Differential Sex-Independent Amygdala Response to Infant Crying and Laughing in Parents versus Nonparents

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Background: *Animal and human studies implicate forebrain neural circuits in maternal behavior. Here, we hypothesized that human brain response to emotional stimuli relevant for social interactions between infants and adults are modulated by sex- and experience-dependent factors.*

Methods: *We used functional magnetic resonance imaging and examined brain response to infant crying and laughing in mothers and fathers of young children and in women and men without children.*

Results: *Women but not men, independent of their parental status, showed neural deactivation in the anterior cingulate cortex, as indexed by decreased blood oxygenation level–dependent signal, in response to both infant crying and laughing. The response pattern changed fundamentally with parental experience: in the amygdala and interconnected limbic regions, parents (independent of sex) showed stronger activation from crying, whereas nonparents showed stronger activation from laughing.*

Conclusions: *Our data show sex- and experience-dependent modulation of brain response to infant vocalizations. Successful recognition and evaluation of infant vocalizations can be critical for bonding mechanisms and for offspring well-being and survival. Thus, the modulation of responses by experience seems to represent an adaptive mechanism that can be related to reproductive fitness.*
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Key Words: Audition, functional magnetic resonance imaging, adaptation, social, emotion, amygdala

Introduction

Recognizing and evaluating infant vocalizations and discriminating between crying and laughing are fundamental operations that caregivers of young children must carry out. In animals, converging evidence demonstrates the importance of parental care for offspring fitness on behavioral, physiologic, and molecular levels (Meaney 2001). Because securing offspring survival is an important element underlying evolutionary selection, it is likely that specific brain mechanisms have developed to subserve these operations. Animal studies have shown that the mammalian forebrain plays a particularly important role in the expression of reproductive physiology and behavior. These are fundamentally different in female and male animals and are reflected in functional and morphologic sex differences in neural forebrain circuits (Simerly 2002). The pivotal role of the forebrain in mammals is further supported by its involvement in the regulation of specific behaviors during nursing and maternal care of offspring (Champagne et al 2001; Sheehan and Numan 2002). For instance, the thalamocingulate division of the forebrain, which has no counterpart in evolutionarily older species, such as reptiles, is believed to have evolved in parallel with social behaviors related to the development of familial acculturation, which are established to a large extent through audiovocal communication (MacLean 1985). The perception of emotional information in species-specific communication sounds of nonhuman mammals—involved in securing emotional bonding and social interactions—depends at least partially on thalamocingulate neural circuits, both in parents (Murphy et al 1981) and offspring (Braun and Poeggel 2001).

In humans, recent imaging studies demonstrate that mothers of young children show neural activation in limbic forebrain structures in response to infant crying compared with neutral sounds (Lorberbaum et al 1999, 2002). Whereas these studies support the concept that limbic areas might be involved in maternal behaviors in humans, they leave open the fundamental questions as to

whether these effects are sex-specific, are related to care-taking behaviors, and are dependent on the type of infant vocalizations. To address these questions, we used infant vocalizations as auditory stimuli for four groups of healthy adult subjects—mothers and fathers of young children, and women and men without children—and measured neural activity with blood oxygen level–dependent (BOLD) functional magnetic resonance imaging (fMRI). We examined sex- and parental status–dependent differences in the brain response pattern to infant vocalizations. In addition, we examined whether possible experience-dependent plastic changes would preserve sex specificity or whether they would produce common alterations both in female and male parents. Finally, we examined whether there are dissociable brain response patterns to the contradictory information conveyed by infant crying and laughing and whether such response patterns would depend on sex- or experience-related factors.

Methods and Materials

Subjects and Data Acquisition

We examined 10 women (age 31.6 ± 4.5 years, mean ± SD) and 10 men (age 36.2 ± 4.7 years) with children younger than 3 years (1.3 ± .8 years), and 10 women (age 27.6 ± 3.7 years) and 10 men (age 28.4 ± 4.8 years) without children. All subjects were recruited from the academic community. They had no personal and family history of mental disorders, including depression and anxiety, and did not use medication or have a history of psychotropic medication use; however, subjects were not formally evaluated in terms of specific personality traits, which can interfere with brain response to emotionally laden stimuli (Canli et al 2002). No subject was professionally involved in infant care; however, they were not formally matched in terms of general experience with infants. Our parental sample included three married couples and one mother who was breast-feeding at the time of the study. Parents were not specifically selected to match on age of their children; however, the mean age of the children of mothers and fathers were not statistically different. The subgroups differed somewhat in age: the fathers were significantly older than the childless women and men, and the parents (33.9 ± 5.1 year) were significantly older than nonparents (28.0 ± 3.7 years), but the age difference between women (29.6 ± 4.5 years) and men (32.3 ± 5.8 years) was not statistically significant. All parents were married, and of the childless subjects, three women and two men were married. There were no differences in socioeconomic status between the subject groups.

