Abnormalities in Emotion Processing within Cortical and Subcortical Regions in Criminal Psychopaths: Evidence from a Functional Magnetic Resonance Imaging Study Using Pictures with Emotional Content

Jürgen L. Müller, Monika Sommer, Verena Wagner, Kirsten Lange, Heidrun Taschler, Christian H. Röder, Gerhardt Schuierer, Helmfried E. Klein, and Göran Hajak

Background: *Neurobiology of psychopathy is important for our understanding of current neuropsychiatric questions. Despite a growing interest in biological research in psychopathy, its neural underpinning remains obscure.*

Methods: *We used functional magnetic resonance imaging to study the influence of affective contents on brain activation in psychopaths. Series containing positive and negative pictures from the International Affective Picture System were shown to six male psychopaths and six male control subjects while 100 whole-brain echo-planar-imaging measurements were acquired. Differences in brain activation were evaluated using BrainVoyager software 4.6.*

Results: *In psychopaths, increased activation through negative contents was found right-sided in prefrontal regions and amygdala. Activation was reduced right-sided in the subgenual cingulate and the temporal gyrus, and left-sided in the dorsal cingulate and the parahippocampal gyrus. Increased activation through positive contents was found left-sided in the orbitofrontal regions. Activation was reduced in right medial frontal and medial temporal regions.*

Conclusions: *These findings underline the hypotheses that psychopathy is neurobiologically reflected by dysregulation and disturbed functional connectivity of emotion-related brain regions. These findings may be interpreted within a framework including prefrontal regions that provide top-down control to and regulate bottom-up signals from limbic areas. Because of the small sample size, the results of this study have to be regarded as preliminary.* Biol Psychiatry 2003;54:152–162 © *2003 Society of Biological Psychiatry*

From the Department of Psychiatry and Psychotherapy (JLM, MS, VW, KL, HT, HEK, GH), University of Regensburg, Regensburg; Clinic for Psychosomatic Medicine and Psychotherapy (CHR), Johann-Wolfgang-Goethe-University, Frankfurt; and the Institute of Neuroradiology (GS), University im Bezirksklinikum, Regensburg, Germany.

Address reprint requests to Jürgen L. Müller, M.D., University of Regensburg, Department of Psychiatry, Universtätsstr. 84, D-93053 Regensburg, Germany.

Received April 11, 2002; revised September 12, 2002; accepted September 23, 2002.

Key Words: Psychopathy, emotion, functional magnetic resonance imaging, International Affective Picture System, valence, arousal

Introduction

The concept of psychopathy has a long and contested tradition in French, German, and Anglo-American psychiatric history. Despite a growing interest in biological research in psychopathy, the neural underpinning of psychopathy remains obscure. Neurobiology of psychopathy is important for our understanding of current neuropsychiatric questions, because psychopathy may provide a context within which to study violent and social behavior, deficient emotion processing, and the neurology of morals and decision-making (Laakso et al 2001). In contrast to antisocial personality disorder, this special subtype of personality disorder is, in particular, characterized by abnormal or deficient emotional responsiveness leading to disturbed social interaction and diminished ability to learn from punishment. In psychopathy, interpersonal behavior has been described as selfish, dominant, manipulative, and superficial; showing a lack of responsibility within relationships; and inability to form long-lasting bonds. Psychopaths are supposed to be impulsive, showing sensation-seeking behavior and having low frustration tolerance. Within the affective domain, psychopaths are described as fearless, shallow, and callous. They are supposed to show emotional detachment, being unable to experience deeper feelings of love; empathy and remorse are found to be lacking because psychopaths are indifferent to feelings of others. As a function of the deficient emotional reactivity, criminal psychopaths have been found to be unable to learn from negative experiences like punishment. Thus, their forensic prognosis is bad (Hare 1978; Hare et al 1978; Herpertz et al 2001a; Patrick 1994; Patrick et al 1994).

0006-3223/03/$30.00
doi:10.1016/S0002-3223(03)01749-3

A growing amount of research has examined the nature and bases of this abnormality in emotion processing. Persons with psychopathy have been found to show reduced electrodermal response to nonconditioned and conditioned anxiety- or punishment-related stimuli (Hare 1978; Hare et al 1978; Patrick 1994; Patrick et al 1994). Neurophysiological studies suggest that the autonomic reactivity is attenuated in psychopathy (Patrick et al 1993). The typical augmentation of the startle response during exposure to aversive stimuli in control group members has been found to be diminished or absent in psychopathy, indicating a low level of defense reaction induced by fear or aversive stimuli. This low defense reaction level is supposed to be based on a general deficit in processing emotional contents (Blair et al 1997; Herpetz et al 2001b; Kiehl et al 1999a, 1999b, 2000; Patrick 1994; Patrick et al 1993, 1994).

