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NEURAL CORRELATES OF SAD FEELINGS IN HEALTHY GIRLS

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Abstract—Emotional development is indisputably one of the cornerstones of personality development during infancy. According to the differential emotions theory (DET), primary emotions are constituted of three distinct components: the neural–evaluative, the expressive, and the experiential. The DET further assumes that these three components are biologically based and functional nearly from birth. Such a view entails that the neural substrate of primary emotions must be similar in children and adults. Guided by this assumption of the DET, the present functional magnetic resonance imaging study was conducted to identify the neural correlates of sad feelings in healthy children. Fourteen healthy girls (aged 8–10) were scanned while they watched sad film excerpts aimed at externally inducing a transient state of sadness (activation task). Emotionally neutral film excerpts were also presented to the subjects (reference task). The subtraction of the brain activity measured during the viewing of the emotionally neutral film excerpts from that noted during the viewing of the sad film excerpts revealed that sad feelings were associated with significant bilateral activations of the midbrain, the medial prefrontal cortex (Brodmann area [BA] 10), and the anterior temporal pole (BA 21). A significant locus of activation was also noted in the right ventrolateral prefrontal cortex (BA 47). These results are compatible with those of previous functional neuroimaging studies of sadness in adults. They suggest that the neural substrate underlying the subjective experience of sadness is comparable in children and adults. Such a similitude provides empirical support to the DET assumption that the neural substrate of primary emotions is biologically based.

Key words: sadness, subjective experience, children, functional magnetic resonance imaging.

Emotional maturation indisputably represents one of the cornerstones of personality development during infancy. Regarding this question, Malatesta and colleagues (1989) have found that emotional expressive patterns tend to show stability during infancy across a wide range of primary emotions. This kind of stability extends to the preschool year, as revealed by the work of LaFrenière and Sroufe (1985). These findings have led some researchers to emphasize the importance of "emotional style" for emotional development. This concept refers to the fact that relatively ingrained and stable components of personality modulate the way children express and experience primary emotions (Malatesta et al., 1989; Tomkins, 1962, 1963, 1991). With respect to this issue, it has been well demonstrated that there are marked individual differences regarding the extent to which children may become emotionally aroused by various types of stimuli (Denham, 1998).

One theoretical view that accords with the concept of emotional style is the differential emotions theory (DET; Izard, 1992). According to the DET, the self and the mental life are based on the early establishment of stable "affective–cognitive" schemas, and emotional development refers to "the processes whereby the emotions system achieves an increasingly complex matrix of functional links with the other subsystems of the individual—the physiological/drive, perceptual, cognitive, and action systems" (Izard, 1994, p. 356). This theory posits that primary emotions are subsystems of the emotion system. Primary emotions are constituted of three distinct components: the neural-evaluative, the expressive, and the experiential (Izard, 1992). The DET further contends that these three components are biologically based and functional nearly from birth (Izard, 1992). It follows from this assumption that the neural substrate of primary emotions must be comparable in childhood and adulthood.

To date, functional neuroimaging studies of sadness in healthy adults (Pardo et al., 1993; George et al., 1995; Lane et al., 1997; Beauregard et al., 1998; Damasio et al., 2000; Lévesque et al., 2003) have found on a more or less consistent basis that the subjective experience of sadness

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Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; BOLD, blood-oxygenation-level-dependent; DET, differential emotions theory; EPI, echoplanar images; fMRI, functional magnetic resonance imaging; FOV, field of view; MNI, Montreal Neurological Institute; MPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; ROI, region of interest; SPM, statistical parametric map; TE, time-echo; TR, time repetition; VLPFC, ventrolateral prefrontal cortex.

