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Aberrant social and cerebral responding in a competitive reaction time paradigm in criminal psychopaths

Ralf Veit [a,*,1], Martin Lotze [b,1], Sven Sewing [a], Heiner Missenhardt [c], Tilman Gaber [a,d], Niels Birbaumer [a,e]

[a] Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Germany
[b] Functional Imaging Unit, Center for Diagnostic Radiology and Neuroradiology, University of Greifswald, Germany
[c] Centre of Psychiatry, Forensic Department, Bad Schussenried, Germany
[d] Max Planck Institute for Biological Cybernetics, Tübingen, Germany
[e] Ospedale San Camillo, Instituto di Ricovero e Cura a Carattere Scientifico, Venezia, Italy

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ABSTRACT

In a previous study (Lotze et al., 2007) we described dorsal medial prefrontal cortex (mPFC) activation in healthy subjects during retaliation in a competitive reaction time task. Interestingly, the less callous the subjects were, the more they responded with ventral mPFC-activation when watching the opponent suffering. In this study we used this paradigm to investigate behavioral and neural responding of ten criminal psychopathic individuals from a forensic psychiatric institution. In contrast to healthy subjects, who show reactive aggressive behavior of inflicting punishment with increasing intensity after experiencing an increasing amount of punishment from a yoked opponent, psychopathic participants did not react with comparable retaliation. However, when psychopaths punished with a high amount they showed increased activation in the hypothalamus, the lateral prefrontal cortex, the posterior cingulate cortex and the amygdala. The trait "physical aggression" showed a positive correlation with hypothalamic activation. Medial prefrontal areas, associated with emotional control and conflict management in healthy subjects performing this paradigm, were inactive in psychopathic subjects during retaliation. When psychopaths observed the yoked opponent being punished they showed increased activation in the dorsal and ventral medial prefrontal cortex, which was positively associated by impulsivity and antisocial behavior of Hare's psychopathy construct. This finding supports the notion that reactive aggression is more related to antisocial behavior and anger management than with emotional and interpersonal characteristics of psychopathy and suggests that two separate brain activation patterns seem to account for these two behavioral dispositions.

Introduction

The competitive reaction time paradigm (Taylor, 1967) is an excellent methodology employed in the laboratory to study direct physical aggression. This task is a widely used valid measure of aggressive behavior, appropriate to induce reactive aggression in a laboratory setting (Giancola and Zeichner, 1995). In a previous study we used the Taylor paradigm (Lotze et al., 2007) and demonstrated that healthy subjects show increased activity in the medial prefrontal cortex (mPFC) when punishing after being provoked. We interpreted this activation as associated with guilt during performing an aggressive act. Interestingly, the activity of the dorsal part of the mPFC was correlated positively with the strength of the selected aversive stimulus during retaliation, whereas the ventral mPFC was activated independent of the applied stimulus strength. The ventral part was active while observing the suffering opponent. Subjects with higher total psychopathy scores based on the Levenson self report scale (LSRS; Levenson et al., 1995) exhibited less ventral mPFC activation.

In light of the above, we were interested in the behavior and functional activation of criminal psychopaths during the performance of this reactive aggression paradigm. These subjects have severe problems in emotional learning and show a failure of differential emotionally conditioned responses in the limbic-prefrontal circuit during Pavlovian classical aversive conditioning (Veit et al., 2002; Birbaumer et al., 2005), and impairment in emotion processing and empathy (Mueller et al., 2003). This callous unconcern for feelings of others is associated with repeated violation of the rights of others as well as a disregard of social norms.

It has been demonstrated that damage to orbital and ventrolateral frontal cortex is related to a heightened risk of aggression (Blair, 2006) and there are many studies showing a strong association between psychopathy and engagement in violent and aggressive

* Corresponding author. Institut für Medizinische Psychologie und Verhaltensneurobiologie, Eberhard-Karls-Universität Tübingen, Gartenstraβe 29; D-72074 Tübingen, Germany. Fax: +49 7071 295956.
E-mail address: ralf.veit@uni-tuebingen.de (R. Veit).
[1] These authors contributed equally to the work.

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behavior (Woodworth and Porter, 2002). Overall, two forms of aggression are distinguished: reactive aggression elicited in response to frustration or provocation and instrumental goal-directed aggression. These types of aggression are mediated by different neural systems. It has been shown that damage of the medial prefrontal lobe results in disinhibition of reactive aggressive behavior as can be found in "acquired sociopathy" (Blair and Cipolotti, 2000). Instrumental aggression, however, is a core feature of developmental psychopathy probably related to a dysfunctional socialization process.

