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Evidence for a different role of the ventral and dorsal medial prefrontal cortex for social reactive aggression: An interactive fMRI study

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Interactive paradigms inducing reactive aggression are absent in the brain mapping literature. We used a competitive reaction time task to investigate brain regions involved in social interaction and reactive aggression in sixteen healthy male subjects with fMRI. Subjects were provoked by increasingly aversive stimuli and were given the opportunity to respond aggressively against their opponent by administering a stimulus as retaliation. fMRI revealed an increase of medial prefrontal cortex (mPFC) activity during retaliation. The dorsal mPFC was active when subjects had to select the intensity of the retaliation stimulus, and its activity correlated with the selected stimulus strength. In contrast, ventral mPFC was active during observing the opponent suffering but also during retaliation independent of the stimulus strength. Ventral mPFC activation, stronger in low callous subjects, correlated positively with skin conductance response during observation of the suffering opponent. In conclusion, dorsal mPFC activation seems to represent cognitive operations related to more intense social interaction processes whereas the ventral mPFC might be involved in affective processes associated with compassion to the suffering opponent.

Keywords: PFC; Social interaction; Imaging; Aggression; Emotion

Introduction

The experience of being unjustly assaulted evokes the impulse to defend oneself and to respond aggressively to the offender. This type of reactive aggression contrasts with instrumental aggression which is purposeful and goal-directed (Berkowitz, 1993). The cognitive control of reactive aggressive impulses, important for social interaction (Siegel, 2004), is motivated by the anticipation of negative consequences and leads to avoidance behavior (Gray, 1982) and the mobilization of empathic feelings (Ohbuchi et al., 1993).

The prefrontal cortex (PFC) plays a central role in many aspects of social cognition (Rilling et al., 2002), including perspective taking (Frith and Frith, 1999), and also in the regulation of emotions such as aggression (for a review, see Blair, 2004). In particular, studies with patients with lesions of the ventral prefrontal lobe demonstrated impairment in identifying emotional expression using face or voice stimuli (Hornak et al., 1996) and deficits in representing the mental states of others when performing verbal tasks based on theory of mind (Stone et al., 1998; Mah et al., 2005). Additionally, lesions of the ventromedial prefrontal cortex disturb the control of reactive aggressive behavior (Grafman et al., 1996; Anderson et al., 1999) which might result in a similar behavior as in other psychopathic individuals (Blair and Cipolotti, 2000). Increased reactive aggressive behavior in subjects without brain lesions is often associated with prefrontal dysfunction (Volkow et al., 1995).

Imaging studies on facial perception demonstrated an increase of activation in the lateral ventral prefrontal areas during observation of angry and fearful facial expressions (Blair et al., 1999) and social norm violations (Berthoz et al., 2002; together with the medial PFC (mPFC)). Imaging studies on social interaction and emotional control identified at least two distinct areas within the mPFC involved in aggression and its control. Activation of the dorsal mPFC has been observed during cognitive regulation of emotional behavior (Ochsner et al., 2004a) and when subjects made judgments about another person's emotional states (Ochsner et al., 2004b). In contrast, activity in the ventral mPFC has been associated with monitoring of one's own feelings (Lane et al., 1997; Phan et al., 2004) and physiological changes that accompany a particular emotional response (Damasio, 1996).

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The present study investigated the role of the PFC with functional magnetic resonance imaging (fMRI) in a paradigm provoking reactive aggression. We used a realistic, dynamic social interaction that involved being offended, retaliating and watching the opponent suffer. Subjects played a competitive reaction time task and, depending on the outcome, either received an aversive stimulus or administered one with an intensity of their choice to their opponent. Reactive aggression was induced by increasing the intensity of the aversive stimulus the subjects received over the course of the experiment. This paradigm was modified for usage in a social interactive imaging setting based on the experimental design from Taylor (1967), a design which reliably induces reactive aggressive behavior (Giancola and Zeichner, 1994). A modification in our paradigm was the reduction of number of winning trials during the course of the experiment. After each retaliation trial, subjects were shown a short video clip of the opponent receiving the aversive stimulus (see Fig. 1). By introducing a second person as a competitor and presenting his pain-related expressive behavior matching the intensity of the retaliation stimulus, we ensured that aggression control was induced. An event-related design that entailed anticipation of an offending aversive stimulation, retaliation and watching the opponent suffering was used to isolate functional brain activity associated with different aspects of aggression and its control. Specifically, we investigated the role of the mPFC during the interaction with an opponent. Additionally, we examined the relationship between brain activity during the different trial phases, skin conductance responses (SCR) as an indicator of autonomic arousal, and self-reported psychopathic personality traits. We hypothesized that the mPFC is critically involved in the regulation of reactive aggression (Taylor et al., 2003; Ochsner et al., 2004a) and that psychopathic personality traits correlating with a lack of peripheral physiological changes correspond with reduced activation within the mPFC. Lack of social affection in psychopathy was repeatedly found to be related to reduced processing of bodily signals during emotions (Damasio, 1996; Birbaumer et al., 2005; "somatic markers").

Material and methods

Subjects

Sixteen healthy male subjects (mean age 28.6 years, standard deviation (SD) 6.5 years), recruited by advertisement in the local newspaper, participated in the fMRI experiment. Two subjects who reported doubts about the veracity of the opponent's role were excluded from the analysis.

The study was approved by the Ethics Committee of the Medical Faculty of the University of Tübingen. Written informed consent was obtained according to the guidelines of the Declaration of Helsinki.

Experimental design

Before scanning, subjects were introduced to their opponent. Subjects were instructed about the competitive reaction time task to perform during scanning. They were told that, if they responded slower to a cue than their opponent, their opponent would be allowed to give them an aversive pneumatic pressure stimulus on the finger; if they responded faster, they would be allowed to administer a stimulus with an intensity of their choice to their opponent. The opponent was an instructed associate of the experimenter, and trial outcome and the intensity of painful stimuli were predefined and identical for all subjects.