Intensity-matched traces of infant crying of distress and infant laughing (samples 261 and 110 of the International Affective Digitized Sounds [IADS] system [Bradley and Lang 1999]) were used as emotional auditory stimuli. These standard IADS sounds, rather than other infant recordings or individual recordings of the parents' own infants, were used because they have been extensively validated in terms of emotional response profiles, although

some specific information about them (e.g., regarding ages of the crying and laughing infants and reasons for the specific vocalizations) is not available. The auditory control stimulus was produced by averaging the frequency spectral components of the two infant vocalizations. The envelope of the resulting sound was pulse-modulated with a repetition rate of 5 Hz and a duty cycle of 50% and was rescaled to match the energy of the infant vocalization stimuli. We did not use amplitude envelope–matched control sounds because in our pilot experiments such sounds were perceived and rated quite similar to the original infant vocalizations, and, in addition, because previous work has shown that such sounds can activate the amygdala by themselves (Lorberbaum et al 2002). During fMRI, these 6-sec stimuli were presented in an event-related fashion (with 19-sec interstimulus intervals) through headphones and were randomly repeated 16 times. Subjects were informed that the determination of sex- and parental experience–dependent brain responses was one goal of the study. They were instructed to listen carefully to the stimuli but not to perform any output task or restrain emotional changes. After scanning, all subjects used the paper-and-pencil version of the Self-Assessment Manikin (SAM; Lang 1980) to rate the stimuli regarding emotional valence and arousal. The study was approved by the University of Basel Ethics Committee, and all subjects provided written, informed consent.

Anatomic (three-dimensional magnetization prepared rapid acquisition gradient-echo T1-sequence) and functional images (470 T2*-weighted gradient-recalled echo-planar sequence; repetition time = 2675 msec; 25 contiguous oblique slices; thickness = 4 mm; in-plane resolution, 2.8 × 2.8 mm^2; slab covered all but the apical ~20 mm of the brain) were acquired on a 1.5-Tesla Symphony scanner equipped with a Quantum gradient system and a circularly polarized head coil (Siemens, Erlangen, Germany).

Data Analysis

After the first four frames were discarded, images were corrected for slice-acquisition time, warped into Talairach space, re-sampled into 3-mm isotropic voxels, corrected for head motion and slow frequency drifts, and smoothed with a 6-mm full-width-at-half-maximum Gaussian kernel (BrainVoyager 4.6, Brain Innovation, Maastricht, The Netherlands).

The variance of all image time series was estimated voxel-wise according to a general linear model (Friston et al 1995) analysis embodying a direct coding of the differences between stimulus-specific BOLD responses (Friston et al 1998). A correction for serial correlations was adopted. The absolute responses to each stimulus type (laughing, crying, neutral sound) were obtained by convolving a boxcar reference function with a gamma kernel.

In the general linear model analysis, the effects of the differential responses to laughing (laughing minus control) and crying (crying minus control), as well as the differential response between crying and laughing (crying minus laughing), were contrasted. The common response to all three stimuli (laughing plus crying plus control) and the response to the control stimulus were used to complete two sets of orthonormal predictors and treated as confounds.