In 1937, Papez hypothesized that the expression and decoding of emotions were the function of a circuit involving the anterior cingulate, hippocampus, fornix, mamillary bodies, anterior thalamus, and the hypothalamus (Papez 1937). Although the anterior thalamus and mamillary bodies are no longer considered to be involved in emotional processes, the amygdala is now believed to play a key role in emotion processing (Haznedar et al 2000). In addition, special consideration is given today to the basal ganglia and to cerebellar regions (Beauregard et al 1998; Lane et al 1997; Paradiso et al 1999). Investigating the neuroanatomy of emotion, a growing body of neuroimaging data using both positron emission tomography and functional magnetic resonance imaging (fMRI) have supported the key position of the orbitofrontal cortex and the dorsolateral prefrontal cortex, the cingulate gyrus, the hippocampus, the insula, temporal regions, and the amygdala in response to emotional stimuli (Canli et al 1998; Grodd et al 1995; Lane et al 1998; Maddock and Buonocore 1997; Paradiso et al 1999; Phillips et al 1998; Schneider et al 1995; Wright et al 2001).

Neuroimaging studies on psychopathy using positron emission tomography (Raine et al 1998), single photon emission computed tomography (SPECT) (Chow 2000; Intrator et al 1997), structural (Anderson et al 1999; Laakso et al 2001) and fMRI (Kiehl et al 2001; Schneider et al 2000a) have supported the hypothesis that psychopathy may be grounded in biological abnormalities. Despite the hypothesized nature of psychopathy, the focus has rarely been on brain activation studies using emotional stimuli. A SPECT study reported on different perfusion patterns during the processing of emotional words (Intrator et al 1997). Using an affective memory task in psychopaths, a recent fMRI study revealed a significantly diminished affect-related activity within the limbic system, whereas increased activation was observed in frontotemporal brain regions (Kiehl et al 2001). The stimulation designs used in earlier studies involve higher cortical functions (e.g., attention, language, and memory) that might obscure atypical activation patterns in emotional networks. To study abnormalities in emotion processing in psychopathy, we looked for stimuli that have proven to directly affect emotion processing.

Looking at pictures with emotional content has been found to be a powerful tool to activate brain structures involved in emotion processing. In neurophysiological studies, emotionally charged pictures have been proven to successfully evoke a spectrum of measurable emotional reactions (Bauer 1998; Bradley et al 1996; Lang et al 1990, 1998a, 1998b). Previous research has shown clear differences in autonomic responses and facial expressions as a function of pleasure and arousal of emotional pictures (Lang et al 1993b). Emotionally charged pictures were successfully used to activate emotion-related brain regions, as well (Critchley et al 2000; Davidson et al 1992; Paradiso et al 1997, 1999; Schneider et al 1999; Whalen et al 1998).

The International Standardized Affective Picture System (IAPS) (CSEA-NIMH 1999; Lang et al 1999) provides a large data set of standardized pictures. Based on the two-dimensional approach by which emotions can be defined, the two independent dimensions of affective valence and arousal, pictures from the IAPS are defined by their placement within a valence and arousal coordinate space (CSEA-NIMH 1999; Lang et al 1993b, 1998, 1999). Previous neuroimaging studies using pictures from the IAPS reported on significant emotion-induced brain activation within an extended circuitry, including the amygdala (Canli et al 2000; Paradiso et al 1999), the insula (Canli et al 1998), the right inferior frontal gyrus (Canli et al 1998; Paradiso et al 1999), the medial and lateral prefrontal cortex (Northoff et al 2000; Paradiso et al 1999), the cingulum (Canli et al 1998), the anterior temporal cortex (Northoff et al 2000), the cerebellum (Paradiso et al 1999), and the visual cortex (Lang et al 1998c; Northoff et al 2000; Paradiso et al 1999).

We report on a whole-brain fMRI study examining the functional circuit of the brain regions associated with the processing of emotional content in psychopathy using pictures from the IAPS. We included only male subjects to avoid gender effects that have been reported earlier (Schneider et al 2000b) and which may possibly confound the data. Existing neuroimaging studies did not take into account that the emotional response to a stimulus persists across the duration of the stimulus presentation (Garrett and Maddock 2001). Thus, in this setup the picture series were separated by a black screen condition to allow the subjective emotional response to the stimuli to decrease.

Methods and Materials

Subjects

In total, 14 participants were examined according to the study protocol. Because of movement artifacts, two participants had to be excluded; the remaining 12 male, right-handed volunteers could be analyzed in this study. Participants with neuropsychiatric disorders other than psychopathy personality disorder were excluded. All participants were free from any documented history of serious head injury. No participant met the DSM-IV criteria for substance dependency within the last 6 months. Depression was clinically excluded and administered using the Hamilton Depression Rating Scale (HAMD) and Beck's Depression Inventory (BDI; Beck and Steer 1987). Participants with an intelligence quotient below 85, measured using Raven's Progressive Matrices (Burke 1958) were excluded. Only right-handed participants, as identified by the Edinburgh Handedness Inventory (Oldfield 1971) were included. The control group ($n = 6$) was composed of healthy male volunteers without any neuropsychiatric history. Criminal psychopaths ($n = 6$) were recruited within a high-security psychiatric facility. The psychopaths were convicted criminals and lacked in responsibility because of mental illness. Instead, or in addition to, a prison sentence they had been convicted to psychiatric treatment within a forensic, high-security facility. Psychopathy was diagnosed using the Hare Psychopathy Checklist-Revised (PCL-R) (Hare 1991). The score of the PCL-R can range from 0 to 40. To assure that both groups were strictly separated, only patients with a score above 30 were defined as psychopaths, whereas control subjects with a score below 10 were included. Factor 1 (assessing the emotional detachment) and factor 2 (assessing the antisocial/behavioral aspects) were separately analyzed (Hare et al 2000; Shine and Hobson 1997). A German version of the Positive and Negative Affect Schedule (PANAS) (Watson 1988) was used to evaluate global affect states before the fMRI run. To explore the influence of positive and negative picture sets on the affect state of the participants, PANAS was reassessed immediately after scanning (Figure 1).

