Neural Circuitry Underlying Voluntary Suppression of Sadness

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Background: *The ability to voluntarily self-regulate negative emotion is essential to a healthy psyche. Indeed, a chronic incapacity to suppress negative emotion might be a key factor in the genesis of depression and anxiety. Regarding the neural underpinnings of emotional self-regulation, a recent functional neuroimaging study carried out by our group has revealed that the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex are involved in voluntary suppression of sexual arousal. As few things are known, still, with respect to the neural substrate underlying volitional self-regulation of basic emotions, here we used functional magnetic resonance imaging to identify the neural circuitry associated with the voluntary suppression of sadness.*

Methods: *Twenty healthy female subjects were scanned during a Sad condition and a Suppression condition. In the Sad condition, subjects were instructed to react normally to sad film excerpts whereas, in the Suppression condition, they were asked to voluntarily suppress any emotional reaction in response to comparable stimuli.*

Results: *Transient sadness was associated with significant loci of activation in the anterior temporal pole and the midbrain, bilaterally, as well as in the left amygdala, left insula, and right ventrolateral prefrontal cortex (VLPFC) (Brodmann area [BA] 47). Correlational analyses carried out between self-report ratings of sadness and regional blood oxygen level dependent (BOLD) signal changes revealed the existence of positive correlations in the right VLPFC (BA 47), bilaterally, as well as in the left insula and the affective division of the left anterior cingulate gyrus (BA 24/32). In the Suppression condition, significant loci of activation were noted in the right DLPFC (BA 9) and the right orbitofrontal cortex (OFC) (BA 11), and positive correlations were found between the self-report ratings of sadness and BOLD signal changes in the right OFC (BA 11) and right DLPFC (BA 9).*

Conclusions: *These results confirm the key role played by the DLPFC in emotional self-regulation. They also indicate that the right DLPFC and right OFC are components of a neural circuit implicated in voluntary suppression of sadness.* Biol Psychiatry 2003;53:502–510 © *2003 Society of Biological Psychiatry*

Key Words: Suppression, volition, metacognition, prefrontal cortex, functional magnetic resonance imaging

Introduction

Emotional self-regulation has been defined as "the extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reaction, especially their intensive and temporal features, to accomplish one's goal" (Thompson 1994). In a colloquial usage, emotional self-regulation often refers either to suppression, maintenance, or enhancement of the subjective emotional experience, but it also applies to the modulation of the behavioral and physiologic dimensions of emotion (Gross 1999). Rationalization and reappraisal are among some of the most prevalent cognitive strategies used to self-regulate emotion (Gross 1999; Hariri et al 2000).

Conscious and voluntary self-regulation of emotion represents indisputably one of the most remarkable mental faculties having emerged throughout the course of human evolution. In our view, this metacognitive capacity constitutes one of the cornerstones on which human societal systems are built. Supportive of such a view, there is mounting evidence that a chronic incapacity to suppress negative emotion may be a key factor in the genesis of depression, anxiety, and aggressive or violent behaviors (Davidson et al 2000; Jackson et al 2000). With respect to major depression, this dysregulation of negative affect may be related to the cognitive/executive inhibitory deficit that characterizes depressed patients. This impairment is manifested by increased choice reaction-time on a Stroop-

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Color-Word test and increased effect of interference on the Visuo-Spatial Interference Test, when compared with normal control subjects (Lemelin et al 1996, 1997).

Regarding the neural bases of such capacity, it was postulated several decades ago that a fronto–limbic network is involved in emotional suppression (Nauta 1971). More recently, evidence from lesion studies in animals, and clinical neuropsychological, psychophysiological, and functional neuroimaging studies in humans have led to the view that a neural circuit comprising several prefrontal cortex (PFC) regions (e.g., orbitofrontal, anterior cingulate) underlies emotional suppression (Davidson et al 2000). The results of a functional magnetic resonance imaging (fMRI) study recently carried out by our group to test the validity of this view (Beauregard et al 2001) demonstrated the involvement of the dorsolateral PFC (DLPFC) and anterior cingulate cortex in voluntary suppression of sexual arousal, a positive emotional state.

In the present study, we used whole-brain fMRI to delineate the neural circuitry associated with the voluntary suppression of sadness, a basic emotion with a negative valence (Plutchik 1994). We predicted *a priori* that various subdivisions of the PFC (DLPFC, orbitofrontal cortex [OFC], medial PFC, and anterior cingulate cortex) would be associated with voluntary suppression of sadness.