Scanning consisted of four sessions with 20 trials each. Each trial started with a verbal cue followed by a visual signal prompting the subject to press a button with the right index finger as quickly as possible. A symbol indicated trial outcome. In the event the subject lost the trial, a visual five-point scale appeared indicating the intensity of the aversive stimulus the subject would receive. The adjustment of the intensity was shown in a dynamic way as if the opponent was adjusting at the same time. The intensity of the pain the subject received increased from an average of 2.33 points on a five-point scale during the first session to an average of 3.92 points during the last phase. This increase was performed over all subjects and was not dependent on the reaction of the subject. In the event the subject won the trial, the five-point scale appeared and this time the subject was allowed to adjust the intensity of the stimulus to be administered to his opponent by pressing a button with the right thumb. The time for adjustment was the same as during the losing trial (3 s). The numbers of "win" (36) and "lost" (44) trials were kept constant during the experiment. Subjects were presented a 3-second pre-recorded view of the opponent to allow observation of retaliation. Video clips were randomly chosen from 6 different pre-recorded video tapes for each stimulus intensity with the restriction that each video tape was shown only once (see Fig. 1 for the timing of the experiment).

The timing of the trials was selected in order to allow optimal modeling in a parametric statistical design and to allow realistic social interaction in the Taylor paradigm. In addition, the timing of the events was jittered (and therefore reducing the effective TR) to account for possible response overlaps in certain areas. For instance, the onsets of the pain stimuli were jittered 2.5 to 4.5 s relatively to the written cue ("you will be now punished") to disentangle anticipatory and pain-related responses, an approach often seen in conditioning paradigms. The inter-trial interval varied between 8 and 16 s, adequate to calculate a reliable implicit baseline. Aversive stimuli were applied using a pneumatic device containing a cylinder (diameter of 7 mm) which was moved by modulated air pressure (Dokoh-Pneu, Erlangen; velocities: 2 m/s to 20 m/s). Pain thresholds for each subject, ranging from 1 (only touch) over 3 (uncomfortable) to 5 (very painful), were determined in repetitive trials before the experiment started.

After each trial phase, subjects rated aggressive feelings, compassion and sympathy towards their opponent on five-point scale from no (0) to high (5) presented visually and answered verbally. Primary psychopathic traits were tested with the self-report psychopathy scale (SRPS; Levenson et al., 1995) after the fMRI investigation. This measure is a widely used instrument to assess psychopathic traits in healthy non-institutionalized individuals. The questionnaire contains 26 items and two derived factors (primary and secondary psychopathy), similar to the factor 1 and factor 2 of the PCL-SV (Hare, 1991). Brinkley et al. (2001) investigated prison inmates with the PCL-SV and the SRPS and found a good concordance between both instruments. The mean total score was 60.85 (SD 4.51; range 53–70), the mean score in factor 1 was 37.60 (SD 4.99; range 27–46) and the mean score in factor 2 was 23.27 (SD range 19–28). We used the median in factor 1 (primary psychopathy) to split the group into high and low callous participants. After completion of the questionnaires, subjects were verbally interviewed about the veracity of the experimental setting.

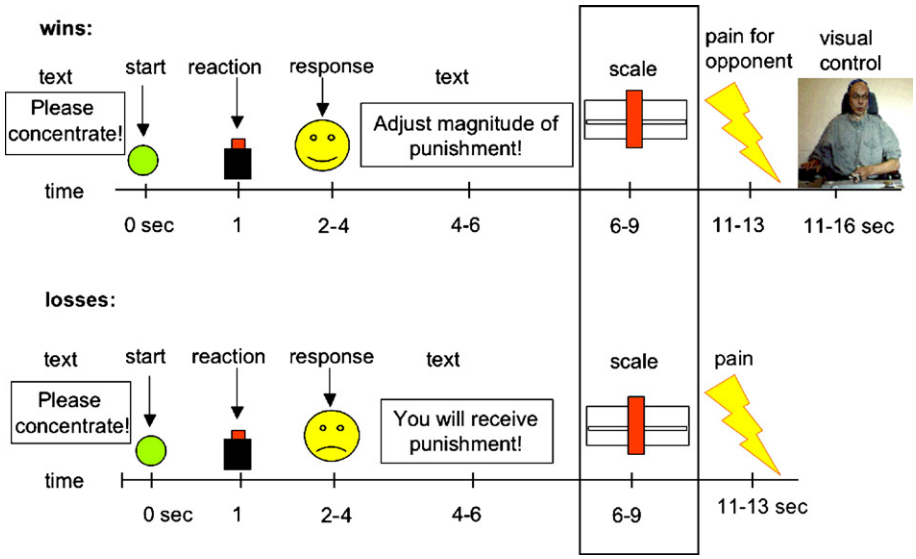

Fig. 1. Overview of the presentation for each subject over the time course of the experiment. Top row shows the winning sessions, bottom row the losses. The box indicates the critical condition retaliation (winning; top) and observing the intensity of future punishment (loosing; bottom). The third critical condition was the observation of the opponent suffering after the winning trial. Wins (top row): after the instruction, a start signal appeared which should be responded by a button hit with the right thumb as fast as possible. In the win situation, subjects received a smiling face as feedback followed by a text requesting the subject to adjust the intensity of the aversive stimulus, which should be applied to the opponent. The adjustment, performed also with the right thumb on two buttons, could be controlled on a visual five-point scale. After 3 s, the subject was told to be able to watch the opponent suffering via a video camera observing his opponent. In fact, but not known to the subject, a video of the opponent was shown selected from one out of six previously taped clips per selected stimulus intensity. Losses (bottom row): the reaction task was followed by a cheerless face. The subject was informed that the opponent adjusts the intensity of the stimulus. The adjustment of the opponent was shown on the same scale and was navigated as if it had been adjusted by a real opponent. Afterwards, the subject was applied a mechanical aversive stimulus as symbolized with an arrow.

Data acquisition

Functional imaging was performed with a 3 T MRI scanner (Siemens Trio) using 305 scans per phase (22 tilted transversal slices, 3 mm+1 mm gap, flip angle 90°) covering the prefrontal to occipital cortex. We used T2*-weighted echo-planar imaging (EPI; TR=1.5 s, matrix size=64×64, TE=30 ms).

Skin conductance and reaction time were measured during the whole experiment. Skin conductance responses were recorded at 16 Hz sampling rate with a commercial ambulatory device equipped with non-magnetic batteries (Varioport, Becker Meditec, Karlsruhe, Germany) using standard Ag/AgCl electrodes filled with unibase electrolyte affixed to the left hand. Peripheral physiological data were processed in Matlab (Matlab6, The Mathworks Inc., Natick, Massachusetts). Skin conductance data were smoothed with a 1 s Gaussian kernel. Amplitude of skin conductance response was determined as the largest change in conductance between 1 s and 5 s after task onset, relative to the preceding smallest value in the interval. For statistical analysis, skin conductance responses (SCR) were log transformed (log(SCR+1)).