Table 1. Sex- and Parental Status–Dependent Effects in All Subjects and in the Subgroups

Group and Stimulus Contrast	Region	x/y/z	z score
Sex Effect (Infant Vocalizations vs. Neutral Control Stimulus, $[C - N] + [L - N]$)			
Women ($n = 20$) vs. Men ($n = 20$)	Right ACC	11/43/17	3.87[a]
Mothers ($n = 10$) vs. Fathers ($n = 10$)	Right ACC	6/50/12	3.30[b]
Childless Women ($n = 10$) vs. Men ($n = 10$)	Right ACC	10/44/22	3.60[b]
Parental Status Effect (Infant Crying vs. Laughing, $[C - L]$)			
Parents ($n = 20$) vs. nonparents ($n = 20$)	Right INS	44/10/6	4.66[a,c]
	Left INS	−40/13/6	4.68[a,c]
	Right AMY	32/−7/−14	3.79[a]
Mothers ($n = 10$) vs. childless women ($n = 10$)	Right INS	42/8/4	2.55[b]
	Left INS	−40/15/6	2.90[b]
	Right AMY	29/−13/−15	2.90[b]
Fathers ($n = 10$) vs. childless men ($n = 10$)	Right INS	43/10/6	3.04[b]
	Left INS	−38/13/6	2.95[b]
	Right AMY	27/−8/−9	2.74[b]

Coordinates are in Talairach space. *C*, infant crying; *L*, infant laughing; *N*, neutral control sound; ACC, anterior cingulate cortex; INS, insula; AMY, amygdala. The peak *z* scores obtained in the entire group comparisons (20 women vs. 20 men; 20 parents vs. 20 nonparents) refer to activity clusters that are significant with whole-brain correction for multiple comparisons, as specified below.

[a]According to randomization.

[b]The subgroup analyses, for which strong hypotheses existed based on the entire group analyses, were small-volume corrected on the basis of Gaussian field theory. Note, the condition $(C - N) + (L - N)$ did not yield significant brain responses for the comparison between parents and nonparents, and the condition $(C - L)$ did not yield significant brain activation for the comparison between women and men.

[c]According to Gaussian field theory.

Stimulus contrasts within the entire group were calculated with a one-sample, two-tailed *t* test and a significance threshold of $p < .001$ (voxel-wise Bonferroni-corrected for whole-brain multiple comparisons). Intergroup contrasts were computed with two-sample, two-tailed *t* tests, and the resulting statistical maps were thresholded according to the Gaussian field theory (Worsley et al 1996, 2002). A height- ($p < .05$) and cluster-level ($p < .001$) significance was accepted with either a whole-brain correction or a small-volume correction (Worsley et al 1996) for multiple comparisons. The small-volume correction criterion was applied only for clusters for which we had strong a priori anatomic hypotheses, that is in the subgroup analyses (Table 1). The resulting clusters of activation also underwent a whole-brain correction criterion for multiple comparisons, based on a randomization technique. A voxel-level threshold has been computed with the AFNI (Analysis of Functional NeuroImages; Cox and Hyde 1997) program AlphaSim (Ward 2000), with a minimum cluster size of 300 mm³, 10,000 simulations, a brain volume of 970.3 mL, and a 6-mm full-width-at-half-maximum spatial smoothing kernel.

To examine possible differences within the subgroups, sex differences were also calculated separately in the parents (mothers vs. fathers) and the nonparents (childless women vs. childless men), and parental status differences were also calculated separately for women (mothers vs. childless women) and for men (fathers vs. childless men). The activation clusters obtained for the contrasts in these subgroups have been thresholded with a small-volume correction for multiple comparisons within the regions of interests corresponding to those clusters that were found active in the entire intergroup contrasts. Thereby, we accepted the spatial coincidence of activation as a strong a priori anatomic hypothesis (Table 1).

To account for interindividual variance and to produce results pertaining to the population, all contrasts were computed with a random-effects model (Worsley et al 2002).

Statistical maps were projected on the folded cortical surface of the Talairach-transformed Montreal Neurologic Institute T1-weighted brain template (www.bic.mni.mcgill.ca).

