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NEURAL BASIS OF EMOTIONAL SELF-REGULATION IN CHILDHOOD

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Abstract—Emotional self-regulation plays a pivotal role in socialization and moral development. This capacity critically depends on the development of the prefrontal cortex (PFC). The present functional magnetic resonance imaging study was conducted to identify the neural circuitry underlying voluntary self-regulation of sadness in healthy girls (aged 8–10). A 2×2 factorial design was implemented with Emotion (No Sadness vs. Sadness) and Regulation (No Reappraisal vs. Reappraisal) as factors. In the No Reappraisal conditions, subjects were instructed to react normally to neutral and sad film excerpts whereas in the Reappraisal conditions, subjects were asked to voluntarily suppress any emotional reaction in response to comparable stimuli. A significant interaction of the Emotion and Regulation factors revealed that reappraisal of sad film excerpts was associated with bilateral activations of the lateral PFC (LPFC; Brodmann areas [BA] 9 and 10), orbitofrontal cortex (OFC; BA 11), and medial PFC (BA 9 and 10). Significant loci of activations were also detected in the right anterior cingulate cortex (BA 24/32) and right ventrolateral PFC (BA 47). In an identical study previously conducted by our group in adult women [Biol Psychiatry 53 (2003) 502], reappraisal of sad film excerpts was associated with activation of the right OFC (BA 11) and right LPFC (BA 9). The greater number of prefrontal loci of activation found in children relative to adults during voluntary self-regulation of sadness may be related to the immaturity of the prefronto-limbic connections in childhood.

Key words: emotional self-regulation, sadness, children, prefrontal cortex, functional magnetic resonance imaging.

According to evolutionary psychology, biologically based emotions represent efficient modes of adaptation to changing environmental demands (Tooby and Cosmides, 1990). From this theoretical perspective, emotions have emerged in the course of evolution by virtue of their capacity to adequately co-ordinate the diverse response systems (e.g. cognitive, subjective, physiological, and behavioral) that characterize emotion's multidimensional nature (Levenson, 1994). As noted by Gross (1999), however, emotions are not always the most pertinent response to the various situations encountered in daily life. Regarding this issue, negative emotions are undoubtedly one of the main causes of human suffering. This is why it is essential for human beings to learn how to properly control their emotional reactions, using their cognitive capacities. This point leads us directly to the construct of emotional self-regulation.

This construct refers to the heterogeneous set of cognitive processes by which emotions are regulated, i.e. the ways individuals influence which emotions they have, when they have them, and how they experience and express these emotions (Gross, 1999). This form of self-regulation implicates changes in one or more of the various response systems of emotion (Gross, 1999). Emotional self-regulation involves generating, maintaining, decreasing, or increasing positive or negative emotions (Masters, 1991; Parrott, 1993; Cole et al., 1994; Langston, 1994). This capacity is associated with several types of adjustments that favor the adaptation to life circumstances (Cole et al., 1994) and allow the realization of personal goals (Thompson, 1990). The cognitive strategies used to self-regulate emotion are numerous and include, among others, rationalization, reappraisal, and suppression (Gross, 1999).

Emotional self-regulation constitutes one of the cornerstones of socialization and moral development (Kochanska et al., 1997). To date, much of the research into the development of emotional self-regulation has focused on infancy and toddlerhood, primarily because a dramatic cognitive maturation is taking place during these developmental periods (Calkins, 2004). Stuss (1992) has proposed that the capacity to self-regulate, a crucial executive function, develops in close relationship with the development of the prefrontal cortex (PFC). This hypothesis has received some empirical support from magnetic resonance imaging (MRI) studies of structural and functional changes in the developing human brain during the first few decades

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Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; BOLD, blood-oxygenation-level-dependent; EPI, echoplanar images; fMRI, functional magnetic resonance imaging; FOV, field of view; IAPS, International Affective Picture System; LH, left hemisphere; LPFC, lateral prefrontal cortex; MNI, Montreal Neurological Institute; MPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; OFC, orbitofrontal cortex; PFC, prefrontal cortex; RH, right hemisphere; ROI, region of interest; SPM, statistical parametric map; TE, time-echo; VLPFC, ventrolateral prefrontal cortex.

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of life (for review, see Casey et al., 2000). In particular, a recent event-related functional MRI (fMRI) study (Bunge et al., 2002) comparing interference reappraisal and response inhibition in children (aged between 8 and 12) and adults has shown that children were more prone to interference and had more difficulty to inhibit inappropriate responses than adults. Moreover, effective interference suppression in children was associated with PFC activation but in the opposite hemisphere compared with adults. Bunge et al. (2002) concluded that the immaturity of the PFC accounted for this difference.