Analysis of the imaging data

Imaging data were analyzed with SPM2 (Wellcome Department of Imaging Neuroscience, London). Preprocessing included spatial realignment and unwarping in phase encoding direction, normalization into the MNI space, and spatial (FWHM 15 mm) and temporal high (cutoff 128 s) and low pass filtering.

For each subject, a general linear model with the conditions "receive aversive stimuli (watching adjustment of stimulus intensity by the opponent)", "retaliate (adjusting the stimulus intensity by oneself)" and "watch the opponent" was created. All conditions were modeled with a canonical hemodynamic response function using standard SPM2 settings. In addition, regressors for the reaction time task, the presentation of the symbols for winning and loosing and the actual reception of the aversive stimuli were integrated in the model as confounds. Random effects *t*-statistics across subjects were calculated separately for each condition. Common effects across conditions (conjunction) were assessed by computing minimal *t*-statistics (Nichols et al., 2005) of the respective conditions.

To investigate areas showing a response related (parametric) modulation, parameter estimates of hemodynamic response amplitudes during each trial and condition were calculated using separate regressors for each single trial in the critical conditions. On the first level, contrast images were then calculated by combining all single trials corresponding to the same intensity levels. The weights for this linear combination were individually summed up to 1 in the contrast vector because every subject had a different number of trials according to the behavioral response (scale adjustment level 1 to 5). The contrast images were then entered into a multiple regression analyses including a constant term for every subject. For all evaluations, effects were considered significant with a threshold of $t=4.20$, corresponding to voxel-wise alpha error of $p=0.0005$ or a whole-brain false discovery rate (FDR; Genovese et al., 2002) of $p<0.05$. To further investigate effects in significantly activated regions, parameter estimates of hemodynamic response amplitudes during each trial and condition were calculated using separate regressors for each single trial in the critical conditions. Peak activity was localized using the SPM toolbox "AAL" (Automated Anatomical Labeling; Tzourio-

Mazoyer et al., 2002) and assigned to a Brodmann's area. SII was selected on the basis of maximal probability maps (Eickhoff et al., 2005). Coordinates of activated voxels are reported in MNI space (Montreal Neurological Institute). To test for the effects of personality traits on the PFC activity, a second level *t*-test between the maps of those subjects who showed low scores of psychopathy (Levenson et al., 1995) from a scale range of 16 to 64 compared to high psychopathy was applied. The two groups were divided at a median of 37. For this comparison, a small volume correction for the PFC (3 subregions: ventral mPFV, dorsal mPFC, ventro-lateral PFC) was applied. We used this test for two conditions: taking revenge and observing the opponent. In order to detect linear relations between stimulus intensity and BOLD effect size, Spearman correlation coefficients were calculated. This was performed for the BETA coefficient of the highest activated voxel within preselected regions of interest (ROIs; dorsal mPFC, right STS, right amygdala) averaged for each subject, stimulus intensity and critical condition by using the Statistical Package for the Social Sciences (SPSS 10.05; see Fig. 3).

Results

Behavioral and peripheral physiological data

A multivariate analysis of variance (MANOVA) with repeated measurements testing for differences in aggressive feelings and intensity of the applied retaliation stimulus over the four experimental sessions revealed that both the intensity of the retaliation stimulus ($F(3,36)=2.86$; $p<0.05$; Fig. 2A) and aggressive feelings against their opponent ($F(3,36)=13.64$; $p<0.001$; Fig. 2B) increased significantly over the course of the experiment. Positive correlations were observed between the received stimulus intensity and aggressive feelings ($r=0.43$; $p<0.001$), received stimulus intensity and retaliation stimulus intensity ($r=0.31$; $p<0.05$) and aggressive feelings and retaliation stimulus intensity ($r=0.49$; $p<0.001$). Thus, aggressive feelings and reactive aggressive behavior were increased according to the applied Taylor paradigm (Taylor, 1967). A session * condition interaction, however, indicated that the intensity of the retaliation stimuli increased significantly less over the course of the experiment than the intensity of the received stimuli ($F(3,36)=13.20$; $p<0.001$). Although subjects expressed aggression and reacted violently against their opponent, their aggressive behavior never reached a point where the subject would exceed the received stimulus intensity. Only a weak negative correlation between received stimulus intensity and feelings of compassion towards the opponent across all subjects was observed ($r=-0.20$; n.s.). SCR amplitudes during observation of the opponent's suffering correlated positively with the administered stimulus intensity ($r=0.29$; $p<0.001$).

Imaging data

Receiving aversive stimuli (watching adjustment of stimulus intensity by the opponent)

After losing the reaction time task, the subjects observed a scale indicating the intensity of the aversive stimulus adjusted by the opponent. This anticipation of future punishment evoked activity in bilateral insula, bilateral thalamus, secondary somatosensory cortex (SII), bilateral putamen and amygdala, right VLPFC, bilateral inferior frontal gyrus pars triangularis and opercularis

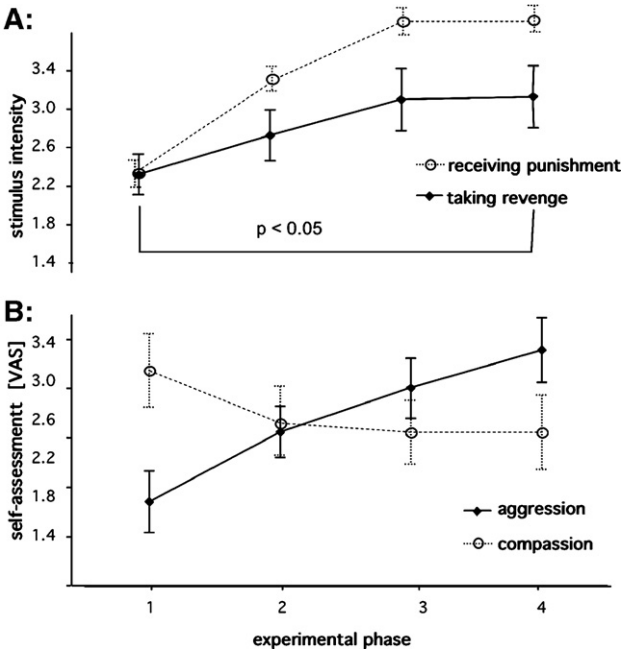

Fig. 2. (A) Mean intensity of received and administered stimuli over the course of the experiment (circles: received; diamonds: administered; standard errors indicated with lines). The intensity of the administered retaliation stimulus increased significantly over the course of the experiment ($p<0.05$; between the 1st and 4th experimental phase) indicating an increase of reactive aggressive behavior. (B) Mean and standard errors of self-ratings of aggressiveness and compassion over the course of the experiment. Compassion did not change but aggression increased significantly ($p<0.001$ between 1st and 4th experimental phase).