Methods and Materials

Subjects

Twenty healthy female volunteers (right-handed Caucasian university students) (age range: 20–30, mean age: 24.3 years) took part in the study. They had no history of psychiatric or neurologic disorder. These subjects all gave written, informed consent, and the study was approved by the ethics committee of Centre hospitalier de l'Université de Montréal, Hôpital Notre-Dame.

Behavioral Procedures

Blood oxygen level dependent (BOLD) signal changes were measured during two experimental conditions: a Sad condition and a Suppression condition. In the Sad condition, subjects first viewed four blocks of emotionally neutral film excerpts and then four blocks of sad film excerpts. On the basis of 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 sec and were separated by resting periods of 15 sec, 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. In the Suppression condition, they were also presented first with four blocks of emotionally neutral film excerpts and, then, four blocks of sad film excerpts. In this condition, subjects were instructed to suppress any emotional reaction to the sad stimuli. That is, they had to voluntarily decrease the intensity of the sad feelings felt in response to the sad film excerpts. To accomplish that goal, subjects were encouraged to distance themselves from those stimuli (i.e., to become a detached observer). Subjects were instructed to look at the stimuli directly during both experimental conditions. 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; that is, the sad and neutral film excerpts appeared equally as often in both conditions, and subjects saw each film excerpt (sad or neutral) only once. The order of presentation of the experimental conditions was counterbalanced across subjects. 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. The emotionally neutral film excerpts were matched to the sad film excerpts with respect to the number and the gender of the individuals involved. 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 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. For each run, an average rating score was computed for the four blocks of sad film excerpts and the four blocks of emotionally neutral film excerpts. At the end of the scanning session, subjects were also asked to complete a "strategy questionnaire," in which they described the emotion regulation strategies they used to inhibit 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 having succeeded in suppressing sad feelings during the Suppression 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 (5 mm thick) were acquired every 2.65 sec 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 to repetition [TR] = 0.8 msec, time to echo [TE] = 54 msec, Flip = 90°, field of view [FOV] = 215 mm, Matrix = 64 × 64). Following functional scanning, high-resolution data were acquired via a T1-weighted, three-dimensional volume acquisition obtained using a gradient echo pulse sequence (TR = 9.7 msec, TE = 4 msec, 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 minor 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 such as 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 that presented signal loss. This procedure was implemented for every subject. The images for all subjects were then spatially normalized (voxel size: 3 × 3 × 3 mm) into an MRI stereotactic space (Talairach and Tournoux 1988) using this masked mean image. Images were then 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.

For the statistical analysis, 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*). For the Sad condition, a "fixed-effects model" was implemented to contrast the brain activity associated with the viewing of the sad film excerpts with that associated with the viewing of the emotionally neutral film excerpts (Sad − Neutral). To delineate the brain regions associated with voluntary suppression of sad feelings, a "fixed-effects model" was also implemented to compare the brain activity associated with the Sad condition with that associated with the Suppression condition. To do so, the brain activity associated with viewing the sad film excerpts in the Sad condition was directly subtracted from the brain activity associated with viewing the sad film excerpts in the Suppression condition. These "fixed-effects models" produced individual contrast images, which were used as raw data for the implementation of a "random-effects model" (Friston and Frackowiack 1997). An a priori search strategy was used, and a small volume correction was performed in the brain regions of interest (ROIs) defined a priori. The search volume corresponding to the ROIs was defined a priori by tracing the neuroanatomic boundaries of these regions on the MR reference image (Montreal Neurological Institute [MNI] template), using small volume correction (SVC) and box volume function in SPM99. For this a priori search, a corrected probability threshold for multiple comparisons of $p < .05$, corrected, was used. Only clusters showing a spatial extent of at least five contiguous voxels were kept for image analysis.