With regard to this question, it is noteworthy that myelination and dendritic development occur later in the human PFC than in other cortical regions. Synaptogenesis reaches a plateau between the ages of 1 and 7 and declines through adolescence to the adult level (Bourgeois et al., 1994; Huttenlocher, 1994; Rakic et al., 1994). This decrease in synaptic number coincides with the continued development of cognitive capacities (Caviness et al., 1996). In addition, cortical gray matter volume achieves its peak at around 5 years of age and decreases from that time forward, while the white matter volume increases constantly until about the age of 20 years (Pfefferbaum et al., 1994). Concerning myelination, Yakovlev and Lecours (1967) have postulated that it might continue in the PFC well into the third decade of life. Interestingly, Fox et al. (2001) have emphasized the obvious similarities between the disinhibited behaviors of adults following damage to the PFC and the emotional reactions and behaviors of normal infants and young children. The cognitive and emotional changes following PFC damage have been attributed to a disruption in the inhibitory control normally exerted by the PFC on subcortical "limbic" structures. In line with this, Posner and Rothbart (1998) have proposed that emotional self-regulation likely involves the interaction of the midfrontal anterior cingulate cortex (ACC) with the amygdala. In addition, early-acquired orbitofrontal cortex (OFC) damage has been associated with disruption to socio-emotional regulation (Eslinger et al., 1997).

The present fMRI study was conducted to identify the neural circuitry underlying voluntary self-regulation of sadness in healthy children. This study represents the continuation of a fMRI study recently carried out by our group (Lévesque et al., 2003) in healthy women. In this previous study, we found that voluntary suppression of sadness was associated with significant loci of activation in the right OFC (Brodmann area [BA] 11) and right lateral PFC (LPFC; BA 9). Based on these findings and the corpus of knowledge abovementioned about the neural substrate underlying the development of emotional self-regulation, we hypothesized that various subdivisions of the PFC (e.g. LPFC, OFC, ACC, and medial PFC [MPFC]) would be associated with voluntary suppression of sadness in children.

EXPERIMENTAL PROCEDURES

Subjects

Fourteen healthy Caucasian right-handed girls (mean age: 9.9; age range: 8–10) took part in this study. None of these subjects presented a history of neurological or psychiatric disorder. According to 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. Several days before the actual experiment, subjects saw a videotape explaining in lay terms what is an MRI scanner and how it works. On the day of the experiment, the experimenter asked whether the subjects (or 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) used 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 allowing to evaluate the emotional state of the subjects during the experiment. To ensure 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 autobiographical events having occurred lately. Finally, in order to avoid as much as possible brain activation patterns due to anxiety or fear, only subjects who appeared and said feeling at ease with the scanning procedure were included in the study.

During scanning. Blood-oxygen-level-dependent (BOLD) signal changes were measured during four experimental conditions. These conditions were organized in a 2×2 factorial design. One factor was Emotion (No Sadness vs. Sadness) and the other factor was Regulation (No Reappraisal vs. Reappraisal). This resulted in the following experimental conditions: No Sadness/No Reappraisal and Sadness/No Reappraisal, during one run; and, No Sadness/Reappraisal and Sadness/Reappraisal, during the other run. The second run began a few minutes after the end of the first run. During both the No reappraisal and the Reappraisal runs, subjects first viewed four blocks of emotionally neutral film excerpts and then, four blocks of sad film excerpts. As Garrett and Maddock (2001) have recently shown that subjective emotional responses persist on average 32 s after the presentation of aversive pictures before self-reported negative feelings show a 74–80% decline, this design was adopted to avoid contamination of the neutral stimuli by the sad stimuli. Each block lasted 48 s and was separated by resting periods of 15 s during which subjects viewed a blue cyan screen. The neutral and sad film excerpts presented in the No Sadness/No Reappraisal and Sadness/No Reappraisal conditions were equivalent but not identical to those presented in the No Sadness/Reappraisal and Sadness/Reappraisal conditions. In the No Reappraisal conditions, subjects were instructed to react normally to the neutral as well as the sad film excerpts. In the Reappraisal conditions, the subjects were asked to suppress as much as possible any emotion they might have with regard to the neutral or the sad film excerpts. More specifically, subjects were instructed to reappraise the stimuli by taking a distance from these stimuli, that is, to become a detached observer. To ensure that the reappraisal strategy was properly understood, subjects were trained 30 min prior to the scanning session. During this pre-scan training, subjects were presented with a series of film excerpts aimed at eliciting different emotions. For each film excerpt, they were instructed to suppress the emotional responses elicited by those film excerpts by taking a distance from these stimuli. To do so, each subject was told to mentally imagine herself sitting in a movie theater, watching herself reacting emotionally on the big screen and then feeling dissociated, i.e. like if the person seen on the screen was not related to her anymore. After having practiced this exercise for a few

minutes, all subjects came to clearly grasp the emotion regulation strategy proposed by the experimenters.