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is associated with activation in several limbic and paralimbic brain regions such as the ventrolateral prefrontal cortex (VLPFC), the medial prefrontal cortex (MPFC), the anterior cingulate cortex (ACC), the anterior temporal pole, the insula, the amygdala, the hypothalamus, the pons, and the midbrain. Guided by this bulk of data and the DET, the present functional magnetic resonance imaging (fMRI) study was conducted to investigate the neural correlates of externally induced sad feelings in healthy children. We predicted a priori that the subjective experience of sadness in healthy children would be associated with significant blood-oxygenation-level-dependent (BOLD) signal changes in the brain regions that have previously been associated with sadness in adults. To our knowledge, this is the first attempt at delineating the neural correlates of the feelings associated with a primary emotion in children.

EXPERIMENTAL PROCEDURES

Subjects

Fourteen healthy Caucasian right-handed girls (age range: 8–10; mean age: 9.8) took part in this study. Girls were studied to allow qualitative comparisons with the results of our previous study conducted in women using exactly the same protocol (Lévesque et al., 2003). None of the subjects presented a history of neurological or psychiatric disorder. As confirmed by the subjects' mothers, all subjects were prepubescent. The parents of the subjects gave written inform consent and the study was approved by the ethics committee of Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame.

Behavioral protocol

Before scanning. To insure that all subjects would feel at ease with the scanning procedure, they first saw (several days before the actual experiment), with their parents and in the comfort of their homes, a videotape explaining in lay terms what is a magnetic resonance imaging (MRI) scanner and how it works. On the day of the experiment, the experimenter asked if the subjects (and their parents) had any question about this videotape. Afterward, a detailed step-by-step explanation of the protocol was given to the subjects regarding their installation in the scanner and the equipment (goggles and headphones) that they would wear during scanning. Subjects were also presented with a numerical (analog) rating scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotion ever felt in one's lifetime) and used to evaluate the emotional state of the subjects during the experiment. To make sure that they understood the various emotional intensities represented by the numbers of the scale, the experimenter asked the subjects to rate from 0 to 8 five sad events having occurred lately in their life. Finally, in order to avoid as much as possible brain activation patterns due to anxiety or fear, only subjects who appeared at ease and said they felt at ease with the scanning procedure were included in the study.

During scanning. BOLD signal changes were measured while subjects first viewed four blocks of emotionally neutral film excerpts (reference task) and, then, four blocks of sad film excerpts (activation task). Based on evidence gathered previously by our group, this design was adopted to avoid contamination of the neutral stimuli by the sad stimuli (unpublished data). Each block lasted 48 s and was separated by resting periods of 15 s during which subjects viewed a blue cyan screen. Subjects were instructed to react normally to the sad film excerpts, that is, to allow themselves to become sad in response to these stimuli. Subjects were also instructed to look directly at both categories of stimuli. Sad film excerpts depicted the death of a beloved person, either a father, a mother, or a friend. Each excerpt depicted either a group of children, or a child and one or more adults. The emotionally neutral film excerpts were matched to the sad film excerpts with respect to the number and gender of the individuals depicted in these excerpts. Emotionally neutral film excerpts depicted various human activities (e.g. interviews, carpentry, etc.). To assess the subjective responses of the subjects to the stimuli, immediately at the end of the run, they were asked to rate verbally using the numerical (analog) rating scale the average intensity of sadness or of any other primary emotions (e.g. happiness, disgust, fear, anger, surprise (Plutchik, 1994) felt during the viewing of both categories of film excerpts. An average rating score was computed for the four blocks of sad film excerpts and the four blocks of emotionally neutral film excerpts.

Image acquisition and analysis

Echoplanar images (EPI) were acquired on a 1.5 Tesla system (Magnetom Vision; Siemens Electric, Erlangen, Germany). Twenty-eight slices (5 mm thick) were acquired every 2.65 s in an inclined axial plane, aligned with the anterior commissure–posterior commissure axis. These T2*-weighted functional images were acquired using an EPI pulse sequence (time repetition [TR]=0.8 ms, time-echo [TE]=54 ms, flip=90°, field of view [FOV]=215 mm, matrix=64×64, voxel size=3.36 mm×3.36 mm×5 mm). Following functional scanning, high-resolution data were acquired via a Tl-weighted three-dimensional volume acquisition obtained using a gradient echo pulse sequence (TR=9.7 ms, TE=4 ms, flip=12° FOV=250 mm, matrix=256×256, voxel size=0.94 mm^3).