and bilateral temporo-parietal junction. The blood oxygen level dependent (BOLD) response within the medial cingulate cortex, bilateral SII and the bilateral anterior insula covaried significantly with the intensity of the indicated aversive stimulus. Additionally, areas involved in visual perception (occipital lobe; temporo-parietal junction) and also the left amygdala, right lingual gyrus and the bilateral thalamus, superior temporal lobe and putamen were activated (Table 1).

Retaliation

After a winning trial, subjects adjusted the scale for the stimulus intensity they intended to administer to their opponent. This condition involved activation in bilateral SII, bilateral inferior parietal lobe, bilateral inferior occipital lobe and fusiform gyrus, bilateral dorsal premotor and primary motor cortex, bilateral anterior cerebellar hemisphere, right triangular gyrus, bilateral dorsal mPFC, left lateral PFC and right ventro-lateral PFC, medial cingulate cortex, left amygdala, right insula, left nucleus ruber, right caudate nucleus and right temporal pole. The BOLD response within the dorsal mPFC and bilateral occipital lobe covaried significantly with the intensity of the applied aversive stimulus (Table 2). The correlation between the BOLD response within the dorsal mPFC and the stimulus intensity ($r=0.26$; $p<0.05$) is depicted in Fig. 3A (left side).

Watching the opponent

Watching the opponent when receiving the retaliation stimulus activated bilateral occipito-temporal areas including movement

Table 1
Receiving aversive stimuli; parametric modulation

Region (Brodmann's area)	*t*-value	MNI coordinates		
		x	*y*	*z*
Right occipital lobe (BA 18)	6.55	12	−78	0
Left occipital lobe, calcarine (BA 37)	5.27	−42	−69	6
Left cerebellar hemisphere; anterior lobe (Larsell IV)	5.75	−15	−54	−15
Right temporo-parietal junction (BA 37)	4.12	60	−69	0
Right secondary somatosensory; SII, OP1	4.07	57	−29	12
Left secondary somatosensory; SII, OP1	3.89	−63	−12	12
Right insula (BA 13)	5.65	66	6	3
Left insula (BA 13)	5.65	−51	9	−3
Medial cingulate gyrus (BA 24)	3.54	12	3	39
Left amygdala	3.67	−24	0	−12
Right putamen	4.79	36	0	−3
Left putamen	4.44	−33	0	−3
Left superior temporal lobe	5.46	−54	6	−3
Right superior temporal lobe	4.92	60	0	−3
Right thalamus–hypothalamus	4.60	12	−18	0
Left thalamus–hypothalamus	4.29	−6	−15	0
Right lingual gyrus (BA 18)	4.31	21	−45	−3

recognition areas (V5; MT), fusiform gyrus and superior temporal sulcus (STS), and right pars triangularis of the inferior frontal gyrus. Both the dorsal and ventral mPFC but also the left ventro-lateral PFC were active. Areas related to the processing of emotions such as the bilateral amygdala, right inferior insula and left anterior temporal pole were also active. In contrast to the retaliation condition, dorsal mPFC activity showed no relevant correlation with the strength of the administered stimulus during the watching condition ($r=-0.10$; n.s; Fig. 3A, right side). Activation in the STS (left: $r=0.48$; $p<0.005$; right: $r=0.34$; $p<0.01$) and the right amygdala ($r=0.32$; $p<0.05$) correlated positively with the strength of the administered stimulus (Fig. 3B).

Conjunction between retaliation and watching the offender

The conjunction between these two conditions revealed a common activation in the dorsal mPFC (Fig. 4A) and activity in the right gyrus frontalis inferior pars opercularis, bilateral STS, precuneus and left amygdala and right parahippocampal areas (Table 3).

Differentiation of the subjects according to psychopathic traits

High callous subjects showed a stronger increase of aggressive behavior (group * phase interaction $F(3,33)=2.79$; $p=0.056$; Fig. 5A) and aggressive feelings (group * phase interaction $F(3,33)=3.59$; $p<0.05$; Fig. 5B) than subjects with low scores. The comparison of brain activation between high and low callous subjects during adjustment of the retaliation stimulus revealed stronger ventral mPFC activity in more empathic (low callous) subjects ($t=3.09$; Fig. 4B). Additionally, during observation of the opponent, low callous subjects showed increased activation in the right ventro-lateral PFC ($t=3.54$).

Discussion

This is the first imaging study that has induced reactive aggression in a social interactive setting by using a modified Taylor (Taylor, 1967) aggression paradigm. In the ventral mPFC, activation was stronger in less callous subjects pointing to the association with empathy. In contrast, the activation of the dorsal mPFC, correlating with revenge intensity, seemed to be related to cognitive operations during more intense social interaction processes. Furthermore, the present study confirms findings, reporting that activity in the ventral mPFC correlates with autonomic responses (Damasio, 1996).

The modified Taylor paradigm used here induced feelings of aggression and provoked reactive aggressive behavior similar to other studies using a comparable setting (Anderson and Bushman, 1997). Participants reacted to the behavior of the opponent in a tit-for-tat strategy in that they adjusted the intensity of the administered stimuli to the intensity of the received stimuli. The increase in the intensity of the received stimuli over sessions let the subjects to raise the intensity of the administered stimuli accordingly. Previous observations demonstrated that high scores on self-report scales of aggression are positively correlated with administered shock intensity (Giancola and Zeichner, 1994). In our study, high callous subjects showed a stronger increase of aggressive feelings and aggressive behavior during the experiment.

fMRI revealed characteristic patterns associated with the three conditions of the experimental paradigm. First, when anticipating aversive stimulation (during the condition in which subjects watched the adjustment of the stimulus they were going to receive), subjects exhibited increased activation in bilateral SII, insula and putamen, the medial cingulate gyrus, left amygdala and the bilateral thalamus and hypothalamus. This pattern of activity is similar to activation observed during pain perception (Davis, 2000; Singer et al., 2004) suggesting pain anticipation during scale adjustment observation.