Results

Response to Infant Vocalizations in All Subjects

To examine the effects of infant vocalizations in all 40 subjects, the brain response to infant crying and laughing was compared with the response to the control stimulus. This contrast produced specific activation in the Heschl's gyri and the polar and temporal planes, and in the superior temporal sulci extending to the superior and middle temporal gyri (Figure 1A). As suggested by the BOLD signal time course (Figure 1B), this brain response pattern was not specific for the type of infant vocalization. Formally, this was supported by a general linear contrast analysis (crying vs. laughing), which did not yield statistically significant differential brain activity when conventional thresholds were used. The response pattern was found in both hemispheres but tended to be more prominent on the right side. Interestingly, cortical or subcortical brain areas belonging to the "limbic" system were not activated in a statistically significant way. As will be shown below, this is related to interaction effects between group- and stimulus-specific patterns of activity that were canceled out considering the different types of stimuli and groups.
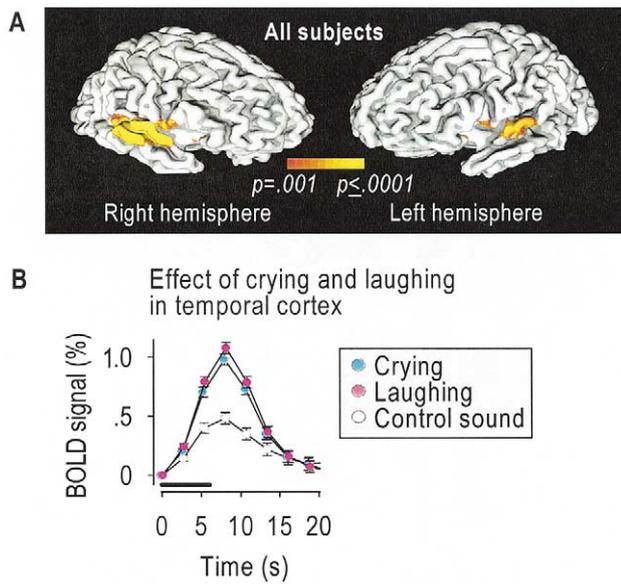
Figure 1. Pattern of human brain response to infant vocalizations. **(A)** Lateral view of right and left hemispheres, with color-coded brain areas that were activated by infant crying and laughing, in contrast to a neutral control stimulus. The subjects group ($n = 40$) was composed of 10 women and 10 men with young children and 10 women and 10 men without children. The activated areas in the temporal cortex included Heschl's gyri, polar and temporal planes, superior temporal sulci, and superior and middle temporal gyri. The p values, corrected for multiple comparisons, were obtained from statistical t maps calculated with general linear model contrasts. **(B)** Blood oxygen level–dependent (BOLD) signal time course (mean and standard error) in activated regions shown in **A**; horizontal line indicates 6-sec duration of stimulation.

Sex-Specific Response to Infant Crying and Laughing

To compare differential brain activation by infant vocalizations in women and men, we computed sex-specific group contrast patterns of response to crying and laughing versus the control stimulus (effect coding scheme: [crying minus control] plus [laughing minus control]). This yielded a significant difference of brain response in women compared with men. The response was locally confined to the right anterior cingulate cortex extending to the right mesial prefrontal cortex (Figure 2A) and was characterized by a BOLD signal decrease in women but not in men in response to infant crying and laughing (Figure 2B). As shown in Table 1, the same sex-related pattern of response was found in the subgroups of subjects, that is, in the comparison between mothers and fathers, and between childless women and men. This response pattern, whereas being specific for sex, did not discriminate the type of infant vocalization (no difference in brain response to infant crying vs. laughing). The alternative effect-coding scheme contrasting laughing and crying,
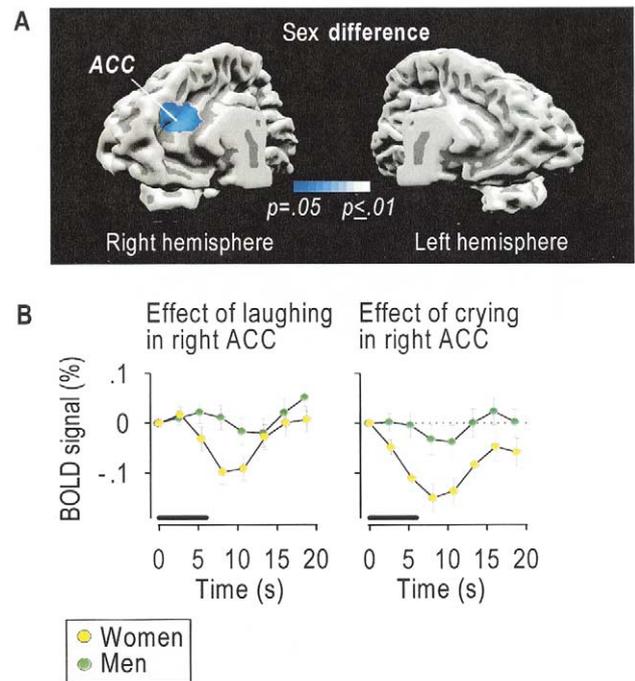