In the Sad condition, the a priori search strategy encompassed the ventrolateral PFC (VLPFC) (Brodmann area [BA] 47), medial PFC (BA 9 and 10), anterior cingulate cortex (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. These brain regions have been found activated on a more or less consistent basis in previous functional neuroimaging studies of sadness (Beauregard et al 1998; Damasio et al 2000; George et al 1995; Lane et al 1997b; Pardo et al 1993). In the Suppression condition, the a priori search strategy included the DLPFC (BA 10), the anterior cingulate cortex (cognitive division) (BA 24b′–c′ and 32′) (Bush et al 2000), the OFC (BA 11), and the medial PFC (BA 9 and 10), based on the hypothesis made by Davidson et al (2000) and on the results of a previous study recently carried out by our group (Beauregard et al 2001).

Results

Self-Report Data

Phenomenologically, the viewing of the sad film excerpts, in both the Sad and the Suppression conditions, induced a transient state of sadness in all subjects. As expected, the mean level of reported sadness was significantly higher in the Sad condition (mean = 5.15; SD = 1.30; range: 2–7) than in the Suppression condition (mean = 1.85; SD = 1.42; range: 0–4) ($p < .0001$). During both experimental conditions, the viewing of the sad film excerpts did not practically produce marked changes in the emotional states other than sadness (mean levels: Sad condition: fear = 1.0; anger = 1.4; surprise = .3; happiness = 0; disgust = .2; Suppression condition: fear = 0; anger = .1; surprise = 0; happiness = 0; disgust = .33), and viewing the emotionally neutral film excerpts did not generate any basic emotion. In addition, the strategy questionnaire completed at the end of the scanning session revealed that, in the Suppression condition, all subjects reported having succeeded in distancing themselves from the sad film excerpts (i.e., in becoming a detached observer). The mean suppression percentage, reflecting the degree to which subjects thought they had succeeded in suppressing sad feelings, was 84% (range: 50%–100%; SD: ± 11).

fMRI Data: Subtraction Approach

SAD CONDITION. The "random-effects model" revealed significant bilateral loci of activation in the anterior temporal pole (BA 38 and BA 21) and the midbrain. Significant loci of activations were also seen in the right VLPFC (BA 47), the left amygdala, and the left insula (Figure 1, Table 1).

SUPPRESSION CONDITION. Significant loci of activation were noted in the right OFC (BA 11) and right DLPFC (BA 9) (Figure 2, Table 2). Additionally, when using a liberal threshold of $p < .05$, uncorrected, for multiple comparisons, activated voxels were found in the right VLPFC (BA 47).

fMRI Data: A Posteriori *Correlational Analyses*

SAD CONDITION. Correlational analyses were conducted betweeen self-report ratings of sadness and BOLD signal increases found in the ROIs. These analyses revealed the existence of positive correlations in the right VLPFC (BA 47; coordinates of maximum = [27, 20, −11]; $z = 2.80$; $p < .05$, uncorrected), the affective division of the left anterior cingulate cortex (BA 24/32;