Second, the intensity of suffering of the opponent correlated positively with the activation in the amygdala and the STS. This finding is consistent with reports of correlations between activity in these areas and the intensity of facial expressions of negative emotions (STS (Narumoto et al., 2001); amygdala (Iidaka et al., 2001)). In the STS, both facial and hand movements are analyzed according to their social relevance (Allison et al., 2000). Close anatomical connections between both areas (Rolls, 2000) underline the importance of information exchange between these areas.

The critical condition in this study was the retaliation condition when the subjects were asked to select the intensity of the stimulus to be applied to their opponent. During this condition, areas related to the visually guided motor response but also associated with social interactive processing (STS, right temporal pole, and dorsal mPFC) were active. We were especially interested in areas correlating with the intensity of the applied retaliation stimulus. These might be related to increasingly conflicting behavior in high provocative situations. Apart from occipital areas, which might be related to enhanced perceptual processes during watching the adjustment of the scale, only dorsal mPFC activation correlated

Table 2
Retaliation; parametric modulation

Region (Brodmann's area)	*t*-value	MNI coordinates		
		x	*y*	*z*
Dorsal mPFC (BA 9/10)	5.58	9	69	15
Right occipital lobe (BA 18)	4.37	18	−84	18
Left occipital lobe (BA 18)	3.95	−24	−90	6

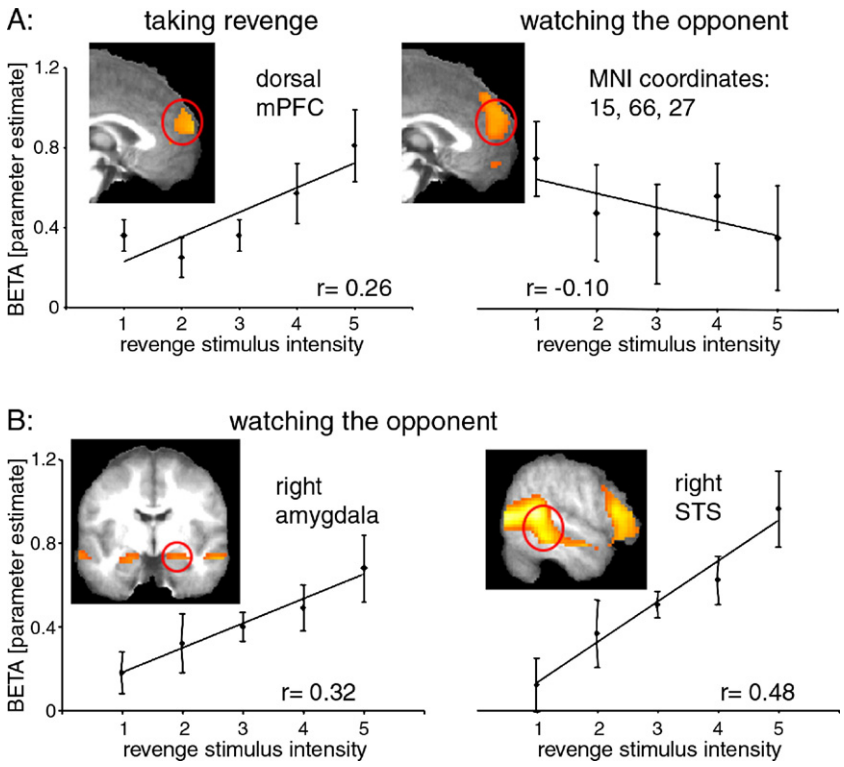

Fig. 3. (A) Intensity of BOLD effect for the dorsal mPFC (coordinates: 15, 66, 27; BA 9) correlated positively with retaliation stimulus intensity ($r=0.26$; $p<0.05$) during the taking retaliation condition (left) but not during the watching condition ($r=-0.10$; n.s.; right). The pictures show activation maps projected on averaged T1 images over all subjects for the main effect (left taking revenge; right watching the opponent) in the sagittal slice with activation peak in mPFC. (B) Intensity of BOLD effect for the right amygdala (left part of the figure; coordinates: 30, 21, −21) and the right STS (right part of the figure; coordinates: 60; −45; 12; BA 22) during watching the opponent correlated positively with the intensity of pain of the opponent (amygdala: $r=0.32$; $p<0.05$; STS: $r=0.48$; $p<0.001$). Pictures show coronal (for amygdala; left) and sagittal (for STS; right) slices of activation maxima of the watching the opponent condition projected on averaged T1 images of all subjects.

with the intensity of the revenge stimulus. Additionally, dorsal mPFC activation was present during both conditions: watching the opponent suffering and retaliation.

Significantly, activity in the ventro-lateral PFC (BA 47) seemed to be related to callousness of subjects when watching the opponent. If the opponent underwent a stronger amount of punishment, the low callous and more empathic subjects showed increased VLPFC activation—significant for the right hemisphere only. VLPFC has been described to correlate with the perception of increasingly emotional stimuli already for the visual (expressive gestures; Lotze et al., 2006) or the auditory domain (prosody; Wildgruber et al., 2005). Recently, this area has been described to be associated with the feeling of sadness after presentation of sad films (Levesque et al., 2003). The results of this study underline the importance of this area for empathic observation of another person (Hynes et al., 2006). The medial and lateral PFC can be anatomically distinguished. A further subdivision of the medial PFC is performed inconsistently in the literature. The ventral part of the mPFC (inferior to the AC–PC axis) is often characterized as 'orbitofrontal cortex' (OFC; Heberlein and Adolphs, 2005), others name it the 'ventral medial PFC' (Davidson et al., 2000). The dorsal mPFC (superior to the AC–PC axis) is sometimes referred to as 'mPFC' (Steele and Lawrie, 2004). In order to make the description of the area as clear as possible, we chose the terms 'ventral' and 'dorsal' mPFC and subdivided it by the height of the anterior commissure ($z=0$). We are aware that there is a considerable overlap between more cognitive and more emotional tasks in this area (Steele and Lawrie, 2004).