Data were analyzed using Statistical Parametric Mapping software (SPM99; Wellcome Department of Cognitive Neurology, London, UK). Images for all subjects were realigned to correct for artifacts due to small head movements. The gradient-recalled echo-planar sequence that we used is associated with large static magnetic field inhomogeneities commonly found near air/tissue interfaces (Cordes et al., 2000). These inhomogeneities can create artifacts like signal loss and voxel shifts in the ventral frontal, medial temporal, and inferior temporal regions (Song, 2001). To correct for such artifacts, a mask was applied to the slices of the mean EPI image which presented signal loss. This procedure was implemented for every subject. The images for all subjects were then spatially normalized into an MRI stereotactic space (Montreal Neurological Institute [MNI] template) using this masked mean image. Even if the subjects were children, the MNI template (adult's template) was used. Indeed, Burgund and colleagues (2002) have shown, in a recent MRI study, that even if there are some small anatomical differences between the brain's structures and sulci of adults (age range: 18–30) compared with those of children (age range: 7–8), such minimal differences do not compromise the usefulness of an adult stereotactic space for children's fMRI images, assuming a functional resolution of 5 mm in images averaged across children. Images were also convolved in space with a three-dimensional isotropic gaussian kernel (12 mm full width half maximum) to improve the signal-to-noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization.

Statistical analyses

The time series of the images were convolved with the delayed box-car function which approximates the activation patterns. Effects at each and every voxel were estimated using the general linear model. Voxel values for the contrasts of interest yielded a statistical parametric map of the *t* statistic (SPM *t*), subsequently transformed to the unit normal distribution, (SPM Z). A "fixed-effects model" was implemented to contrast the brain activity associated with the viewing of the sad film excerpts and that

Table 1. Significant loci of activation during sadness (Sad-Neutral)[a]

Region	Brodmann area	Talairach and Tournoux coordinates, mm			Z-statistic	Corrected *P* value
		x	y	z		
R Anterior temporal pole	21	50	7	−26	3.65	$P<0.002$
R MPFC	10	3	56	17	3.13	$P<0.014$
R Midbrain		3	−30	−9	3.06	$P<0.019$
L MPFC	10	−1	57	−15	2.96	$P<0.022$
L Anterior temporal pole	21	−50	4	−28	2.84	$P<0.023$
L Midbrain		−3	32	−8	2.82	$P<0.037$
R VLPFC	47	3	56	17	2.57	$P<0.002$

[a] Stereotaxic coordinates are derived from the human atlas of Talairach and Tournoux (1988) and refer to medial–lateral position (x) relative to midline (positive=right), anterior–posterior position (y) relative to the anterior commissure (positive=anterior), and superior–inferior position (z) relative to the commissural line (positive=superior). Designation of Brodmann areas for cortical areas is also based on this atlas. L, left; R, right.

associated with the viewing of the emotionally neutral film excerpts (Sad−Neutral). This "fixed-effects model" produced individual contrast images, which were used as raw data for the implementation of a "random-effects model" (Friston and Frackowiak, 1997). An a priori search strategy was used and a small volume correction was performed in the following brain regions of interest (ROIs): VLPFC (Brodmann area [BA] 47), MPFC (BA 9 and 10), ACC (affective division: rostral areas of BA 24a–c and 32, ventral areas of BA 25 and 33; Bush et al., 2000), anterior temporal pole (BA 21 and 38), insula, amygdala, hypothalamus, pons, and midbrain. The search volume corresponding to the ROIs was defined by tracing the neuroanatomical boundaries of these regions on the MR reference image (MNI template), using the small volume correction function and box volume function in SPM99. For this a priori search, a corrected probability threshold for multiple comparisons of $P<0.05$ corrected was used. Only clusters showing a spatial extent of at least five contiguous voxels were kept for image analysis.