Figure 2. Sex difference in human brain response to infant vocalizations. Differential brain responses to crying and laughing in women ($n = 20$) vs. men ($n = 20$). **(A)** Medial side of isolated hemispheres, with color-coded brain area that showed a significant sex difference of response. The p values, corrected for multiple comparisons, were obtained from statistical t maps calculated with general linear model contrasts (further details in Table 1). **(B)** Blood oxygen level–dependent (BOLD) signal time course (mean and standard error) in activated region; horizontal line indicates 6-sec duration of stimulation. ACC, anterior cingulate cortex.

however, did not yield any sex-specific group effects. The BOLD signal decrease in response to infant vocalization found in women, which was not present in men, suggests that neural activity was decreased in women during the presentation of infant crying and laughing. In general, BOLD signal decreases need to be interpreted with caution, because they could represent vascular stealing effects related to perfusion reserve reallocation phenomena resulting from neural activation within nearby areas (Harel et al 2002); however, in the entire brain, and specifically in nearby areas, we found no increase in BOLD signal that could account for vascular stealing. Thus, these findings suggest that women had neural deactivation in the anterior cingulate and mesial prefrontal cortex in response to infant vocalizations (Shmuel et al 2002).

Parental Status–Specific Response to Infant Crying and Laughing

To compare differential brain activation by infant vocalizations in parents and nonparents, we first applied the

same effect-coding scheme that we used to discern the sex differences ([crying minus control] plus [laughing minus control]); however, this comparison did not yield any brain areas that were different in parents compared with non-parents. Thus, we examined whether this was related to differential parental responses to different types of infant vocalization. To calculate the group contrast between parents and nonparents, we used a stimulus contrast, which allowed us to detect differential brain responses to infant crying and laughing in the two groups. Using this alternative effect-coding scheme (crying minus laughing), we found differential brain responses specifically in the right amygdala, the middle cingulate cortex (right more than left), the insulae (bilateral), the left ventral prefrontal cortex, and the left temporoparietal junction (Figure 3A). In the right amygdala (Figure 3B) and the other areas shown in Figure 3A, the BOLD signal time course in the parents was characterized by a greater response to infant crying than laughing, whereas in the nonparents, the response was greater to infant laughing than crying. This group (parents vs. nonparents) $\times$ stimulus (crying vs. laughing) interaction is illustrated in Figure 3C. Because of susceptibility-induced signal loss and geometric distortions typically associated with T2*-weighted echoplanar images of subcortical structures (Merboldt et al 2001), the exact localization of response in the amygdala is generally difficult to determine; however, the focus of BOLD response is quite lateral and somewhat dorsal relative to the center of the amygdala. As shown in Table 1, the same parental status–dependent pattern of response was confirmed in the subgroups of subjects, that is, in the comparison between the 10 mothers and the 10 childless women, and between the 10 fathers and the 10 childless men; however, the significance level in the middle cingulate, the ventral prefrontal cortex, and the temporoparietal junction did not survive correction for multiple comparisons when we considered only these subgroups of 10 subjects each.

Emotional Valence and Arousal

Infant vocalizations increased arousal moderately (mean $\pm$ SD SAM ratings in mothers/fathers/childless women/childless men for crying: 6.8 $\pm$ 2.3/7.0 $\pm$ 1.7/7.0 $\pm$ 2.1/6.5 $\pm$ 2.1; laughing: 6.3 $\pm$ 2.0/6.5 $\pm$ 2.5/6.9 $\pm$ 2.2/6.2 $\pm$ 2.2), crying was associated with negative (2.8 $\pm$ 1.4/2.4 $\pm$ 1.3/2.5 $\pm$ 1.3/2.2 $\pm$ 1.1) and laughing with positive (7.6 $\pm$ 1.8/7.9 $\pm$ 1.6/7.9 $\pm$ 1.1/7.8 $\pm$ 1.2) emotional valence. The control stimulus was rated neutral (5.1 $\pm$ 2.1/4.8 $\pm$ 1.9/5.6 $\pm$ 1.8/5.1 $\pm$ 2.1) and was associated with low arousal (5.0 $\pm$ 2.2/4.5 $\pm$ 1.8/4.9 $\pm$ 1.9/5.0 $\pm$ 2.0). Although the emotional valence of crying versus laughing was significantly different for all groups, no group differences were found for the other ratings; consistent with