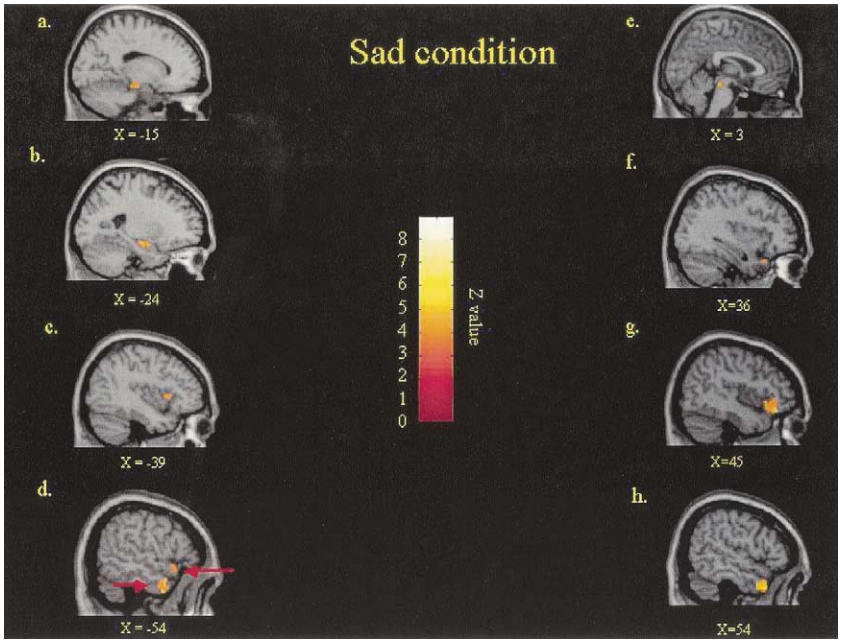

Figure 1. Statistical activation maps for limbic/paralimbic regions defined a priori. Images are sagittal sections for the data averaged across subjects. In the Sad condition, greater activation during the viewing of sad film excerpts relative to the viewing of emotionally neutral film excerpts, was noted in the left midbrain **(a)**, the left amygdala **(b)**, the left insula **(c)**, the left anterior temporal pole (upper arrow, BA 38, lower arrow, BA 21) **(d)**, the right midbrain **(e)**, BA 38 of the right anterior temporal pole (**f**), the right ventrolateral prefrontal cortex (BA 47) **(g)**, and BA 21 of the right anterior temporal pole (**h**).

coordinates of maximum = [−3, 38, 1]; $z = 3.69$; $p < .05$, uncorrected), and the left insula (coordinates of maximum = [−42, 9, −2]; $z = 2.01$; $p < .05$, uncorrected).

SUPPRESSION CONDITION. Positive correlations were found between the self-report ratings of sadness and BOLD signal increases in the right OFC (BA 11; coordinates of maximum = [27, 34, −19]; $z = 2.50$; $p < .05$, uncorrected) and right DLPFC (BA 9; coordinates of maximum = [36, 34, 28]; $z = 3.13$; $p < .05$, uncorrected).

Discussion

The main goal of the present study was to identify the neural substrate associated with voluntary suppression of sadness. This study comprised two experimental conditions, a Sad condition and a Suppression condition. In the Sad condition, significant loci of activation were noted, bilaterally, in the anterior temporal pole (BA 21 and 38) and the midbrain. Significant loci of activation were also seen in the right VLPFC (BA 47), left amygdala, and left

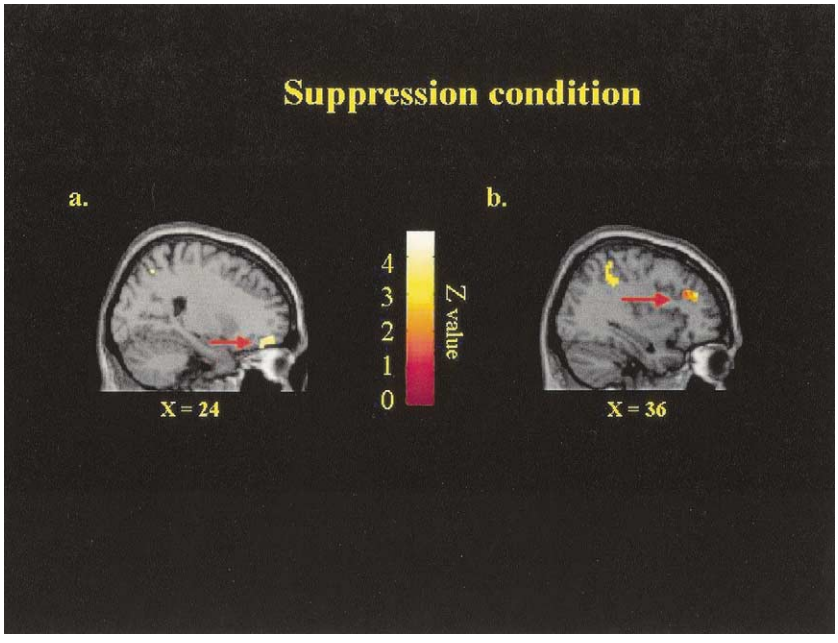

Figure 2. Statistical activation maps during the Suppression condition. Images are sagittal sections for the data averaged across subjects. Significant loci of activation were observed in the in the right dorsolateral prefrontal cortex (BA 9) **(a)** (arrow) and right orbitofrontal cortex (BA 11) **(b)** (arrow).

Table 1. Significant Loci of Activation in the Sad Condition

Region	Brodmann Area	Talairach Coordinates (mm) x	y	z	*Z* Statistic	Corrected *p* Value
Search Volume Defined a Priori						
L anterior temporal pole	21	−54	2	−24	3.89	<.002
L midbrain		−15	−21	−12	3.78	<.006
R anterior temporal pole	21	54	5	−15	3.72	<.004
R ventrolateral PFC	47	45	26	−11	3.70	<.031
L amygdala		−24	−4	−15	3.70	<.003
R midbrain		3	−30	−11	3.63	<.010
R anterior temporal pole	38	36	13	−26	3.41	<.036
L insula		−39	15	−1	3.36	<.005
L anterior temporal pole	38	−54	8	−5	3.35	<.043

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 are also based on this atlas. L, left; R, right.

insula. In the Suppression condition, significant loci of activation were detected in the right OFC (BA 11) and right DLPFC (BA 9).