Written informed consent was obtained from all subjects, and all procedures were conducted as approved by the local Ethics Committee.

Stimulation Protocol

IAPS. Using fMRI, we stimulated 12 male, right-handed volunteers with pictures from the IAPS (CSEA-NIMH 1999; Lang et al 1993b, 1998c, 1999), charged with neutral, negative, and positive emotional load. Previous to this study, the IAPS pictures had been rated by a sample of German students for standardization (Meinhardt 2000). Positive pictures included images such as happy couples, puppies, food such as ice cream, and others. Neutral images included, for example, buildings, a black book, and a fork. Negative pictures included threatening animals or faces, heavily wounded persons, and skull and bones. Pictures were stored on a personal computer and were presented using a video-beamer on a screen that could be seen via a mirror fixed at the head coil of the MRI.

Using a block design, a series with four neutral pictures was presented in the beginning of one fMRI run. Then, in an alternating way, a series of five positive pictures and a series of five negative pictures were projected four times. Each picture was presented for 3 sec. Between one picture series and the following picture series, a black screen condition of 10 sec was included. Because the subjective reaction to an emotional stimulus exceeds the time of stimulus presentation, this black screen condition was necessary to allow for the decline of the subjective emotional reaction (Garrett and Maddock 2001). The whole run consisted of two series of neutral pictures, four series of positive and four series of negative pictures. Before scanning, the participants were instructed to allow themselves to feel the emotions the pictures suggest.

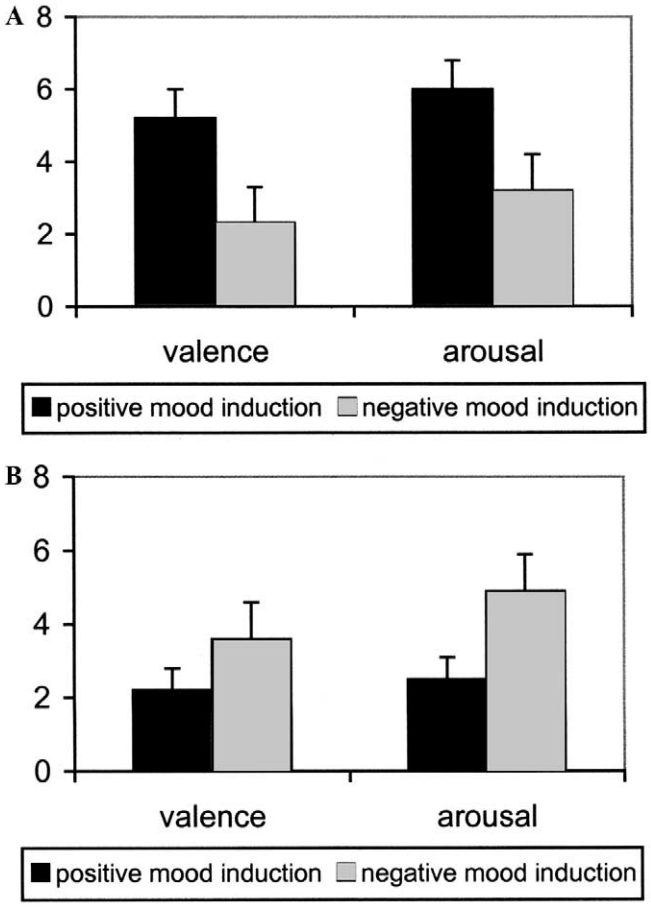

Figure 1. Positive and Negative Affect Schedule: ratings after mood induction. **(A)** Decrease of positive valence and arousal ratings after negative mood induction for both groups (psychopaths and control subjects). **(B)** Increase of the negative valence and arousal ratings after negative mood induction for both groups.

SELF-ASSESSMENT MANIKIN. To evaluate the individual assessment of pictures, subjects were presented the same pictures immediately after scanning using the self-assessment manikin (SAM) (Lang et al 1993a, 1993b). The scale ranged from 1 (very unpleasant) to 9 (very pleasant) for ratings of emotional valence

and from 1 (not at all) to 9 (very strong) for ratings of emotional arousal, with 5 representing a neutral rating in both dimensions. For valence and arousal, separate data analyses were performed using repeated-measure analysis of variance (ANOVA) with the two factors Emotion (pleasant/unpleasant/neutral) and Group (patients and control subjects).