previous studies in which identical (Bradley and Lang 1999) or similar stimuli of infant vocalizations (Leger et al 1996) were used, the valence and arousal ratings did not significantly differ between groups. The dissociation between psychometric and neural activation pattern differences, for example in the amygdala, between specific subject groups in response to emotional stimuli is consistent with previous studies (Hariri et al 2002); however, we did not use the subjective ratings as covariates in the fMRI data analysis.

Discussion

Response to Infant Vocalizations in All Subjects

Irrespective of sex and parental status, infant vocalizations compared with the control stimulus, which was similar in its spectral composition and sound intensity but fundamentally different in its temporal structure compared with the infant vocalizations, produced neural activity in the Heschl's gyri and the temporal and polar planes, which encompass the "belt" and "parabelt" areas of the auditory cortex (Hackett et al 2001; Penhune et al 1996; Rademacher et al 1993; Rivier and Clarke 1997; Wallace et al 2002). These areas represent an early, nonprimary stage of cortical processing. In monkeys, neurons in the anterior belt are particularly involved in the recognition of the biological salience of species-specific communication calls, whereas neurons in the posterior belt participate in analyzing the spatial location of such calls (Tian et al 2001). In humans, belt areas carry out complex operations in the processing of temporal, spectral, and spatial auditory information (Kaas and Hackett 2000), show different patterns of neural response (Seifritz et al 2002), and represent an early segregation step in the auditory "what" and "where" neural streams (Rauschecker and Tian 2000). Furthermore, infant crying and laughing, compared with a control stimulus, produced neural activation in the superior temporal sulci extending to the superior and middle temporal gyri and the temporal plane, which was more intense on the right side. These findings, including the fact that there were no differences between the degree of activation in response to crying and laughing, correspond with previous evidence that these areas in the human auditory cortex are relatively specific for processing human speech and nonspeech vocal sounds (Belin et al 2000, 2002) and that the right hemisphere areas are involved in understanding prosody of speech (George et al 1996).

Sex-Specificity of Brain Response to Infant Vocalizations

Infant vocalizations produced a circumscribed neural activity change in the right anterior cingulate extending to
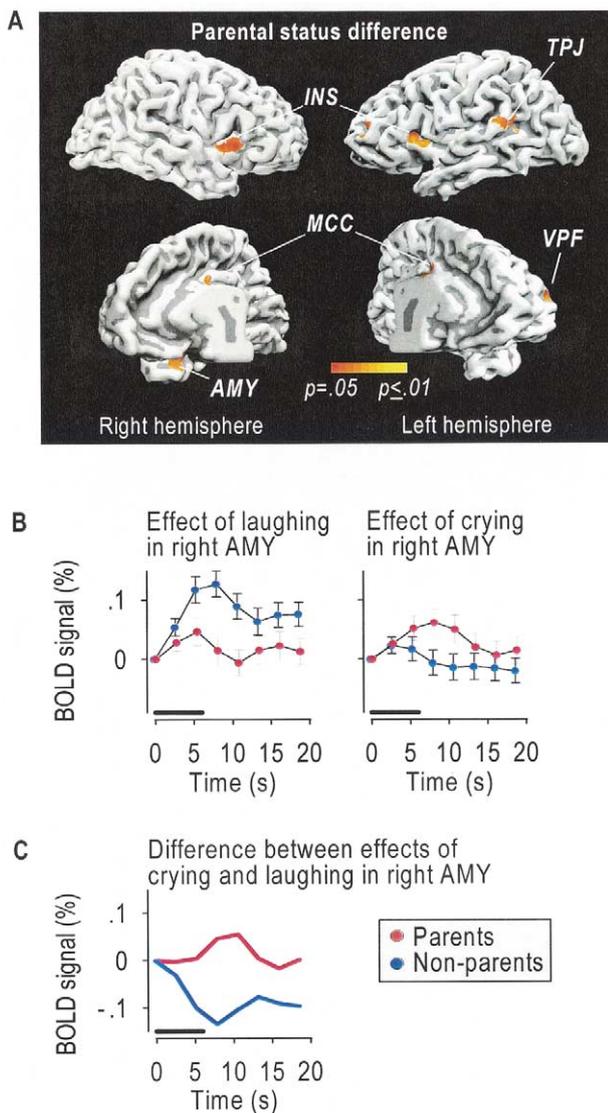
Figure 3. Parental status effect on human brain response to infant crying and laughing. Differential brain responses to crying and laughing in parents (*n* = 20) versus nonparents (*n* = 20). (**A**) Lateral and medial sides of isolated hemispheres. The *p* values, corrected for multiple comparisons, were obtained from statistical *t* maps calculated with general linear model contrasts (further details in Table 1). Note, except for left VPF (x/y/z coordinates, −43/43/16; *z* score, 3.51), right MCC (2/1/31; *z* score, 3.79), and left TPJ (−50/−47/16; *z* score, 3.55), all areas are corrected for multiple comparisons considering all voxels of the whole brain. (**B**) Blood oxygen level–dependent (BOLD) signal time course (mean and standard error) in the right amygdala; horizontal line indicates 6-sec duration of stimulation. (**C**) The group (parents vs. nonparents) × stimulus (crying vs. laughing) interaction in the right amygdala is illustrated by the positive net effect of crying minus laughing in parents and the negative net effect of crying minus laughing in nonparents. The same pattern of BOLD signal time course as that illustrated in **B** and **C** was present in the other brain areas shown in **A**. VPF, ventral prefrontal cortex. INS, insula; TPJ, temporoparietal junction; MCC, middle cingulate cortex; AMY, amygdala.