Brain Regions Activated in the Sad Condition

In regard to the activations noted in the anterior temporopolar cortex, activity of this cortical region have been reported, in healthy subjects, during memory-driven sadness (Lane et al 1997b), script-generated anger and anxiety (Damasio et al 2000; Dougherty et al 1999; Kimbrell et al 1999), normal anticipatory anxiety (Chua et al 1999; Reiman et al 1989), and film-induced sexual arousal (Beauregard et al 2001). This paralimbic region receives inputs from unimodal and heteromodal sensory regions, as well as limbic inputs. As Mesulam (1985) proposed, and in light of the previous functional brain imaging studies of emotion, it seems conceivable that the anterior temporopolar activations found here, during the viewing of the sad films excerpts, was associated with imparting affective tone to the subjects' experience.

In other respects, the activations seen in the midbrain are not surprising because this brain region has been found activated in several functional neuroimaging studies of various emotional states (e.g., disgust, sadness, anger, fear, happiness, pain, and anxiety) (Damasio et al 2000; Fredrikson et al 1995; Lane et al 1997b; Rauch et al 1997; Tölle et al 1999). It has been shown that this brain region mediates, at least in part, autonomic responses, such as skin conductance responses (Sequeira and Roy 1993) and body temperature changes (Nagashima et al 2000). Given the close relationship between autonomic responses and the subjective experience of emotion (Damasio et al 2000), the mesencephalic activations seen in this study likely reflected the autonomic responses accompanying subjects' sad feelings.

The VLPFC has been seen activated, in healthy subjects, during external (e.g., looking at human faces) and/or internal (e.g., recalling appropriate life events) induction of sadness (Beauregard et al 1998; Damasio et al 2000; George et al 1995; Pardo et al 1993), anxiety (Fredrikson et al 1995; Kimbrell et al 1999), and anger (Dougherty et al 1999; Kimbrell et al 1999). Taken together with the present results, these findings suggest that this prefrontal cortical region participates in aspects of emotion processing that are not exclusively related to a discrete emotion in particular. 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 and perirhinal cortex, and subiculum, it seems conceivable that the VLPFC may be implicated in the integration of viscerosensory information with affective signals (Price 1999). The fact that ventromedial

Table 2. Significant Loci of Activation in the Inhibition Condition

Region	Brodmann Area	Talairach Coordinates (mm) x	y	z	*Z* Statistic	Corrected *p* Value
Search Volume Defined a Priori						
R OFC	11	24	46	−17	3.29	<.024
R DLPFC	9	36	25	26	2.84	<.032

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 are also based on this atlas. R, right; OFC, orbitofrontal cortex; DLPFC, dorsolateral prefrontal cortex.

prefrontal lesions are correlated with the absence of autonomic responses to emotionally laden (positive or negative) pictures (Damasio et al 1990) appears to support such a view. In addition, the positive correlation found here between self-report ratings of sadness and BOLD signal increases in the right VLPFC suggests that this paralimbic area is also involved in the subjective dimension of the sad experience. Interestingly, increased VLPFC activity has been reported in association with sad thoughts/sadness in subjects with major depressive disorder (Brody et al 2001). It thus appears that this brain region is associated with the processing of normal as well as pathologic aspects of sadness.

The amygdaloid activation noted here is consistent with the results obtained in previous positron emission tomography (PET) (Blair et al 1999; Lane et al 1997b; Reiman et al 1997; Schneider et al 1995) and fMRI (Beauregard et al 2001; Karama et al 2002; Schneider et al 1997; Whalen et al 1998) studies on positive and negative emotions. The appraisal function of the amygdala is well documented at this point in the literature (for a review, see Lane and Nadel 2000), and it seems possible that the amygdala activation seen in this study reflects the appraisal process of the stimuli through which significance was attributed to the sad film excerpts.

