived maternal care group relative to the lower perceived maternal care group ($p < .05$, corrected). (b) compares the activity of the higher and lower perceived maternal care groups in the left hippocampus, $t = -2.64$ ($p < .05$).

Figure 3. Areas of activation in the contrast (infant cry minus control sound). Areas in red show greater activations in the higher perceived maternal care group relative to the 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.

Table 1

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

	<u>Higher PMC group</u>	<u>Lower PMC group</u>
	<i>n</i> = 13 Mean (<i>SE</i>)	<i>n</i> = 13 Mean (<i>SE</i>)
Age	30.87 (1.67)	34.46 (1.89)
Handedness (L/R)	2/11	1/12
No. 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)

*
 $p < .0001$.

PBI, Parental Bonding Instrument.

Table 2

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

Anatomical area	Brodmann area	Side	z-score	Cluster size	Tailarach coordinates		
					x	y	z
Higher 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). PMC, perceived maternal care.

Table 3

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

Area of activation	Brodmann area	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
Precentral gyrus/inferior frontal gyrus	9	R	5.96	4147	42	9	32
Inferior/middle frontal gyrus	9	L	3.91	1826	-40	11	26
Precentral gyrus	6,4	R	3.85	2419	43	-7	47
	4	L	4.13	871	-42	-12	54
Precentral 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).

Table 4
Activation results of the group comparison in the contrast of ‘infant cry’ minus ‘control sound’

Area of activation	Brodmann area		Side	t-score	Cluster size	Tailarach coordinates		
						x	y	z
Higher PMC group > Lower 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). PMC, perceived maternal care.

Table 5
Convergence of voxel-based morphometry (VBM) and functional magnetic resonance imaging (fMRI) results

VBM results	Brodmann area	Side	fMRI data results				Correlations			
			t-score	Cluster size	Tailarach coordinates			VBM-fMRI	PBI-VBM	PBI-fMRI
					x	y	z			
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	3.40	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	3.00	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).

 $p < .001$

**
 $p < .01$

*
 $p < .05$.