PANAS. The participants were asked to fulfill out the PANAS (Watson 1988) to evaluate the influence of positive and negative picture contents on the affect state. Two criteria were selected to apply specifically for arousal and emotion: we chose "freude" (pleasure) and "stolz" (pride) for positive affect, "ärger" (anger) and "schuld" (guilt) for negative affect, "angeregt" (stimulated) and "begeistert" (enthusiastic) for positive arousal, and "erschrocken" (startled) and "gereizt" (irritated) for negative arousal. The data of the different scales was analyzed using a repeated-measure ANOVA. Appropriate planned *t* tests followed.

fMRI Data Acquisition

Functional MRI was performed on a 1.5-Tesla (Siemens Symphony, Erlangen, Germany) MR-system with a standard 25-mT-gradient system using a standard head coil (MRI Unit, Neuroradiology Section, Bezirksklinikum, Regensburg, Germany) for measuring the blood oxygen level-dependent (BOLD) contrast. Shimming was optimized with an automated Siemens shim adjust. To prevent head motion, foam pads were placed inside the head coil. For anatomical coregistration, a T1-weighted isotropic three-dimensional gradient echo sequence (MPRAGE [magnetization prepared rapid gradient echo]; time to repetition [TR] = 11.1 msec; time to echo [TE] = 4.3 msec; time of acquisition [TA] = circa 8.52 min; 170 slices; matrix = 224 × 256, field of view (FOV) = 256 × 256 mm; voxel size = 1 × 1 × 1 mm^3) was used to obtain structural three-dimensional volumes. Blood oxygen level dependent images were obtained covering the whole brain using a (20 slices) echo planar imaging (EPI) sequence (100 measurements; TR = 2092.0 msec; TE = 60 msec; scan time = 2 sec; total scan time = 6 min; matrix = 64 × 64; FoV = 240 × 240 mm; slice thickness = 5.0 cm; distance factor .2; pixel size = 3.75 × 3.75 mm). The first four images were discarded to allow for T1 stabilization.

fMRI Data Analysis

Functional MRI data were statistically analyzed using BrainVoyager 4.6 software package (http://www.brainvoyager.com) (Goebel 1996; Goebel et al 1996, 1998). Functional and anatomical images of all participants were transformed into the standard space corresponding to the atlas of Talairach and Tournoux (1988). Three-dimensional data preprocessing included head movement assessment, high frequency filtering, spatial and temporal Gaussian smoothing (3 mm and 4), and removal of linear trends. Because of movements artifacts, 2 of the 14 participants had to be excluded from data analysis. Thus, the data sets of 12 out of 14 participants could be analyzed. To minimize the risk of false-positive findings, a minimal cluster size of 60 pixels was postulated. The differences between the resting and the stimulation condition were statistically evaluated using a general linear model corresponding to a delayed boxcar design considering the hemodynamic response function (Boynton et al 1996). The principal analyses consisted of the comparison between the positive and negative pictures. Processing of positive contents was analyzed comparing the BOLD response induced by the positive pictures between control subjects and psychopaths. In addition, processing of negative contents was analyzed comparing the BOLD response induced by negative pictures between the two groups. Considering the hemodynamic response delay, a lag of 3–6 sec was accounted (Boynton et al 1996). Using the general linear model, the correlation maps were computed (Friston et al 1995). According to Rothstein et al (2001), activated regions were evaluated within a confidence range above 3.5 to illustrate the network involved in emotion processing. All results were corrected for serial correlation. Because fMRI research focusing on subcortical and limbic regions is interfered with by susceptibility artifacts, original EPI data and the coregistered three-dimensional volumes, including the superimposed volume time course of one participant, are illustrated in Figure 2.

Results

Age

The control group ($n = 6$) was composed of healthy male volunteers with a mean age of 28.0 years (SD = 4.14). Mean age of criminal psychopaths ($n = 6$) was 33.0 years (SD = 8.0). There was no significant age difference between the two groups [$t(10) = 1.9$; ns].

HAMD and BDI

The HAMD was administered to determine whether either of the two groups showed evidence of clinical depression. Neither group scored near the lower cutoff for depression (i.e., HAMD score greater than 20 and BDI score greater than 17). In HAMD, psychopaths had a mean score of 5.3 (SD = 3.4), whereas control subjects had a mean score of .8 (SD = 1.1). In BDI, the mean score of psychopaths was 10.8 (SD = 1.5), whereas the control subjects mean score was .8 (SD = 1.6). Although far below the lower cut-off for clinical depression, there was a significant difference between both groups in BDI scores [$t(10) = -11.3$; $p < .001$] (Beck and Steer 1987).

PCL-R

According to the inclusion criteria, psychopaths had a PCL-R score above 30, whereas control subjects ranged below 10. The mean of the total PCL-R score in psychopaths was 36.8 (SD = 2.6; range = 34–40). Mean of subscale factor 1 applying for emotional detachment was 15 (SD = 1.4; range = 13–16). Mean of subscale factor 2 applying for antisocial behavior was 16 (SD = 2.3; range = 12–18).