Concerning the activation of the insula, this region has been reported to be activated, in healthy subjects, during recall-induced sadness (Damasio et al 2000; Lane et al 1997b; Liotti et al 2000), happiness (Damasio et al 2000), fear (Damasio et al 2000), and anger (Damasio et al 2000), as well as in normal anticipatory anxiety (Chua et al 1999; Reiman 1997). In view of the rich interconnection of the insula with regions involved in autonomic regulation (Cechetto 1994), the insular activation noted here may be a neural correlate of the autonomic changes associated with the subjective experience of sadness. This conclusion appears even more plausible when considering the positive correlation we found between self-report ratings of sadness and activated voxels in the left insula.

The positive correlation found between average ratings of sadness and BOLD signal increases in the affective division of the anterior cingulate cortex fits rather nicely with the results of a recent PET study by Lane et al (1997a). Indeed, the results of this PET investigation suggested that the rostral portion of the anterior cingulate gyrus plays a pivotal role in the interoceptive or exteroceptive detection of emotional signals, and, hence, in emotional awareness.

Brain Regions Activated in the Suppression Condition

In the Suppression condition, significant loci of activation were noted in the right OFC (BA 11) and right DLPFC (BA 9). When using a liberal threshold of $p < .05$, uncorrected, for multiple comparisons, activated voxels were also found in the right VLPFC (BA 47). This VLPFC activation was probably related to the residual sad feelings experienced by the subjects during the Suppression task. With respect to the right DLPFC activation, the present results demonstrate that, in addition to being involved in the voluntary suppression of a positive emotional reaction, such as sexual arousal (Beauregard et al 2001), the lateral portion of the right DLPFC is also associated with the voluntary suppression of a negative emotion, such as sadness. These results, and the positive correlation found between the self-report ratings of sadness and the significant loci of activation in the right DLPFC, are consistent with a variety of evidence from experimental lesion studies in animals, and clinical neuropsychological and functional brain mapping studies in humans, indicating that the DLPFC is a key structure involved in willed actions (Frith and Dolan 1996), with the holding in mind of information on which an action is to be based (Fuster 1999; Goldman-Rakic 1987; Roberts and Wallis 2000), and with reappraisal, which is a cognitive form of emotion regulation (Ochsner et al 2002). In our previous study, BA 10 of the right DLPFC BA was associated with the suppression of sexual arousal. In this study, the group analysis revealed activation only in BA 9 of the DLPFC; however, careful examination of the individual statistical parametric maps revealed that five subjects were also showing activation in BA 10 of the DLPFC ($p < .001$, uncorrected). At this point, few things are known about the respective roles of the DLPFC's BA 9 and BA 10 in emotional suppression. Regarding this issue, Dias et al (1996) have shown that, in monkeys, BA 9 of the DLPFC is involved in inhibitory control, namely, in attentional set-shifting capacity. In humans, further studies are needed to delineate the functional specificity of these two prefrontal subregions with respect to emotional self-regulation.

Human and animal neuropsychological studies suggest that the OFC exerts an inhibitory control to protect goal-directed behavior from interference (Casey et al 1997; Fuster 1999; Roberts and Wallis 2000). Also, by virtue of its anatomic projections into autonomic centers, it has been proposed that the OFC initiates or controls the autonomic responses that are associated with emotional experience (Öngür et al 1998; Rempel-Clower and Barbas 1998). Furthermore, the OFC is the prefrontal area that has the strongest links with the anterior temporal pole (Cavada et al 2000; Morecraft et al 1992). It is also heavily connected with the amygdala and the insular cortex (Cavada et al 2000). The connections between the OFC, the insula, and the anterior temporal pole have been studied carefully by Mesulam and colleagues, who proposed that these three cortical regions form an integrated

unit on the basis of similarities in cytoarchitectonic trends and connections (Mesulam and Mufson 1982; Morán et al 1987). It is also well demonstrated, in nonhuman primates, that the OFC has heavy connections with several intraprefrontal regions, such as BA 9 of the DLPFC (Cavada et al 2000). The positive correlation found, in the Suppression condition, between the self-report ratings of sadness and the BOLD signal increases in the right OFC (BA 11), lend some more support to the view that the OFC, through its anatomic projections to limbic and paralimbic structures, is a key structure involved in behavioral inhibition and voluntary suppression of emotion.