The dorsal mPFC is active during social interaction and mentalizing (Frith and Frith, 1999; Gallagher et al., 2002; Gallagher and Frith, 2003; Kampe et al., 2003). In the present study, activity in the dorsal mPFC was modulated by stimulus intensity especially during the retaliation condition in all subjects. When selecting the strength of the retaliation, stimulus subjects find themselves in a state of conflict between retaliation for being unjustifiably offended and responding cooperatively. This situation entails the representation of one's own feelings and the opponent's feelings and goals, as well as selecting between different competing response alternatives (acting friendly or aggressively). This conflict has been associated with dorsal mPFC function already by Ramnani and Owen (2004) who reviewed multiple imaging studies. Together with the role of the dorsal mPFC in emotional regulation (Ochsner et al., 2004a), an increasing activation of the dorsal mPFC during an increasing stimulus intensity applied in the present study is comprehensible. When subjects had to select the intensity of the retaliation stimulus, they had to suppress conflicting feelings of compassion and aversion towards the offender and integrate these into one adequate response. Despite the increase of activity within the dorsal mPFC with an increasing intensity of the administered stimuli, its activity might therefore not be associated with aggression per se but with suppression of interference from the emotional processing with decision-making.

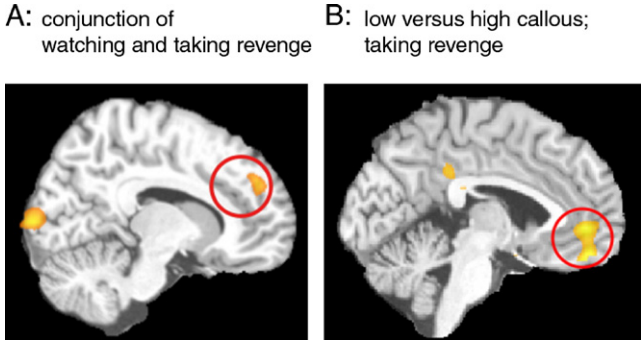

Fig. 4. Activation maxima within the mPFC projected on sagittal slices of the MNI single subject reference brain. (A) The conjunction of brain activity during retaliation and when watching the opponent suffering showed common activation in the dorsal mPFC (coordinates: 15, 66, 27; BA 9). This area was supposedly involved in the cognitive aspect of social interaction and making decisions. (B) Brain activity during retaliation of subjects with low psychopathy and callousness scores minus subjects with high psychopathy revealed activation in the ventral mPFC (coordinates: 18, 45, −9; BA 10). This area might therefore represent empathy and compassion and was also active during watching the opponent suffering in all subjects.

Additionally, the dorsal mPFC was active in both conditions "retaliation" and "observing the opponent" and therefore might represent cognitive operations related to more intense social interaction processes. The representation site active during both conditions is located near the paracingulate and dorsal mPFC activation site reported in studies investigating "theory of mind" tasks (Gallagher and Frith, 2003).

Interestingly, dorsal mPFC activation was only modulated by retaliation but not by an increasing amount of suffering of the opponent during passive observation. The conflict therefore might be related to the need for action and not to empathic feelings towards the opponent.

In contrast, the ventral mPFC was active in all participants during observation of the offender's suffering. During retribution, it was active only in subjects with lower callous personality traits and supposedly more compassion. The ventral mPFC has been linked to physiological changes that constitute part of a particular emotional response ("somatic markers" (Damasio, 1996)). The functional relevance of the ventral mPFC for SCR modulation has been demonstrated previously (van Honk et al., 2001). In the present study, increased ventral mPFC activity in subjects who showed constant compassion and less aggressive behavior might reflect the stronger emotional arousal of these subjects, indicated by their stronger SCR, and possibly related to feelings of personal guilt. Together with other areas, this region is highly important for moral reasoning (Moll et al., 2005). Increased ventral mPFC activity in low callous subjects might reflect anticipation of the opponent's suffering and higher awareness of being the agent of this suffering. In line with this interpretation, a recent study demonstrated that patients with lesions in the ventral mPFC are unable to experience regret in a gambling task (Camille, 2005). In the prisoner's dilemma, a situation where the subject is in a conflict whether to cooperate with another person or select one's own advantage at the expense of the other person, the ventral mPFC is active only during cooperation which might be related to empathy and compassionate emotions towards the other person (Rilling et al., 2002).

Table 3
Conjunction; retaliation and watching the opponent

Region (Brodmann's area)	*t*-value	MNI coordinates		
		x	*y*	*z*
Dorsal mPFC (BA 9)	5.02	12	48	33
Right frontal triangular gyrus (BA 45)	6.55	54	27	6
Left frontal orbital gyrus (BA 47)	4.52	−42	33	−9
Right STS (BA 21)	7.04	48	−66	0
Left STS (BA 21)	4.47	−48	−69	6
Right precuneus (BA 18)	5.92	15	−96	9
Left superior occipital lobe (BA 18)	4.50	−15	−99	15
Right parahippocampal	4.52	27	−24	−18
Left amygdala	4.21	−18	−6	−15

This study is the first to provoke a reactive aggressive behavior in a neuroimaging experiment. The rather explorative procedure results in several limitations which have to be mentioned. The results obtained from the comparison between high and low callous subjects should be interpreted with caution since the size of these groups is small. Additionally, the different feelings and emotions that the subjects experienced during the interactive paradigm could only be partially controlled. For instance, the interpretation of ventral mPFC activation being associated with feelings of compassion has to be proven in more stringently controlled paradigms. It could well be that retribution might also be experienced as a correct response to an unjustified assault and retaliation is not a sign of poor control but rather selecting a reasonable response. Whether the