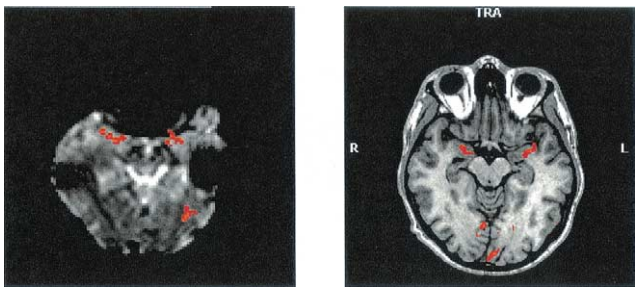

Figure 2. Brain activation in subcortical regions. Echoplanar-imaging sequences and corresponding corregistered T1 images. L, left; R, right; TRA, transversal.

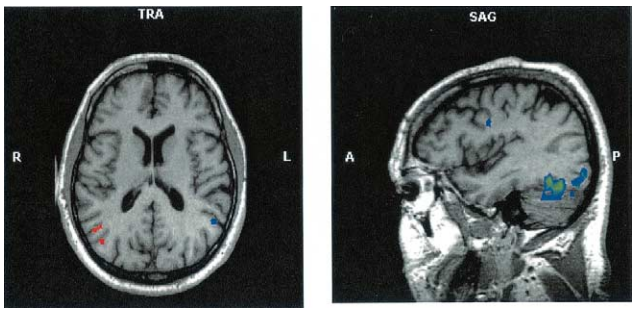

Figure 3. Differences in processing of positive emotions. Regions of interest showing significantly increased activation in psychopathy (blue) compared with control subjects (red). Confidence range .35-.8; minimal cluster size = 60; corrected for serial correlation. p(corrected) $< .001$. Note the lateralization of temporal activation and the frontal overactivation in psychopaths. A, anterior; L, left; R, right; SAG, sagittal; TRA, transversal.

SAM

Subject ratings on emotional valence were scored on a scale of 1 to 9, in which 1 means very unpleasant, 5 neutral, and 9 very pleasant. For valence, there was no significant group difference [$F(1,10) = .3$; ns], but a main effect for valence [$F(2,20) = 33.29$; $p < .001$]. Pleasant pictures were rated significantly higher (mean = 6.8; SD = .9) than neutral pictures [mean = 4.5; SD = 1.7, $t(11) = -4.73$; $p < .001$] and the mean score for the neutral picture set was significantly higher than that of the unpleasant picture set [mean = 3.0; SD = 1.4; $t(11) = 2.29$; $p < .05$].

Subject ratings on arousal were scored on a scale of 1 (not at all) to 9 (very strong), with five representing a neutral rating. There were no significant differences between both groups regarding the arousal ratings [$F(1,11) = 3.9$; ns], but there was a main effect for arousal [$F(2,22) = 7.4$; $p < .01$]. T tests revealed that positive (mean = 3.2; SD = 1.9) and negative pictures (mean = 4.3; SD = 2.4) evoked more excitement than neutral pictures (mean = 2.3; SD = 1.6). In contrast to the significant difference between negative and neutral pictures [$t(11) = -4.17$; $p < .01$], the test between positive and neutral picture sets missed the significance level [$t(11) = -1.79$; ns].

PANAS

To quantify the mood induction effect, we analyzed representative items of the PANAS. Positive affect, negative affect, positive arousal, and negative arousal were separately evaluated for both groups.

In the baseline condition, there were no group effects for positive [$t(10) = -1.55$; ns] and negative [$t(10) = 2.18$; ns] affect or positive [$t(10) = -1.81$; ns] and negative [$t(10) = 2.28$; ns] arousal.

For positive and negative affect, ANOVA revealed no significant main effect for Group [$F(1,10) = .25$; ns] and no significant interaction for Group × Induction [$F(2,20) = .52$; ns] but a significant interaction for Affect × Induction [$F(2,20) = 13.0$; $p < .001$; see Figure 1a and 1b]. After negative mood induction, positive affect (mean = 2.3; SD = .9) was significantly lower than after positive mood induction [mean = 5.3; SD = 2.2; $t(11) = -4.4$; $p < .01$]. Negative affect was significantly lower after positive mood induction (mean = 2.2; SD = .6) than after negative mood induction [mean = 3.6; SD = 1.8; $t(11) = 3.0$; $p < .05$; see Figure 1a and 1b].

Also, for positive and negative arousal, there was no significant main effect for Group [$F(1,10) = .0$; ns] and no significant interaction for Group × Induction [$F(2,20) = 1.2$; ns]; however, ANOVA revealed a significant interaction for Induction × Arousal [$F(2,20) = 8.5$; $p < .01$]. After negative mood induction, positive arousal (mean = 3.3; SD = 1.5) was significantly lower than after positive mood induction [mean = 6.0; SD = 2.4; $t(11) = -2.7$; $p < .05$]. Negative arousal was significantly lower after positive mood induction (mean = 2.5; SD = 1.2) than after negative mood induction [mean = 4.9; SD = 2.6; $t(11) = 3.9$; $p < .001$; see Figure 1a and 1b].

Imaging Data

We compared the brain activation patterns induced by positive and negative pictures between both groups.