With regard to the neuroanatomic and neuropsychological findings presented above, and the paradigm used in the Suppression condition, we submit that, first, the right DLPFC holds in mind the instruction "to become a detached observer" and then sends an executive command to the right OFC, which is charged to inhibit, through the integrated unit proposed by Mesulam and Mufson (1982) as well as through the amygdala and the midbrain, the various dimensions (e.g., cognitive, behavioral, physiologic, feeling) associated with the experience of sadness. The positive correlations found between the self-report ratings of sadness and BOLD signal increases in the right DLPFC (BA 9) and right OFC (BA 11) suggest that higher residual levels of sadness, during the Suppression task, led to greater activation/work in these two prefrontal regions.

Contrary to our *a priori* hypothesis, as well as to the results of our recent fMRI study regarding the neural substrate of volitional suppression of sexual arousal (Beauregard et al 2001), no significant activation was noted in the anterior cingulate cortex during voluntary suppression of sad feelings. To interpret this negative result, we decided to examine the individual statistical parametric maps produced in the Suppression condition. These maps revealed that the cognitive division of the anterior cingulate cortex was activated in 75% of the subjects while they attempted to voluntarily suppress sadness. These maps also showed an important degree of interindividual variability. That is, the activated voxels in the cognitive division of the anterior cingulate cortex were not consistently localized, across subjects, in the same sub-areas of this cortical region. Thus, it appears that interindividual variability, in terms of functional neuroanatomy, may account for the apparent absence of anterior cingulate activation during the Suppression condition.

Clinical Implications

From a clinical perspective, our results are particularly important given the notion that a permanent inability to suppress a negative emotion, such as sadness, may be crucially related to the etiology of major depression (Davidson et al 2000). Such inability may result from a dysfunction in the neural circuit identified here. Indeed, as recently reviewed by Brody et al (2001), depressed patients often show decreased activity in DLPFC (BA 9) and increased activity in VLPFC (BA 47). Brody et al (2001) also reported that, in several studies, a negative correlation has been found between the scores of depressed patients on the Hamilton Depression Rating Scale and either metabolism or regional cerebral blood flow in the prefrontal cortex. In view of these findings, Brody et al (2001) have proposed that, in major depression, ventral prefrontal and limbic circuits (originating in the VLPFC and ventral anterior cingulate cortex) override the relatively hypoactive dorsal circuit (originating in the DLPFC and dorsal anterior cingulate cortex) and may allow the content of depressive/sad thoughts to be prominent.

Regarding the OFC, a recent study conducted with elderly depressed patients has shown that, compared with normal control subjects, these patients had an increased density of medial OFC white matter lesions (MacFall et al 2001). Furthermore, a correlation analysis revealed that this prefrontal cortical region was significantly correlated with the severity of depression of these patients (MacFall et al 2001). These results contribute to the growing evidence that the OFC is critically involved in affective disorders.

Study Limitations

Last, we would like to acknowledge some of the limitations of this study. First, no objective measures were performed before and immediately after the two experimental conditions to characterize the subjects' emotional state. Instead, self-report ratings were used. Self-report data are extremely susceptible to bias: the subjects knew that their task was to suppress sadness (Suppression condition), and it should not be terribly surprising that their sadness ratings were lower in the Suppression condition than in the Sad condition. A more objective measure would have definitely bolstered the results of this study, even though the results in the Suppression condition are in keeping with our predictions and the literature. Second, we could not verify that the subjects had indeed performed the suppression task in the way they were requested. At the end of the Suppression condition, subjects were asked to report if they have had difficulty performing the suppression 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 during the Suppression condition. Again, as we had no objective means to verify subjects' assertions, we relied on their honesty to interpret the results.

In conclusion, the present fMRI study shows that, in normal female subjects, the right DLPFC and right OFC cortex are associated with voluntary suppression of sadness. These results confirm the involvement of the DLPFC in emotional self-regulation. They also support the view that various subdivisions of the PFC are components of a neural circuit that underlies this metacognitive capacity. From a clinical perspective, our findings highlight the fact that a "good functioning" of the DLPFC and OFC is essential to the volitional regulation of emotional impulses mediated by limbic/paralimbic structures. Indeed, a defect in the neural circuit evidenced here may lead to an inability to suppress a negative emotion, such as sadness. Such defect may be intimately linked to the etiology of major depression.

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