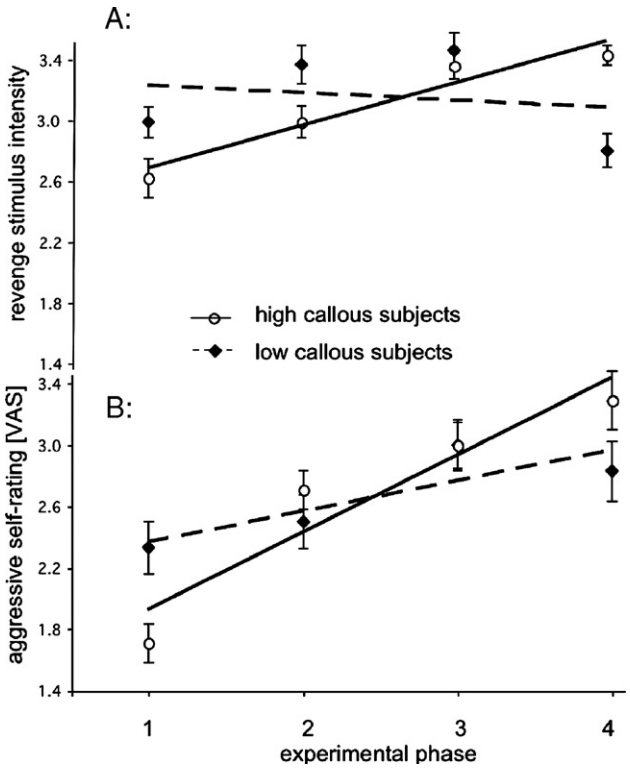

Fig. 5. (A) The increase of the retaliation stimulus over the time course of the experiment (phase 1 to 4) differed between subjects who scored low (circle) and high (diamond) in callous personality traits (group-phase interaction $F(3,33)=2.79$; $p=0.056$). (B) Aggressive feelings against the opponent increased significantly more in subjects who were more callous (group-phase interaction $F(3,33)=3.59$; $p<0.05$).

mPFC is involved in a function specific to the modulation of reactive aggression or is more generally associated with cooperative interaction and competitive behavior has to be explored in future studies.

In conclusion, this study points to differential function of the medial prefrontal cortex: whereas the dorsal mPFC may represent operations related to conflict management and response selection in aggression-provoking situations, the ventral mPFC might be involved in affective processes associated with compassion to the suffering opponent.

It seems both challenging and promising to extend this study on reactive aggression to criminal psychopaths—a group of persons who show abnormalities in the processing of emotional pictures (Muller et al., 2003) and conditional learning (Veit et al., 2002; Birbaumer et al., 2005). Although the more callous subjects investigated in the present study did also score quite high on the Levinson scale, an institutionalized population of criminal psychopath might differ considerably in their behavior and activation maps. Nevertheless, we would expect a deficit of the ventral mPFC activation in these patients, mirroring the known deficit in anticipation of the opponent's suffering (Rilling et al., 2002), without a substantial change in the dorsal mPFC. Given that psychophysiological responses are important constituents of emotions, biofeedback training in these patients might enhance empathic feelings by increasing their bodily response.

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References

Allison, T., Puce, A., McCarthy, G., 2000. Social perception from visual cues: role of the STS region. Trends Cogn. Sci. 4, 267–278.

Anderson, C.A., Bushman, B.J., 1997. External validity of trivial experiments: the case of laboratory aggression. Rev. Gen. Psychol. 1, 19–41.

Anderson, S.W., Bechara, A., Damasio, H., Tranel, D., Damasio, A.R., 1999. Impairment of social and moral behavior related to early damage in human prefrontal cortex. Nat. Neurosci. 2, 1032–1037.

Berkowitz, L., 1993. Aggression: 1st Causes Consequences and Control. Temple Univ. Press, Philadelphia.

Berthoz, S., Armony, J.L., Blair, R.J., Dolan, R.J., 2002. An fMRI study of intentional and unintentional (embarrassing) violations of social norms. Brain 125, 1696–1708.

Birbaumer, N., Veit, R., Lotze, M., Erb, M., Hermann, C., Grodd, W., Flor, H., 2005. Deficient fear conditioning in psychopathy: a functional magnetic resonance imaging study. Arch. Gen. Psychiatry 62, 799–805.

Blair, R.J.R., 2004. The roles of the orbital frontal cortex in the modulation of antisocial behavior. Brain Cogn. 55, 198–208.

Blair, R.J., Cipolotti, L., 2000. Impaired social response reversal. A case of 'acquired sociopathy'. Brain 123, 1122–1141.

Blair, R.J., Morris, J.S., Frith, C.D., Perrett, D.I., Dolan, R.J., 1999. Dissociable neural responses to facial expressions of sadness and anger. Brain 122, 883–893.

Brinkley, C.A., Schmitt, W.A., Smith, S.S., Newman, J.P., 2001. Construct validation of a self-report psychopathy scale: does Levinson's self-report psychopathy scale measure the same constructs as Hare's psychopathy checklist revised? Pers. Individ. Differ. 31, 1021–1038.

Camille, N., 2005. The involvement of the orbitofrontal cortex in the experience of regret. Science 304, 1167–1170.

Damasio, A.R., 1996. The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philos. Trans. R Soc. Lond. 351, 1413–1420.

Davidson, R.J., Putnam, K.M., Larson, C.L., 2000. Dysfunction in the neural circuitry of emotion regulation—A possible prelude to violence. Science 289, 591–594.

Davis, K.D., 2000. The neural circuitry of pain as explored with functional MRI. Neurol. Res. 22, 313–317.

Eickhoff, S.B., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G.R., Amunts, K., Zilles, K., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage 25, 1325–1335.

Frith, C.D., Frith, U., 1999. Interacting minds—A biological basis. Science 286, 1692–1695.

Gallagher, H.L., Frith, C.D., 2003. Functional imaging of 'theory of mind'. Trends Cogn. Sci. 7, 77–83.

Gallagher, H.L., Jack, A.I., Roepstorff, A., Frith, C.D., 2002. Imaging the intentional stance in a competitive game. NeuroImage 16, 814–821.

Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. NeuroImage 15, 870–878.

Giancola, P.R., Zeichner, A., 1994. Neuropsychological performance on tests of frontal-lobe functioning and aggressive behavior in men. J. Abnorm. Psychol. 103, 832–835.

Grafman, J., Schwab, K., Warden, D., Pridgen, A., Brown, H.R., Salazar, A.M., 1996. Frontal lobe injuries, violence, and aggression: a report of the Vietnam Head Injury Study. Neurology 46, 1231–1238.

Gray, J.A., 1982. The Neuropsychology of Anxiety. Oxford Univ. Press, New York.

Hare, R.D., 1991. PCL-R—The Psychopathy Checklist-Revised. Multi-Health Systems, Toronto.