ACTIVATION DIFFERENCES INDUCED BY POSITIVE PICTURE SERIES BETWEEN PSYCHOPATHS AND CONTROL SUBJECTS. In psychopaths, relative to control subjects, increased activation (Figure 3, depicted in blue) was found bilaterally in the fusiform cortex, the parietal cortex, the cerebellar hemispheres, the temporal and precentral cortex, and unilaterally left-sided in the gyrus frontalis inferior (see Table 1, Figure 3, depicted in blue). In

Table 1. Regions of Interest Showing Significantly Increased Activation in Psychopaths through Positive Picture Contents Compared with Control Subjects

ROI	Laterality	x	y	z	Voxel	*t*	*p* (corrected)
Frontal lobe							
Gyrus Paraecentralis	L	−45	−7	38	95	−4.3	<.001
Gyrus Frontalis Inferior	L	−44	7	27	254	−3.98	<.001
Gyrus Paraecentralis	R	38	−3	29	176	−4.37	<.001
Temporal Lobe							
Gyrus Temporalis Superior	L	−50	−52	17	280	−4.77	<.001
Gyrus Temporalis Medius	R	57	−57	3	64	−3.69	<.001
Gyrus Temporalis Medius	L	−49	−51	−3	1872	−5.51	<.001
Parietal Lobe							
Gyrus Supramarginalis	R	31	−46	31	176	−4.46	<.001
Gyrus Angularis	L	−38	−66	34	342	−4.22	<.001
Occipital Lobe							
Gyrus Fusiformis	L	−18	−86	−17	630	−4.99	<.001
Gyrus Fusiformis	R	16	−84	−14	>2000	−4.29	<.001
Cerebellum							
Hemisphere	L	−18	−46	−22	241	−3.96	<.001
Hemisphere	R	21	−46	−25	175	−4.21	<.001

Confidence range = .35–.8; minimal cluster size = 60. The effect was corrected for serial correlation. Cluster with *p* (corrected) < .001 are listed. x,y,z are coordinates according to Talairach system. Also see Figure 4. ROI, region of interest; L, left; R, right.

psychopaths, relative to control subjects, reduced activation was found bilaterally in the occipital cortex and unilaterally right-sided in the medial frontal gyrus and medial temporal gyrus (see Table 2, Figure 3, depicted in red).

ACTIVATION DIFFERENCES BY NEGATIVE PICTURE SERIES BETWEEN PSYCHOPATHS AND CONTROL SUBJECTS . In psychopaths, relative to control subjects, bilaterally increased activation (Table 2, Figure 4, depicted in blue) was revealed in the medial temporal gyrus and in the occipital and the parietal cortex; bilaterally increased activation was found left-sided in the precentral cortex and the superior temporal gyrus and right-sided in the inferior and medial frontal gyrus, the anterior cingulate, and the amygdala (see Table 3, Figure 4, depicted in blue). In contrast, in psychopaths, relative to control subjects, reduced activation was found unilaterally right-sided in the subgenual cingulate, the medial temporal gyrus, the gyrus fusiformis, and unilaterally left-sided in the lobulus paracentralis, the dorsal cingulate, and the parahippocampal gyrus (see Table 4, Figure 4, depicted in red).

Discussion

Ever since early clinical descriptions were made, abnormal or deficient emotional response has been considered to be a hallmark of psychopathy (Herpetz and Sass 2000). Neurophysiological data have supported the hypothesis that psychopathy may be grounded in a deficient function of the emotion-related brain circuit, leading to poor passive-avoidance learning, reduced fear response, and a poverty in affective reaction (Hare 1968; Hare and Quinn 1971; Hare et al 1978; Herpetz and Sass 2000; Herpetz et al 2001b; Kiehl et al 1999b, 2000; Patrick 1994; Patrick et al 1993). In contrast to neurophysiological research, im-

Table 2. Regions of Interest Showing Significantly Reduced Activation through Positive Pictures in Psychopaths Compared with Control Subjects

ROI	Laterality	x	y	z	Voxel	*t*	*p* (corrected)
Frontal Lobe							
Gyrus Frontalis Medius	R	35	29	−3	80	4.36	<.001
Temporal Lobe							
Gyrus Temporalis Medius	R	43	−58	17	343	4.91	<.001
Occipital Lobe							
Gyrus Lingualis	L	−21	−64	−3	88	3.95	<.001
Gyrus Fusiformis	R	24	−62	−7	84	3.21	<.001

Confidence range = .35–.8; minimal cluster size = 60. The effect was corrected for serial correlation. Cluster with *p* (corrected) < .001 are listed. x,y,z are coordinates according to Talairach system. Also see Figure 4. ROI, region of interest; R, right; L, left.