RESULTS

Self-report data

From a phenomenological perspective, the viewing of the sad film excerpts induced a transient state of sadness in all subjects. Actually, all subjects reported feeling sad during the viewing of the sad film excerpts and some of them even cried. The mean level of reported sadness was 5/8 (S.D.=2; range 2–8). The viewing of the sad film excerpts did not produce other significant change of the emotional state than sadness (mean levels: happiness: 0; anger: 0; disgust: 0.9; surprise: 0.5; fear: 0.5) Likewise, the viewing of the neutral film excerpts did not generate any marked alteration of the emotional state (Mmean levels: sadness: 0.0; happiness: 0.8; anger: 0.1; disgust: 0; surprise: 0.9; fear: 0.3).

FMRI data (Sad−Neutral)

From a functional neuroanatomical perspective, the subtraction of the brain activity associated with the viewing of the neutral film excerpts from that associated with the viewing of the sad film excerpts revealed significant bilateral activations in the midbrain, anterior temporal pole (BA 21), and MPFC (BA 10). A significant locus of activation was also noted in the right VLPFC (BA 47; Table 1; Fig. 1).

DISCUSSION

This fMRI study was undertaken to identify the neural correlates of sad feelings in healthy children. Results showed that the transient state of sadness, externally induced using sad film excerpts, was associated with significant loci of activation in the midbrain, the anterior temporal pole (BA 21), the MPFC (BA 10), and the right VLPFC (BA 47).

Comparison with previous functional neuroimaging studies of sadness in adults

Collectively, the neural correlates of sadness found here in children are comparable to those reported in previous functional neuroimaging studies of sadness in adults. Indeed, significant loci of activation have been previously noted in the midbrain (Lane et al., 1997), the anterior temporal pole (Lane et al., 1997), the MPFC (Beauregard et al., 1998; Lane et al., 1997), and the right VLPFC (Beauregard et al., 1998) when sad feelings were induced externally (e.g. with sad film excerpts). Significant loci of activation have also been seen in the midbrain (Damasio et al., 2000), the anterior temporal pole (Damasio et al., 2000), and the MPFC (George et al., 1995) while subjects had to recall and/or re-enact sad events.

Our group has recently conducted a fMRI study in healthy women (20 subjects; age range: 20–30) using exactly the same protocol and the same film excerpts than in the present investigation (Lévesque et al., 2003). Phenomenologically, the scores on the emotion rating scale were very similar. As mentioned above, the mean level of reported sadness in girls was 5/8 (S.D.=2; range 2–8) whereas, in women, this level was 5.15/8 (S.D.=1.30; range: 2–7). Moreover, as it is the case here for girls, women did not report experiencing other primary emotion during the viewing of the sad film excerpts. Thus, based on the self-report data, it appears that in these two studies, both groups of subjects experienced sadness with a relative specificity, and that the intensity of the sad feelings was analogous.

Likewise, the patterns of brain activation associated with sadness were relatively comparable in these two fMRI studies. Indeed, for both girls and women, the viewing of