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 scene contained either a child or two children, or a child and one or more adults. Emotionally neutral film excerpts depicted various human activities (e.g. interviews, carpentry, etc). Neutral film excerpts were matched to the sad film excerpts with respect to the number and the gender of the individuals depicted in the film clips. Overall, a total of eight different sad film excerpts and eight different neutral film excerpts were used. Their utilization was counterbalanced across conditions and subjects, i.e. the sad and neutral film excerpts appeared as equally often in the No Reappraisal and the Reappraisal runs, and subjects saw each film excerpt (sad or neutral) only once. In addition, the order of presentation of the experimental conditions was counterbalanced across subjects. To assess the subjective responses of the subjects to the stimuli, immediately at the end of each run, they were asked to rate verbally—on a visual analog rating scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotion ever felt in one's lifetime)—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. At the end of the scanning session, subjects were asked to complete a "strategy questionnaire" in which they described the emotion regulation strategies they used to suppress the sad feelings generated by the sad stimuli. In this questionnaire, subjects were also asked to evaluate (in percentage) the degree to which they thought they had succeeded in suppressing sad feelings during the Sadness/Reappraisal condition.

Image acquisition and analysis

Echoplanar images (EPI) were acquired on a 1.5 Tesla system (Magnetom Vision; Siemens Electric, Erlangen, Germany). Twenty-eight slices (voxel size: 3.36 mm×3.36 mm×5 mm) were acquired every 3 s (2.65 s of acquisition time and 0.35 s of silence) 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 (echo-spacing time=0.8 ms, time-echo [TE]=54 ms, Flip=90°, field of view [FOV]=215 mm, matrix=64×64). Following running, high-resolution data were acquired via a TI-weighted three-dimensional volume acquisition obtained using a gradient echo pulse sequence (time repetition=9.7 ms, TE=4 ms, Flip=12° FOV=250 mm, matrix=256×256).

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, and 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.

Initially, we normalized the data using the brain template for children developed by Wilke and co-workers (Wilke et al., 2002) at Cincinnati Children's Hospital Medical Center. Then we normalized the data using the adult template found in statistical parametric map (SPM; the MNI template). The results obtained with the two templates were comparable, in keeping with the Burgund et al. (2002) study, which recently showed that even if there are some small anatomical differences between the brain' structures and sulci of children (age range: 7–8) and those of adults (age range: 18–30), such differences do not compromise the usefulness of an adult stereotactic space for children's functional images. Based on this, we decided to use the SPM adult template because it allows the conversion of MNI template coordinates into Talairach and Tournoux (1988) coordinates.

Statistical analyses

The time series of the images were convolved with the hemodynamic response function which approximates the activation patterns. Effects at each and every voxel were estimated using the general linear model. Realignment parameters and conditions constants were included as regressors in the model. Voxel values for the contrasts of interest yielded a SPM of the *t* statistic (SPM *t*), subsequently transformed to the unit normal distribution (SPM Z). A "fixed-effects model" was implemented to circumscribe the brain activity associated with the main effect of Emotion, the main effect of Regulation, as well as the interaction between the Emotion and Regulation factors. This "fixed-effects model" produced individual contrast images, which were used as raw data for the implementation of a "random-effects model" (Friston and Frackowiack, 1997). The main effect of Emotion was obtained by differentiating the sad conditions and the non sad conditions [(Sad/No Reappraisal+Sad/Reappraisal)−(No Sadness/No Reappraisal+No Sadness/Reappraisal], regardless of the reappraisal effect. The main effect of Regulation was obtained by differentiating the reappraisal conditions and the non reappraisal conditions [(Sad/Reappraisal+No Sad/Reappraisal)−(Sad/No Reappraisal+No Sad/No Reappraisal)], regardless of the sadness effect. Finally, the interaction between the Emotion and Regulation factors was calculated to verify which brain regions were activated as a consequence of Regulation, especially when there was an emotional challenge [(1−1 −1 1)=(−(−1 1)+(−1 1)]. Contrary to the main effect of Regulation contrast, which pertained to brain regions activated by regulation when there is no sadness, this interaction contrast allowed to target specifically the brain regions implicated in emotional regulation. We also looked at the possibility of a negative interaction between the Emotion and Regulation factors, to determine whether there was brain regions more activated as a consequence of sadness when subjects did not regulate. In addition, parameter estimates (β) were computed for the brain regions seen activated in the interaction contrasts, using a one-way ANOVA.

An a priori search strategy was used and a small volume correction was performed in the brain regions (ROIs) defined a priori. The search volume corresponding to the ROIs was defined a priori by tracing the neuroanatomical boundaries of these regions on the magnetic resonance reference image (MNI template), using small volume correction 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 (voxel-level statistics). Only clusters showing a spatial extent of at least five contiguous voxels were kept for image analysis. A whole-brain search was also carried out.