Heberlein, A.S., Adolphs, R., 2005. Functional anatomy of human social cognition. In: Easton, A., Emery, N.J. (Eds.), The Cognitive Neuroscience of Social Behavior. Psychology Press, New York.

Hornak, J., Rolls, E.T., Wade, D., 1996. Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. Neuropsychologia 34, 247–261.

Hynes, C.A., Baird, A.A., Grafton, S.T., 2006. Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. Neuropsychologia 44, 374–383.

Iidaka, T., Omori, M., Murata, T., Kosaka, H., Yonekura, Y., Okada, T., Sadato, N., 2001. Neural interaction of the amygdala with the prefrontal and temporal cortices in the processing of facial expressions as revealed by fMRI. J. Cogn. Neurosci. 13, 1035–1047.

Kampe, K.K., Frith, C.D., Frith, U., 2003. "Hey John": signals conveying communicative intention toward the self activate brain regions associated with "mentalizing," regardless of modality. J. Neurosci. 23, 5258–5263.

Lane, R.D., Fink, G.R., Chau, P.M., Dolan, R.J., 1997. Neural activation during selective attention to subjective emotional responses. NeuroReport 8, 3969–3972.

Levenson, M.R., Kiehl, K.A., Fitzpatrick, C.M., 1995. Assessing psychopathic attributes in a noninstitutionalized population. J. Pers. Soc. Psychol. 68, 151–158.

Levesque, J., Eugene, F., Joanette, Y., Paquette, V., Mensour, B., Beaudoin, G., 2003. Neural circuitry underlying voluntary suppression of sadness. Biol. Psychiatry 53, 502–510.

Lotze, M., Heymans, U., Birbaumer, N., Veit, R., Erb, M., Flor, H., Halsband, U., 2006. Differential cerebral activation during observation of expressive gestures and motor acts. Neuropsychologia 44, 1787–1795.

Mah, L.W., Arnold, M.C., Grafman, J., 2005. Deficits in social knowledge following damage to ventromedial prefrontal cortex. J. Neuropsychiatry Clin. Neurosci. 17, 66–74.

Moll, J., Zahn, R., de Oliveira-Souza, R., Krueger, F., Grafman, J., 2005. Opinion: the neural basis of human moral cognition. Nat. Rev., Neurosci. 6, 799–809.

Muller, J.L., Sommer, M., Wagner, V., Lange, K., Taschler, H., Roder, C.H., Schuierer, G., Klein, H.E., Hajak, G., 2003. 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. Biol. Psychiatry 54, 152–162.

Narumoto, J., Okada, T., Sadato, N., Fukui, K., Yonekura, Y., 2001. Attention to emotion modulates fMRI activity in human right superior temporal sulcus. Brain Res. Cogn. Brain Res. 12, 225–231.

Nichols, T., Brett, M., Andersson, J., Wager, T., Poline, J.B., 2005. Valid conjunction inference with the minimum statistic. NeuroImage 25, 653–660.

Ochsner, K.N., Ray, R.D., Cooper, J.C., Robertson, E.R., Chopra, S., Gabrieli, J.D., Gross, J.J., 2004a. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. NeuroImage 23, 483–499.

Ochsner, K.N., Knierim, K., Ludlow, D.H., Hanelin, J., Ramachandran, T., Glover, G., Mackey, S.C., 2004b. Reflecting upon feelings: an fMRI study of neural systems supporting the attribution of emotion to self and other. J. Cogn. Neurosci. 16, 1746–1772.

Ohbuchi, K., Ohno, T., Mukai, H., 1993. Empathy and aggression: effects of self-disclosure and fearful appeal. J. Soc. Psychol. 133, 243–253.

Phan, K.L., Taylor, S.F., Welsh, R.C., Ho, S.H., Britton, J.C., Liberzon, I., 2004. Neural correlates of individual ratings of emotional salience: a trial-related fMRI study. NeuroImage 21, 768–780.

Ramnani, N., Owen, A.M., 2004. Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. Nat. Rev., Neurosci. 5, 184–194.

Rilling, J., Gutman, D., Zeh, T., Pagnoni, G., Berns, G., Kilts, C., 2002. A neural basis for social cooperation. Neuron 35, 395–405.

Rolls, E.T., 2000. The orbitofrontal cortex and reward. Cereb. Cortex 10, 284–294.

Siegel, A., 2004. The Neurobiology of Aggression and Rage. CRC Press.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for pain involves the affective but not sensory components of pain. Science 303, 1157–1162.

Steele, J.D., Lawrie, S.M., 2004. Segregation of cognitive and emotional function in the prefrontal cortex: a stereotactic meta-analysis. NeuroImage 21, 868–875.

Stone, V.E., Baron-Cohen, S., Knight, R.T., 1998. Frontal lobe contributions to theory of mind. J. Cogn. Neurosci. 10, 640–656.

Taylor, S.P., 1967. Aggressive behavior and physiological arousal as a function of provocation and the tendency to inhibit aggression. J. Personal. 35, 297–310.

Taylor, S.F., Phan, K.L., Decker, L.R., Liberzon, I., 2003. Subjective rating of emotionally salient stimuli modulates neural activity. NeuroImage 18, 650–659.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15, 273–289.

van Honk, J., Schutter, D.J., d'Alfonso, A., Kessels, R.P., Postma, A., de Haan, E.H., 2001. Repetitive transcranial magnetic stimulation at the frontopolar cortex reduces skin conductance but not heart rate: reduced gray matter excitability in orbitofrontal regions. Arch. Gen. Psychiatry 58, 973–974.

Veit, R., Flor, H., Erb, M., Hermann, C., Lotze, M., Grodd, W., Birbaumer, N., 2002. Brain circuits involved in emotional learning in antisocial behavior and social phobia in humans. Neurosci. Lett. 328, 233–236.

Volkow, N.D., Tancredi, L.R., Grant, C., Gillespie, H., Valentine, A., Mullani, N., Wang, G.J., Hollister, L., 1995. Brain glucose metabolism in violent psychiatric patients: a preliminary study. Psychiatry Res. 61, 243–253.

Wildgruber, D., Riecker, A., Hertrich, I., Erb, M., Grodd, W., Ethofer, T., 2005. Identification of emotional intonation evaluated by fMRI. NeuroImage 24, 1233–1241.