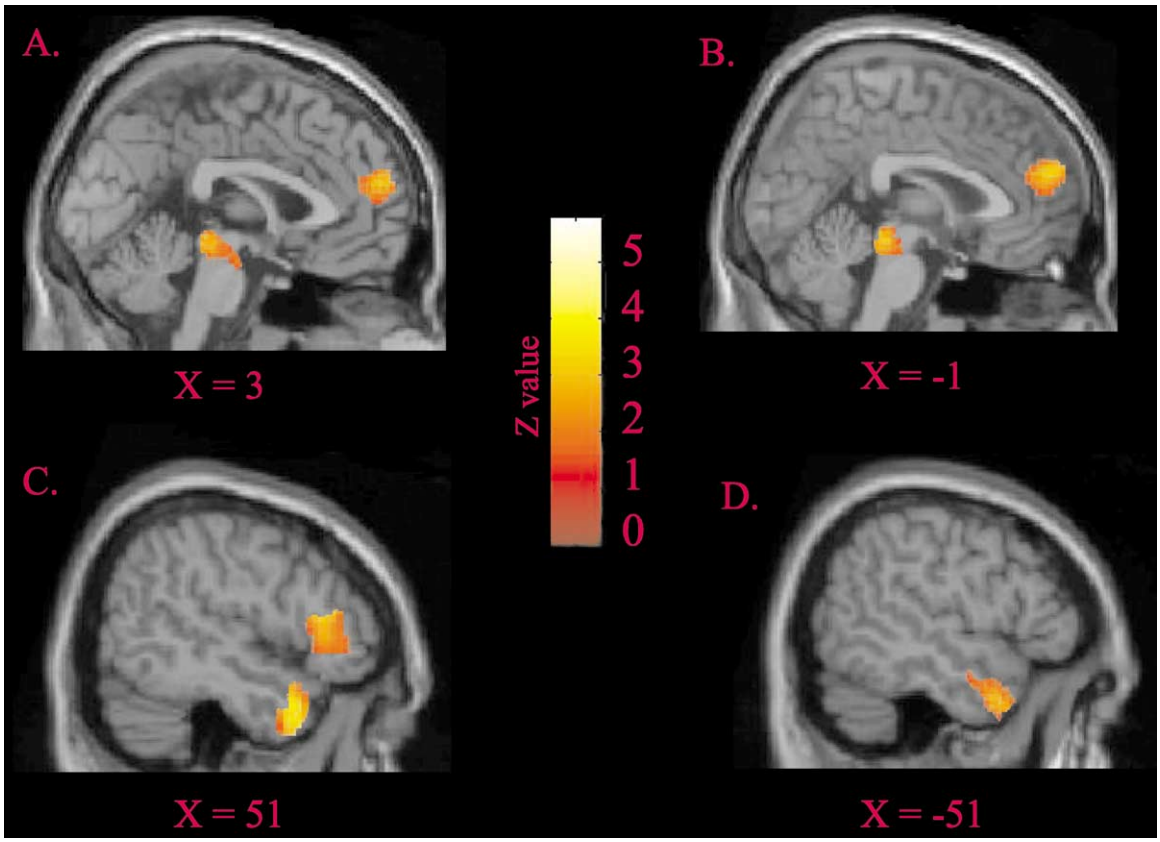

Fig. 1. Statistical activation maps for the brain regions defined a priori. Images are sagittal sections for the data averaged across subjects. During the transient state of sadness, significant loci of activation were noted in a) the right MPFC (BA 10) and the right midbrain, b) the left MPFC (BA 10) and the left midbrain, c) the right VLPFC (BA 47) and the right anterior temporal pole (BA 21), and d) the left anterior temporal pole (BA 21).