In the Sadness conditions, the a priori search strategy encompassed the ventrolateral PFC (VLPFC; 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 (BA21 and 38), insula, amygdala, hypothalamus, and midbrain. These brain regions have been found activated on a more or less consistent basis in previous functional neuroimaging studies of sadness (Pardo et al., 1993; George et al., 1995; Lane et al., 1997; Beauregard et al., 1998; Damasio et al., 2000; Lévesque et al., 2003). In the Reappraisal conditions, based on the results of previous studies recently carried out by our group (Beauregard et al., 2001; Lévesque et al., 2003) as well as by

Table 1. Interaction of Emotion and Regulation factors

Region	Brodmann area	Talairach coordinates (mm)			*z*-statistic	Corrected *P* value	Number of voxels
		x	y	z			
L LPFC	10	−27	56	14	4.62	<0.001	194
L LPFC	9	−30	36	26	4.21	<0.001	131
L MPFC	10	−6	56	14	4.15	<0.001	25
R LPFC	9	36	39	23	3.55	<0.004	94
L OFC	11	−18	55	−15	3.55	<0.015	15
R VLPFC	47	48	31	−17	3.48	<0.020	50
L MPFC	9	−6	37	37	3.21	<0.004	8
R LPFC	10	36	45	20	3.19	<0.013	123
R OFC	11	3	54	−18	2.93	<0.001	5
L OFC	11	−3	52	−15	2.81	<0.002	10
R MPFC	10	3	55	14	2.78	<0.011	18
R ACC	24/32	3	38	19	2.72	<0.004	15
R MPFC	9	3	48	27	2.34	<0.042	12

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.

other researchers (Ochsner et al., 2002; Hariri et al., 2003), the a priori search strategy included the LPFC (BA 10), ACC (cognitive division; BA 24b′–c′ and 32′; Bush et al., 2000), OFC (BA 11), and MPFC (BA 9 and 10).

RESULTS

Self-report data

From a subjective perspective, the viewing of the sad film excerpts, in both the Sadness/No Reappraisal and Sadness/Reappraisal conditions, induced a transient state of sadness in all subjects. The mean level of reported sadness was significantly higher in the Sadness/No Reappraisal condition (mean=4.9, S.D.=2.0, range: 2–8) than in the Sadness/Reappraisal condition (mean=3.2; S.D.=2.3, range: 1–8; $P<0.01$). During both conditions, the viewing of the sad film excerpts did not induce other significant changes in the emotional state than sadness (mean levels: *Sadness/No Reappraisal condition*: fear=0.5; anger=0; surprise=0.5; happiness=0; disgust=0.9; *Sadness/Reappraisal condition*: fear=1.1; anger=0.1; surprise=0.4; happiness=0.5; disgust=0.6). In addition, viewing the emotionally neutral film excerpts during the No Sadness/No Reappraisal as well as in the No Sadness/Reappraisal conditions did not generate any basic emotion. Finally, the strategy questionnaire completed at the end of the scanning session revealed that, in the Reappraisal conditions, all subjects reported having succeeded in distancing themselves from the neutral and the sad film excerpts, i.e. in becoming a detached observer. The mean percentage reflecting the degree to which subjects thought having succeeded in suppressing sad feelings was 84% (range: 40–100; S.D.: ±21).

fMRI data

Main effect of Emotion. Significant loci of activation were noted in the right VLPFC (BA 47; x=3, y=56, z=17, *z* score=2.57, $P<0.002$) and, bilaterally, in the midbrain (right hemisphere [RH]: x=3, y=−39, z=−9, *z* score=3.06, $P<0.019$; left hemisphere [LH]: x=−3, y=32, z=−8, *z* score=2.82, $P<0.037$), anterior temporal pole (BA 21; RH: x=50, y=7, z=−26, *z* score=3.65, $P<0.002$; LH: x=−50, y=4, z=−28, *z* score=2.84, $P<0.023$), and MPFC (BA 10; RH: x=3, y=56, z=17, *z* score=3.13, $P<0.014$; LH: x=−1, y=57, z=−15, *z* score=2.57, $P<0.002$).

Main effect of Regulation. Significant loci of activation were seen bilaterally in the LPFC (BA 10; RH: x=27, y=49, z=22, *z* score=5.68, $P<0.003$; LH: x=−27, y=54, z=22, *z* score=4.86, $P<0.008$), MPFC (BA 10; RH: x=3, y=53, z=17, *z* score=7.34, $P<0.001$; LH: x=−3, y=53, z=17, *z* score=7.12, $P<0.001$), OFC (BA 11; RH: x=3, y=56, z=−16, *z* score=2.85, $P<0.005$; LH: x=−3, y=53, z=8, *z* score=3.11, $P<0.002$), and VLPFC (BA 47; RH: x=26, y=20, z=−20, *z* score=3.78, $P<0.008$; LH: x=−27, y=11, z=−21, *z* score=3.72, $P<0.009$). A significant locus of activation was also detected in the right MPFC (BA 9; x=6, y=48, z=30, *z* score=3.05, $P<0.007$).