the right mesial prefrontal cortex in women but not in men, irrespective of parental status. These findings are not explained by previously reported sex-differences in responding to adult voices (Shaywitz et al 1995) or to adult laughing and crying (Sander and Scheich 2001; Sander et al 2003). In women, we found a BOLD signal decrease in response to crying and laughing, whereas in men, notably, no signal changes were observed in this region. These effects are not likely to be associated with nonspecific effects of estrogen on BOLD response, which would be expected to increase rather than decrease its amplitude (Dietrich et al 2001). In addition, ruling out possible confounds deriving from local perturbations in the hemodynamics, the present finding suggests to represent neural deactivation in the females' right anterior cingulate and mesial prefrontal cortex (Gusnard and Raichle 2001; Harel et al 2002; Shmuel et al 2002; Simpson et al 2001; Wade 2002). The localization is reminiscent of comparative anatomic studies in the human brain, which have shown macroscopic differences between female and male brains in this (Allen et al 2002) and interconnected (Gur et al 2002) regions. Our finding that functional sex differences were lateralized to the right hemisphere is furthermore consistent with the fact that previously reported morphologic sex differences in this prefrontal area are mainly characterized by lateralized size differences; most interestingly, the degree of this asymmetry is correlated across sexes with a temperamental predisposition to withdrawal-related behavior, including fear and anticipatory worry, a personality trait that is more prevalent in women than in men (Pujol et al 2002). The amount by which possible age-related changes in brain size, which are regionally different for women and men, might have biased these results cannot be determined in the present study.

Recent evidence suggests that neural deactivation in the anterior cingulate is related to gating processes suppressing less-relevant sensory information to optimize the cognitive and emotional resource recruitment for goal-directed behaviors (Gusnard and Raichle 2001) or anticipated emotional states (Simpson et al 2001). As such, our findings converge with the role of the prefrontal cortex, including the anterior cingulate, as a central relay station integrating emotional and cognitive processes (Bush et al 2000) and social decision making (Bechara et al 1997). This could particularly be important for successfully evaluating infant vocalizations. Our study cannot distinguish whether the observed sex specificity of brain response is the result of sex-related socialization factors or other mechanisms; however, recent evidence suggests that preference for specific sensory signals is also found in monkeys (Alexander and Hines 2002).