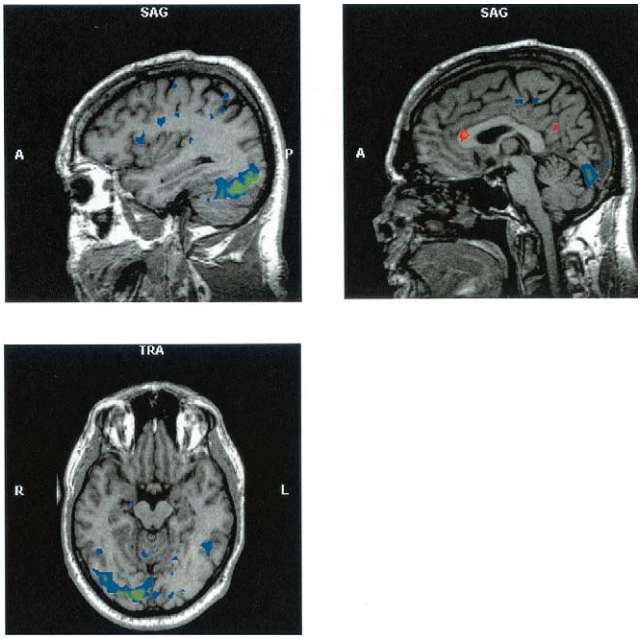

Figure 4. Differences in processing of negative emotions. Regions of interest showing significantly increased activation in psychopathy (blue) compared with control subjects (red). Confidence range .35-.8; minimal cluster size = 60; corrected for serial correlation. p(corrected) $< .001$. Note the overactivation of the prefrontal cortex (sagittal view) and of right amygdala (axial view) in psychopaths. Underactivation was observed in the subgenual cingulate (sagittal view, depicted in red). A, anterior; P, posterior; R, right; L, left; SAG, sagittal; TRA, transversal.

aging data on psychopathy are rare using affective memory tasks (Intrator et al 1997; Kiehl et al 2001) or aversive classical conditioning (Schneider et al 2000a). In neurophysiological investigations, pictures from the IAPS (CSEA-NIMH 1999; Lang et al 1993a, 1993b, 1999) have been found to directly induce emotions (Bradley et al 1996; Lang et al 1990, 1998a, 1998b). Thus, we used pictures from the IAPS with pleasant and unpleasant emotional contents to investigate function and functional interaction of different parts within the emotion-related brain circuit in psychopaths. Compared with control subjects, we found different activation patterns in psychopaths, with parts of the emotion-related brain circuit being significantly overactive, whereas other parts were underactive (see Table 1 and 2 and Figures 3 and 4). The results of this study are in agreement with the hypotheses that dysregulation and disturbed functional connectivity are the neurobiological underpinnings of neuropsychiatric disorders as shown here in psychopaths.

In psychopaths, negative emotions induced increased activation right-sided in prefrontal regions, anterior cingulate, and amygdala, whereas positive emotions induced increased activation in left gyrus frontalis. In psychopaths, reduced activation through negative pictures was found in right subgenual cingulate and right medial temporal gyrus, in left lobulus paracentralis, left dorsal cingulate, and left parahippocampal gyrus (see Table 4, Figure 4). Alternatively, positive emotions induced reduced activation in right medial frontal and right medial temporal gyrus (see Tables 1 and 2, Figure 3). Thus, we found abnormal activation patterns in psychopaths within important cortical and subcortical parts of the emotion-related brain circuit responsible for the antagonistic function. Our data are supported by the results of earlier studies reporting on frontotemporal overactivation in psychopaths (Intrator et al 1997; Kiehl et al 2001). The emphasis on the role of the frontal cortex in psychopathy is further supported by lesion data on "acquired psychopathy" (Adolphs et al 1994; Angrilli et al 1999), reporting on behavioral changes following prefrontal lesions (Bechara et al 2000a, 2000b; Blair and Cipolotti 2000; Damasio 1996) and on violence (Müller et al 2001; Raine et al 1998a, 1998b). Orbitofrontal and dorsolateral prefrontal cortex are critically involved in regulating and modulating emotional behavior and stress responses (Baker et al 1997; Damasio et al 2000; Drevets 2000; Herpetz et al 2001a; Kimbrell et al 1999). Prefrontal regions are directly connected with subcortical structures of the limbic system (Damasio et al 2000). In this neural circuit, frontal regions are supposed to modulate or inhibit amygdala-driven responses and may, thus, provide top-down control of the amygdala (Herpetz et al 2001a; Morgan et al 1993; Paradiso et al 1999). In relation to control subjects, the current study on psychopathy shows increased activation in orbitofrontal and dorsolateral prefrontal regions, right amygdala, and right insula through negative pictures. Thus, our data are in good agreement with the hypothesis of a top-down modeling effect via orbitofrontal cortex and amygdala (Beauregard et al 2001; Damasio et al 200l; Davidson and Irwin 1999; Herpetz et al 2001a; Morgan et al 1993; Paradiso et al 1999) that might be dysfunctional in psychopaths.