Interaction between Emotion and Regulation. Significant loci of activation were measured bilaterally in the LPFC (BA and 10), OFC (BA 11), and MPFC (BA 9 and 10). Significant loci of activation were also noted in the right ACC (rostral portion, BA 24/32) and right VLPFC (BA 47; Table 1; Fig. 1, Fig. 2). No significant brain activation was found in the negative interaction contrast.

DISCUSSION

The goal of this study was to identify the neural circuitry underlying voluntary self-regulation (suppression) of sadness in healthy children. The experimental design comprised two factors—Emotion (No Sadness vs Sadness) and Regulation (No Reappraisal vs Reappraisal)—and four conditions: 1) No Sadness/No Reappraisal, 2) Sadness/No Reappraisal, 3) No Sadness/Reappraisal, and 4) Sadness/Reappraisal. The main effect of Sadness was associated with significant BOLD

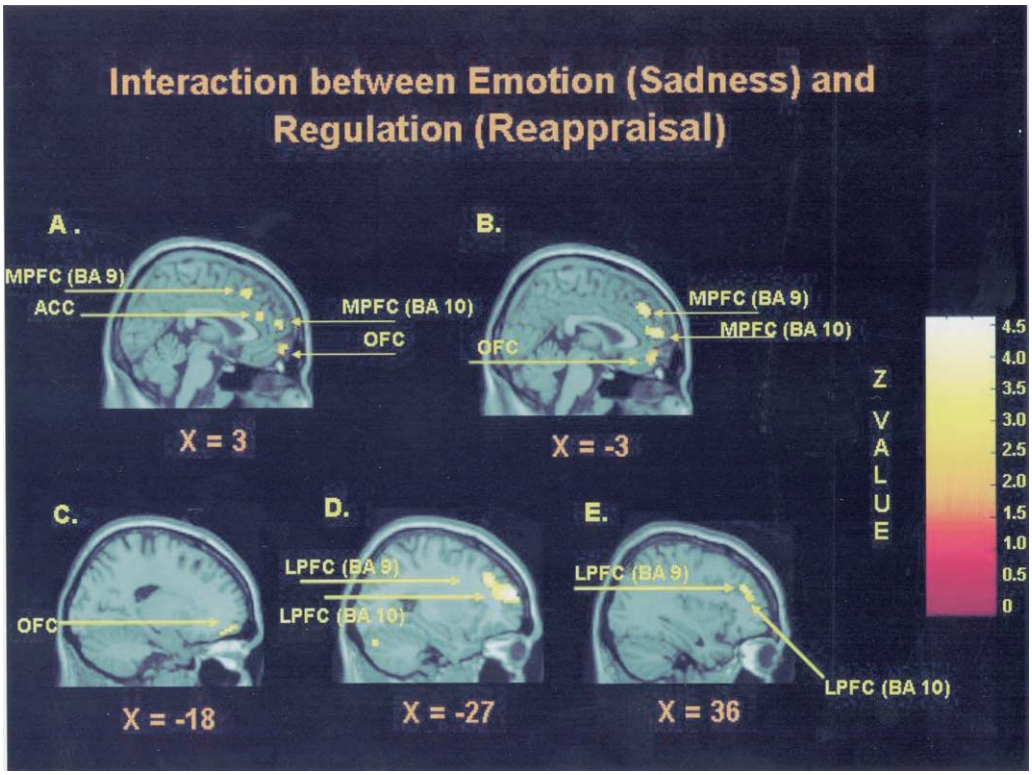

Fig. 1. Images are sagittal sections for the data averaged across subjects. Significant loci of activation were observed in (a) the right OFC (BA 11), right MPFC (BA 9 and 10), and right ACC (BA 24/32), (b) the left OFC (BA 11) and left MPFC (BA 10), (c) the left OFC (BA 11), (d) the left LPFC (BA 9 and 10), and (e) the right LPFC (BA 9 and 10).

signal increases in the right VLPFC (BA 47), and in the midbrain, anterior temporal pole (BA 21) and MPFC (BA 10), bilaterally. The main effect of Regulation was associated with increased neural activity, bilaterally, in the LPFC (BA 10), MPFC (BA 10), OFC (BA 11), VLPFC (BA 47), as well as in the right MPFC (BA 9). Finally, the interaction of the Emotion and Regulation factors (Sadness/Reappraisal condition) led to increased neural activity, bilaterally, in the LPFC (BA and 10), OFC (BA 11) and MPFC (BA 9 and 10), as well as in the right ACC (rostral part, BA 24/32) and right VLPFC (BA 47).