the sad film excerpts was associated with activation of the anterior temporal pole (BA 21) and the midbrain, bilaterally, as well as with activation of the right VLPFC (BA 47). Such a similitude provides empirical support to our a priori hypothesis. However, there were also some differences in the patterns of brain activation noted in these two investigations. Actually, significant loci of activation in the amygdala, the insula and the anterior temporal pole (BA 38) were found only in women, whereas the MPFC (BA 10) was activated only in girls. To account for these differences, we examined the individual SPMs generated in the two studies. Interestingly, in girls, the amygdala was activated in 40% of the subjects while the insula was activated in 60% of the subjects. In addition, the anterior temporal pole (BA 38) was found activated in 80% of the subjects. These loci of activation barely fell short of statistical significance. In women, activation of the MPFC was noted in 40% the subjects. Again these BOLD signal increases were just beneath significance. Of note is the fact that, in both groups of subjects, the individual SPMs revealed an important degree of interindividual variability in terms of the functional neuroanatomy underlying sad feelings (as in the case of another fMRI study recently carried out by our group; see Eugène et al., 2003). That is, across subjects belonging to the same group (girls versus women), the activated voxels in a given brain region were not consistently localized within the same regional subdivisions. Therefore, it seems reasonable to assume that individual differences in regional cerebral patterns of activation may be responsible, at least in part, for the differences found between girls and women with respect to the neural correlates of sadness. Differences in what Davidson (1992) has termed “affective style” could be related to the inter-individual variability noted in these two studies. It is conceivable that other personality variables may also underlie such inter-individual variability. With respect to this issue, there is mounting evidence that neural activity in the cerebral cortex may be related to specific dimensions of personality (Sugiura et al., 2000). Alternatively, we cannot rule out the possibility that differences in brain maturation could account for some of the differences in patterns of brain activation found between these two studies (although no clear relationship has been evidenced yet between brain maturation and emotional development).

Role of the various brain regions activated in children during sadness

Activation of the anterior temporal pole has been reported, in healthy adults, during normal anticipatory anxiety (Reiman et al., 1989; Chua et al., 1999), script-generated anger and anxiety (Dougherty et al., 1999; Damasio et al.,

2000; Kimbrell et al., 1999), film-induced sexual arousal (Beauregard et al., 2001), and memory-driven sadness (Lane et al., 1997). This paralimbic cortical region receives inputs from unimodal and heteromodal sensory regions as well as limbic inputs. It has been proposed by Mesulam (1985) that the anterior temporopolar region may be associated with imparting affective tone to the individual's experience. In this context, it is possible that the anterior temporopolar activations of the anterior temporal pole seen here reflected the attribution of the emotional (sad) color to the subjective experience externally induced by the sad film excerpts.

The midbrain has been found activated in functional neuroimaging studies of various emotional states (e.g. disgust, sadness, anger, fear, happiness, pain and anxiety) (Fredrikson et al., 1995; Lane et al., 1997; Rauch et al., 1997; Tölle et al., 1999; Damasio et al., 2000; Lévesque et al., 2003). There is some evidence suggesting that this cerebral structure is involved in the mediation of autonomic responses such as skin conductance responses (Sequeira and Roy, 1993) and body temperature changes (Nagashima et al., 2000). Given that autonomic responses often accompanied the subjective experience of primary emotions (Damasio et al., 2000), the bilateral midbrain activations noted here may be related to the autonomic responses associated with subjects' sad feelings.

The MPFC has been reported to be activated in several functional neuroimaging studies of sadness conducted in healthy adults (Beauregard et al., 1998; Damasio et al., 2000; George et al., 1995, 1996; Lane et al., 1997; Reiman et al., 1997). This prefrontal cortical region has also been associated with other positive (e.g. happiness) and negative (e.g. disgust) emotions, regardless of the emotion-induction procedure used (e.g. film, pictures, recall of emotional events; George et al., 1996; Lane et al., 1997; Reiman et al., 1997; Teasdale et al., 1999). The MPFC, which sends extensive connections to the hypothalamus and brain stem and is the site of convergence for limbic inputs, has been postulated to participate in the integration of cognition and emotion (Mesulam, 1985). In keeping with this, studies of patients with damage to the MPFC suggest that this cortical area is involved in the conscious monitoring of the individual's emotional state (Damasio et al., 1994). The bilateral MPFC activations found here may be related to such a metacognitive process.