Experience-Dependent Changes in Brain Response to Infant Crying and Laughing

The brain responses to infant vocalizations dramatically changed with parental status. Parents showed a vocalization-specific pattern of response, with greater activation by infant crying than laughing. Nonparents, on the other hand, showed greater response to infant laughing than crying. This differential neural activation pattern was found in the amygdala, the middle cingulate cortex, the insula, the ventral prefrontal cortex, and the temporoparietal junction, areas that represent elements of an attentional network regulating cognitive and emotional processes (Albright et al 2000). For instance, some specific functions that are modulated by the amygdala include the processing of biologically significant stimuli, the recognition of emotions, and the evaluation of their salience (Adolphs 2002; Dolan 2002; LeDoux 2000). The focus of activity was localized to the lateral and dorsal portion of the amygdala. Because the lateral amygdala plays a key role in conditioning, as established in animals (Quirk et al 1997), this finding is suggestive for the view that the stimulus-specific pattern of amygdala response in parents might result from associative learning mechanisms. Interestingly, previous findings suggest that regions corresponding to this dorsolateral aspect of the amygdala are involved in resolving biologically relevant associative ambiguity (Whalen 1998), specifically if a context-dependent stimulus is presented and more information is required to decipher its predictive value (Whalen et al 2001). Our findings that parents respond stronger to crying than laughing fit with these concepts and seem to be biologically meaningful in terms of adaptation to the specific demands associated with successful infant care. This is also supported by electroencephalographic evidence that suggests that evoked responses to infant crying, compared with responses to other auditory stimuli, habituate slower in mothers of young children (Purhonen et al 2001). Notably, the pattern of brain activity we found in parents is somewhat different from previous findings in mothers of young children. This might be related to methodologic differences. Whereas our stimuli were brief, Lorberbaum et al (1999, 2002) presented infant crying to the subjects for as long as 30 sec, which could result in amygdala habituation phenomena during the presentation of the stimuli, which is often found in block design fMRI studies (Zald 2003). Interestingly, Lorberbaum et al (2002), who used white noise control stimuli that were matched to the original infant cries in their amplitude envelope, did not find amygdala responses if they contrasted the cries with the envelope-matched control sounds; however, they did find significant activity in the right amygdala in their group of breast-feeding women, both by contrasting the cries with rest or the control sounds with rest.

Our finding that similar neural response patterns were found in female and male parents converges with studies in nonhuman mammals, in which the expression of paren-tal behaviors depends on hormonal factors that are at least homologous in female and male subjects (Reburn and Wynne-Edwards 1999). For example, increases in prolactin levels have been implicated in parenting behaviors not only in female but also in male mammals (Dixson and George 1982), and, whereas estradiol plays a role in regulating maternal behaviors in female animals, the conversion of testosterone into estradiol is believed to be involved in regulating paternal behavior in male animals (Trainor and Marler 2002). Similar findings are increasingly being obtained in humans (Wynne-Edwards 2001); for example, human fathers show different peripheral steroid hormone levels compared with childless men (Storey et al 2000).

The changes in the context of parenthood are paralleled in female and male animal behavior, which can change fundamentally with appropriate exposure to offspring (vom Saal and Howard 1982), and are likely to provide a selective advantage (Gubernick and Teferi 2000). We suggest that our findings represent at least some aspect of neural plasticity underlying this adaptive cascade. Interestingly, pathophysiologic maladaptive plastic alterations observed (for instance) in affective disorders take place in brain areas that correspond with those we found to be sexually dimorphic as well as those we found to be altered with parenthood (Davidson et al 2002; Drevets 2001); however, not only pathologic but also physiologic factors, such as normal personality trait variations, can modulate the neural response in the amygdala to emotionally laden stimuli (Canli et al 2002). An important aspect, for methodologic reasons not addressed in the current study, is whether the group and stimulus-type interaction is subject to differential temporal profiles, and whether different brain areas exhibit different habituation-like adaptation phenomena (Fischer et al 2003).

Our results show that both sex-specific and experience-dependent neural plasticity shape the human brain response to infant crying and laughing in specific brain areas. The finding that the brain areas exhibiting experience-dependent plasticity were not colocalized with those showing sex-dependent differences suggests that they might subserve specific and status-dependent roles in processing such stimuli. Although the sex-dependent effect on brain response was independent of the message conveyed by the stimulus (crying or laughing), the effect of the experience-dependent response pattern discriminated between different stimulus qualities. These experience-dependent neuroplastic changes in the human brain, irrespective of sexually dimorphic functions, are likely to subserve the biological needs of parental care. This can be

a critical element in bonding and in securing offspring well-being and survival, thus fostering the reproductive fitness of subsequent generations.

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