Brain regions associated with the interaction of Emotion and Regulation

The activation of the LPFC (in BA 9 and 10) fits rather nicely with the various lines of evidence suggesting that this prefrontal cortical region plays a pivotal role in metacognition, i.e. the ability to monitor and control the information processing necessary to produce voluntary action (Flavell, 1979), as well as in the selection and control of behavioral strategies and action (Fuster, 1999), especially the inhibition of inherent response tendency (Goldman-Rakic, 1987; Damasio, 1995; Frith and Dolan, 1996; Fuster, 1997; for a review, see Aron et al., 2004). Furthermore, the parameter estimates of LPFC suggest that BA 10 of this prefrontal area is more likely to be involved in regulation when there is an emotional challenge rather than when there is no such challenge, contrary to BA 9 of LPFC which seems to be involved in the regulation of both emotionally neutral and sad states (Fig. 2).

From a neural systemic point of view, the OFC is located at the junction of the prefrontal associative cortex and the limbic system. This prefrontal region has strong links with the LPFC, anterior temporal pole and insula, and it sends extensive projections to the amygdala, lateral hypothalamus, diencephalon, brain stem and spinal cord (Morecraft et al., 1992; Cavada et al., 2000). Neuropsychological studies indicate that damage to the OFC leads to a *frontal lobe syndrome* (Silver and Yudofsky, 1987) or *pseudopsychopathic syndrome* (Stuss and Benson, 1984) that is characterized by distractibility, impulsivity, emotional outbursts, shallowness, argumentativeness, verbal and physical aggressiveness, lack of concern of consequences of behavior, failure to observe social and moral rules, and risky decision-making behavior. Interestingly, individuals with OFC lesions show abnormal autonomic responses to emotional elicitors, difficulty to experience emotion related to situations that would normally evoke emotion, and impaired understanding of the adverse consequences of detrimental social behaviors (Damasio et al., 1990; Anderson et al., 1999). These findings indicate that the OFC is crucially involved in the protection of goal-directed behaviors from interference (Casey et al., 1997; Fuster, 1999; Roberts and Wallis, 2000) and the regulation of socio-emotional behavior (Mesulam, 1986; Damasio et al., 1990; Elliott, 1990; Cummings, 1993; Bechara et al., 1994; Giancola and Zeichner, 1994; Damasio, 1995; Lapierre et al., 1995; Grafman et al.,