Activation of the VLPFC has been reported, in adult subjects, during externally (e.g. looking at human faces) and/or internally (e.g. recalling appropriate life events) induced sadness (Pardo et al., 1993; George et al., 1995; Beauregard et al., 1998; Damasio et al., 2000), anxiety (Fredrikson et al., 1997; Kimbrell et al., 1999), and anger (Dougherty et al., 1999; Kimbrell et al., 1999). These findings suggest that the VLPFC participates in aspects of emotion processing that are not exclusively related to a discrete emotion in particular. Given the fact that this prefrontal cortical region receives extensive sensory inputs (olfactory, gustatory, visceral afferent, somatic sensory, and visual) as well as limbic inputs from the amygdala, entorhinal and perirhinal cortex, and subiculum, it seems plausible that the VLPFC activation noted here may be associated with the integration of viscerosensory information with information signaling changes in the subjects' emotional state.

Factors influencing the neural processing related to emotion with regard to emotional development

The fact that the neural correlates of sadness found here in children are comparable to those reported in previous functional neuroimaging studies of sadness in adults fits rather nicely with one of the assumptions of the DET. Indeed, this theory postulates that the neural-evaluative component of primary emotions is biologically based and functional from birth or nearly after (Izard, 1992). Such a view entails that the neural substrate of primary emotions is similar in children and adults. Another assumption of the DET is that emotional experience is a direct product of the neural-evaluative component. Therefore, the experiential dimension of emotion does not develop over time (Izard, 1992). With regard to this issue, the DET further contends that the motivational/feeling states associated with primary emotions remain invariant across lifespan (Campos and Barrett, 1984; Emde, 1980), and that only cognitive development and social learning can give rise to secondary emotions such as contempt, guilt or shame (Ackerman et al., 1998). This last assumption has been overtly questioned by Dunn (1994) who argues that, as children grow up, there are important changes in emotion eliciting conditions that necessarily imply changes in the emotional experience itself. For Dunn and other proponents of the cognitive perspective to emotional development, emotion is a function of cognition inasmuch as it refers to various relations among external incentives, thoughts and detected changes in internal feeling states (Kagan, 1978, 1984, 1994; Mandler, 1984, 1990).

Besides cognitive development, social environment (Dickson et al., 1998) and culture (Mesquita and Frijda, 1992) are two other factors playing a pivotal role in emotional development. According to the social view of emotion, the transaction between the individual and the environment constitutes the core aspect of emotional development (Dickson et al., 1998). Emotions are not encapsulated in the individual, "... but are socially constructed, dynamically created out of the constituents' interaction" (Dickson et al., 1998, p. 256). In the cultural perspective, emotion "...is an event-elicited response set that involves one's relationship to some object or person (possibly the self), and that involves control precedence" (Frijda and Mesquita, 1998, p. 276). Within the cultural perspective, the precedence or the context that precedes an emotion is a crucial aspect of emotional development and may vary tremendously from one culture to another. For instance, Iktu Inuits have different words for sadness depending on the eliciting conditions (Briggs, 1970).

Whether or not the neural substrate of primary emotions is present and functional from birth or nearly after, we submit that cognitive development, social environment and culture all contribute to emotional development and influ-

ence the nature of the emotional experience across lifespan by modulating neural processing in the brain regions underlying the various components (e.g. cognitive, experiential, physiological, behavioral) of emotion. For instance, a moral value inculcated in a 6-year-old child by her parents may exert a major influence on the way this child will later react emotionally to certain types of situations or events. By definition, such a regulating influence implies a modulation of the neural circuitry related with the diverse aspects of emotion.

CONCLUSION

In this fMRI study, an externally induced state of sadness was associated, in healthy girls, with significant loci of activations, bilaterally, in the midbrain, the MPFC (BA 10), and the anterior temporal pole (BA 21). A significant locus of activation was also found in the right VLPFC (BA 47). These results are compatible with those of previous functional neuroimaging studies of sadness in adults. They suggest that the neural substrate underlying the subjective experience of sadness is comparable in children and adults. Such a similitude provides empirical support to the DET assumption that the neural substrate of primary emotions is biologically based. However, as our subjects were aged between 8 and 10 years, our results cannot validate the DET assumption saying that the neural substrate of primary emotions is functional from birth or nearly after.

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