One major result of this fMRI study is a highly significant increase in BOLD response in the right amygdala while viewing negative emotional pictures in psychopathy. Activation of the amygdala has been successfully obtained earlier using pictures from the IAPS and other stimulation methods (Lane et al 1999; Morris et al 1999; Paradiso et al 1999; Schneider et al 1998, 1999; Whalen et al 1998). Most of these studies reported on amygdala activation in processing negative emotions (Lane et al 1997, 1999; Schneider et al 1998, 2000b; Zalla et al 2000); however, data on amygdala activation in psychopaths is inconsistent (Kiehl et al 2001; Schneider et al 2000). Schneider et al (2000) reported on increases in activation of amygdala and dorsolateral prefrontal cortex

Table 3. Regions of Interest Showing Significantly Increased Activation through Negative Picture Contents Compared with Control Subjects

ROI	Laterality	x	y	z	Voxel	*t*	*p* (corrected)
Frontal Lobe							
Gyrus Paraecentralis	L	−35	−14	45	309	−5.23	<.001
Gyrus Frontalis Inferior	R	41	−4	32	811	−3.81	<.001
Gyrus Frontalis Medius	R	38	−12	57	158	−4.74	<.001
Gyrus Cinguli	R	4	−18	43	93	−4.10	<.001
Temporal Lobe							
Gyrus Temporalis Medius	L	−48	−49	−6	1312	−6.10	<.001
Gyrus Temporalis Superius	L	−52	−50	16	616	−5.74	<.001
Gyrus Temporalis Medius	R	54	−39	2	563	−4.92	<.001
Corpus Amygdaloideum	R	18	−9	−12	62	−3.67	<.001
Insula	R	34	−13	14	263	−4.27	<.001
Parietal Lobe							
Precuneus	L	−5	−61	46	447	−3.81	<.001
Lobus Parietalis Inferius	R	38	−57	45	768	−5.24	<.001
Occipital Lobe							
Occipital Cortex	L	−19	−84	−27	>988	−5.43	<.001
Occipital Cortex	R	28	−74	−21	>4000	−8.15	<.001

Confidence range = .35–.8; minimal cluster size = 60; the effect was corrected for serial correlation. Cluster with *p* (corrected) < .001 are listed. x,y,z are coordinates according to Talairach system. See also Figure 4. ROI, region of interest; L, left; R, right.

by an aversive conditioning task. In contrast, Kiehl et al (2001) found a reduced activation in amygdala, striatum, and cingulate in psychopathy. Because Kiel and colleagues used a memory task, this discrepancy may be grounded in the stimulation paradigm. Kiehl et al (2001) reported on hippocampal underactivation in psychopaths. Our data revealed an increased hippocampal activation in psychopaths. Hippocampal and parahippocampal regions are found to be involved in emotion processing and in psychopaths (Laakso et al 2000; Lane et al 1997; Sitoh and Tien 1997; Suzuki et al 1992). Nevertheless, the meaning of hippocampus in emotion processing and regulation in psychopaths has to be addressed in further studies. The hippocampus is also involved in memory consolidation that might explain, more specifically, the different imaging results between the two studies (i.e., the one involving a memory component finds the hippocampus activated, whereas the one without an explicit memory component does not activate the hippocampus).

Surprisingly, we found an increased activation of the left temporal region in psychopaths, whereas right temporal regions showed a reduced activity. Evidence from psychophysiological as well as lesion studies associated the left temporal regions with hyperarousal, whereas right temporal regions seem to be associated with hypoarousal (Braun et al 1999; Davidson and Irwin 1999; Davidson et al 1996; Kenworthy et al 2001). Regarding the arousal effect assessed by the SAM, psychopaths and control subjects did not differ significantly in this study. Nevertheless, there might be a difference in neurobiological underpinnings in arousal-related brain function localized in the temporal cortex. This finding emphasizes the

Table 4. Regions of Interest Showing Significantly Reduced Activation through Negative Pictures in Psychopaths Compared with Control Subjects

ROI	Laterality	x	y	z	Voxel	*t*	*p* (corrected)
Frontal Lobe							
Lobus Paracentralis	L	−16	32	44	106	4.34	<.001
Gyrus Cinguli	L	−6	34	7	87	3.78	<.001
Gyrus Cinguli, Subgenual Cingulate	R	4	27	16	250	4.86	<.001
Temporal Lobe							
Gyrus Hippocampalis	L	−28	−49	−4	308	5.422	<.001
Gyrus Temporalis Medius	R	42	−72	16	444	5.51	<.001
Occipital Lobe							
Gyrus Cinguli	L	−5	−62	11	227	4.68	<.001
Gyrus Fusiformis	R	24	−62	−5	262	3.79	<.001

Confidence range = .35–.8; minimal cluster size = 60; the effect was corrected for serial correlation. Cluster with *p* (corrected) < .001 are listed. x,y,z are coordinates according to Talairach system. See also Figure 4. ROI, region of interest; L, left; R, right.

hypothesis of a lateralization of arousal regulation in temporal regions (Braun et al 1999; Kenworthy et al 2001). This finding, as well, has to be focused on in further studies.

There are several shortcomings of our study that have to be addressed. First, the number of participants is small. Second, we did not evaluate the electrophysiological response to our stimulation design during the EPI sequences. Thus, the results of this study have to be regarded as preliminary.

In psychopaths, different activation patterns have been found while processing positive and negative valenced emotional stimuli. Significantly increased activation, as well as reduced activation, have been found in different parts of the emotion-related brain circuit compared with healthy control subjects. These findings emphasize the importance of function and functional interaction between the different parts of the neural network involved in emotion processing. The results of this study support the hypothesis that disturbed interaction between top-down control via prefrontal regions and bottom-up signals via limbic areas are the neurobiological underpinnings of psychopaths.

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