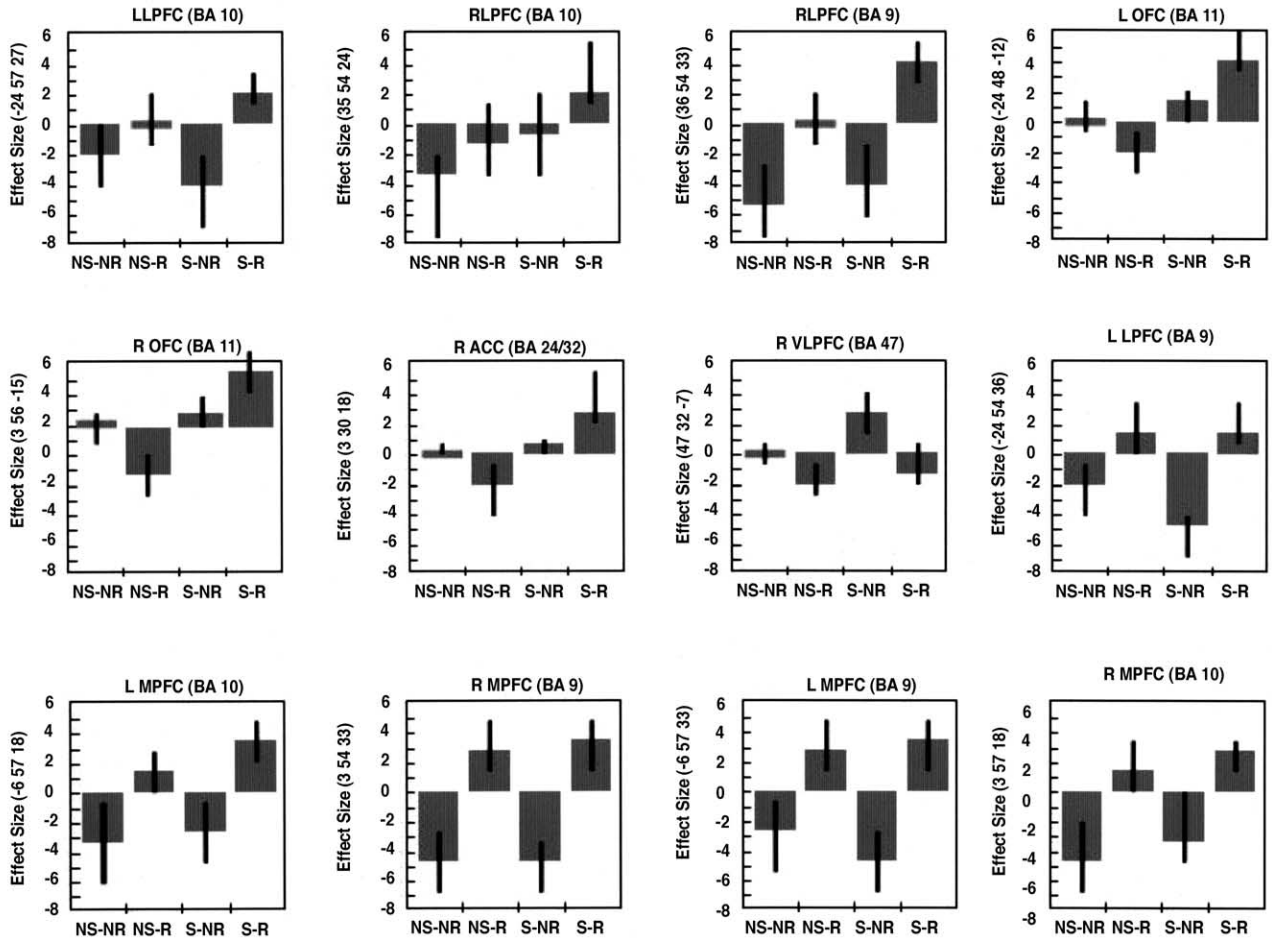

Fig. 2. Histograms representing the percentage of signal change across conditions at the local maxima in the LPFC (BA 9 and 10) and MPFC (BA and 10), bilaterally, as well as in the right ACC (BA 24/32), right VLPFC (47), and left OFC (BA 47). NS-NR, No Sadness/No Reappraisal; NS-R, No Sadness/Reappraisal; S-NR, Sadness/No Reappraisal; S-R, Sadness/Reappraisal.

1996; Zald and Kim, 1996; Fuster, 1997; Dolan, 1999; Eslinger, 1999; Grafman and Litvan, 1999). The parameter estimates of OFC indicate that that the OFC activation was markedly stronger for the Sadness/Reappraisal condition than for the other conditions (Fig. 2). In the context of the present study, we propose that the OFC activation noted in the interaction contrast was related to the inhibition of the physiological and subjective aspects of sadness associated with neural activity in the midbrain, anterior temporal pole (BA 21), and right VLPFC (BA 47).

The parameter estimates of the right rostral ACC clearly point to an involvement of this brain region in emotional self-regulation (Fig. 2). By virtue of its anatomic connections with brain regions implicated in the modulation of autonomic and endocrine functions such as the OFC, amygdala, hypothalamus, periaqueductal gray, dorsal motor nucleus of the vagus, and preganglionic sympathetic neurons in the intermediolateral cell column of the spinal cord (for a review, see Benes, 1997), the rostral subdivision of the ACC appears to play a key role in the regulation of the autonomic aspect of emotional responses (Vogt et al., 1992; Devinsky et al., 1995; Bush et al., 2000). In line with this view, we submit that the rostral ACC (BA 24/32) activation noted during the reappraisal of the sad film excerpts was related to the suppression of the autonomic and endocrine responses associated with sad feelings.

The VLPFC has been seen activated in healthy adults during external (e.g. looking at human faces) and/or internal (e.g. recalling appropriate life events) induction of sadness (Pardo et al., 1993; George et al., 1995; Beauregard et al., 1998; Damasio et al., 2000). In this study, the most robust activation of the right VLPFC was related to the Sadness/No Reappraisal condition (Fig. 2). Given the sensory inputs (olfactory, gustatory, visceral afferent, somatic sensory, and visual) as well as the limbic inputs that this cortical region receives from the amygdala, entorhinal cortex, perirhinal cortex, and subiculum, it seems conceivable that the right VLPFC activation noted here reflected the integration of viscerosensory information with information signaling modifications in the subjects' emotional state (Price, 1999).

The MPFC has been postulated to be implicated in theory-of-mind tasks (inferences about the mental states of others; Fletcher et al., 1995) and metacognitive represen-

tation of one's own emotional state (Reiman, 1997; Lane, 2000). This cortical region receives sensory information from the body and the external environment via the OFC and is heavily interconnected with limbic structures such as the amygdala, ventral striatum, hypothalamus, midbrain periaqueductal gray region, and brainstem autonomic nuclei (Barbas, 1993; Carmichael and Price, 1995). Such anatomical relationships suggest a role for the MPFC in the integration of the visceromotor aspects of emotional processing with information gathered from the internal and external environments. It thus appears plausible that the MPFC activation seen here was associated with the conscious monitoring of the subjects' emotional state. The parameter estimates of the MPFC (mostly of BA 9) indicate that this cortical region is not only involved in the regulation of sad stimuli but also in the regulation of emotionally neutral stimuli (Fig. 2).

As we mentioned earlier in the Results section, no significant activation was found in the negative interaction contrast. However, when a more permissive statistical threshold was used ($P<0.05$ uncorrected), a significant locus of activation was seen in the right anterior pole (BA 21), a brain region known to be crucially involved in emotion processing. Given that individual SPM maps revealed that this brain activation was not present in all subjects, it seems likely that inter-subject variability accounted for the lack of statistical significance in this cortical region.

Comparison with previous functional neuroimaging studies of emotional self-regulation

The present results are fairly consistent with those of previous fMRI studies of emotional self-regulation conducted either by our group or other research teams. In the first of these studies (Beauregard et al., 2001), we found that sexual arousal induced by erotic film excerpts was associated with activation of the right amygdala, right anterior temporal pole, and hypothalamus. In addition, voluntary suppression of sexual arousal was associated with activation of the right LPFC (BA 10) and right ACC (BA 32). The cognitive strategy adopted to modulate sexual arousal was identical to that used in the present investigation to regulate sadness. In another of these studies, Ochsner and colleagues (2002) have shown that the reappraisal of negative pictures (selected from the International Affective Picture System [IAPS]; Lang et al., 1998) was associated with activation of the dorsal and ventral regions of the left LPFC, as well as the dorsal MPFC. Of note, the increased activation of the ventral LPFC during reappraisal was correlated across subjects with decreased activation in the amygdala. Along the same lines, Hariri and co-workers (2003) demonstrated that whereas perceptual processing of threatening and fearful non-face (IAPS) stimuli was associated with a bilateral amygdala response, cognitive reappraisal of the same stimuli was associated with a reduction of this amygdala response and a concomitant increase in response of the right PFC and the ACC.

Recently, we have carried out a fMRI study in adult women using the same protocol and film excerpts than those utilized in the current investigation (Lévesque et al., 2003). Neurally, reappraisal of sad film excerpts recruited more prefrontal cortical areas in girls than in women. Indeed, in girls, this task was associated with numerous loci of activation in the LPFC (BA 9 and 10), OFC (BA 11), MPFC (BA 9 and 10), rostral ACC (BA 24/32), and VLPFC (BA 47). In contrast, in women reappraisal of sad film excerpts was associated with activation of the right OFC (BA 11) and right LPFC (BA 9). In agreement with this, it has been demonstrated that children show greater volume of PFC activity than adults when performing tasks requiring active maintenance and/or reappraisal of different types of information (e.g. Go/NoGo paradigm; Cohen et al., 1994; Casey et al., 1995). Likewise, Tamm et al. (2002) found that children activated more extensively than young adults discrete regions of the PFC during a Go/NoGo task. Furthermore, a fMRI study conducted by Gaillard et al. (2000) demonstrated that verbal fluency was associated with similar brain regions in both children and adults. However, it was observed that children had, on average, 60% greater extent of activation than adults. Casey et al. (1995), as well as Gaillard et al. (2000), suggested that the greater activation found in children compared with adults may reflect maturational differences with respect to the PFC. In keeping with this view, the greater number of prefrontal loci of activation found in children relative to adults during voluntary self-regulation of sadness may be related to the immaturity of the prefronto-subcortical (limbic) connections in childhood.

Limitations of the present study

Lastly, we would like to mention some of the limitations of this study. First, no objective measures were collected relative to the developmental stage of the subjects from a neuroendocrine perspective. Second, no objective measures were acquired before and immediately after the four experimental conditions to evaluate the subjects' emotional state. Instead, self-report ratings were used. Since self-report data are extremely susceptible to bias, a more objective measure would have definitely reinforced the results of this study, even though the results in the Reappraisal conditions were in keeping with our predictions and the literature. Third, we could not verify that the subjects have effectively performed the reappraisal task the way they were requested to. At the end of the Reappraisal conditions, subjects were asked to report if they have had difficulty performing the reappraisal task, what strategy they used to suppress sadness, and if they were witnessing internal speech while doing this task. Nobody reported performing another task or being distracted. Again, as we had no objective means to verify subjects' assertions, we relied on their honesty to interpret the results. In keeping with this, future studies should use eye-tracking to assure that subjects keep their eyes open and really look at the visually presented stimuli during emotional self-regulation tasks. Fourth, film excerpts were not matched in terms of age of subjects, as children were present only in sad film excerpts. Fifth, the fact that the four sad films were always presented after the four neutral films for both the Regula-

tion and the No Regulation conditions may have produced a time confound.

CONCLUSION

In conclusion, the present fMRI study demonstrated that conscious and voluntary reappraisal of sadness in healthy girls was associated with bilateral activation of the LPFC (BA 9 and 10), OFC (BA 11), MPFC (BA 9 and 10), rostral ACC (BA 24/32), and activation of the right VLPFC (BA 47). In an identical study previously conducted by our group in adult women (Lévesque et al., 2003), reappraisal of sad film excerpts was associated with activation of the right OFC (BA 11) and right LPFC (BA 9). The greater number of prefrontal loci of activation found in children relative to adults during voluntary self-regulation of sadness may be related to the immaturity of the prefronto-limbic connections in childhood.

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