Reactive aggression is mediated by medial amygdala, the medial hypothalamus, and the dorsal half of the periaqueductal gray (PAG) (Gregg and Siegel, 2001). The amygdala and orbital frontal cortex are parts of a neural circuitry involved in the modulation of reactive aggression and fear. It has been found that lower cerebral blood flow during rest in the lateral orbital frontal cortex (BA 47) is associated with a history of reactive aggression in patients with antisocial personality disorder (Goyer et al., 1994). Soderstrom et al. (2002) reported that reduced prefrontal functioning is more associated with reactive than instrumental aggression. However, little is known about the circuit responsible for instrumental aggression. This type of aggression is assumed to be regulated by cortical "cognitive" systems and less dependent on the "emotional" hypothalamic and limbic systems (Nelson and Trainor, 2007).

Most imaging studies investigating violence and aggression at a behavioral level used structural neuroimaging techniques. Only a few studies using functional neuroimaging exist. Blair et al. (1999) demonstrated that the paracingulate cortex was activated when subjects viewed aggressive facial expressions using fMRI. Pietrini et al. (2000) conducted a PET study using script driven imagery and found a pronounced deactivation of the ventral mPFC during evoked aggressive emotions.

The present study focused on the question, which cerebral areas associated with aggression and aggression control are active in psychiatric inmates with psychopathy during retaliation and opponent observing. In these patients we expected a deficit in mPFC activation. For retaliation we focused on the dorsal mPFC, associated with decreased emotion control and feelings of guilt, while for opponent observation we expected decreased ventral mPFC-activity, associated with the known deficit in empathic responding.

Materials and methods

Participants

10 male psychopathic patients (mean age: 31.0 years; SD 5.8 years) from two forensic psychiatric institutions in Germany participated in the study. Psychopathy in the sample was diagnosed by experienced clinicians using the PCL:SV (Hart et al., 1995). The screening version of the PCL (PCL:SV, Hart et al., 1995) was developed to measure psychopathy in civic or forensic settings. The screening version consists of a 12-item scale on the basis of the PCL-R. The PCL: SV has comparable validity and reliability as the full PCL-R version. Psychopaths had a mean PCL:SV total score (score ranges from 0 to 24) of 16.11 (SD 3.62). This is slightly lower than the standard value (cutoff: 18) reported for U.S. populations of psychopaths, but in accordance with German and European norms (Cooke et al., 2004).

Most of the participants committed a wide range of criminal acts including homicide, rape, assault, burglary and more. Their criminal careers reached back to childhood. Each participant was accompanied by members of the forensic psychiatric department. In addition, we used the self report scale (LSRS) of Levenson et al. (1995) to compare our results with our previous study (Lotze et al., 2007) of non-clinical individuals, as well with other studies using self report ratings of psychopathic traits (Rilling et al., 2007). This scale was developed for assessing psychopathic characteristics or traits in non-institutionalized samples. The questionnaire contains 26 items in a 4-point scale divided into two factors (primary and secondary psychopathy), similar to the factor 1 and factor 2 of the PCL-R (Hare, 1991). The psychopathic subjects had a total score in the LSRS of 62.50 (SD 9.98), in line with Brinkley et al. (2001), who investigated prison inmates and considered participants with scores of 58 and more as psychopathic. The Buss-Perry (BP) aggression questionnaire (Buss and Perry, 1992) was administered to assign different components of aggression (physical and verbal aggression, anger and hostility). This scale comprises 29 items using a 5-point scale from 1 (extremely uncharacteristic of me) to 5 (extremely characteristic of me). Participants were paid 200 € in arrangement with the psychiatric institutions. The study was approved by the Ethics Committee of the local Medical Faculty. Written informed consent was obtained according to the guidelines of the Declaration of Helsinki.

Experimental design

After providing informed consent, the experimenter briefly introduced the alleged participant to the opponent (a confederate of the lab), but no further social interaction was allowed. Thereafter, the participants were told that the opponent would participate in the reaction time competition in a different room. A modified version of the Taylor Aggression Paradigm (TAP) was used to measure physical aggression. Participants were told that if they react faster than the opponent they were allowed to administer physical punishment with a "shot" of a projectile to the opponent's middle finger. If they would loose, because of the slower reaction times the opponent would be allowed to treat them with the same punishing stimulus. In order to provoke reactive aggression the intensity of the pain stimulus increased from an average of 2.33 points on a 5-point scale during the first run to an average of 3.92 during the last run of scanning. Details of stimulus design and the time course of the trials are given in the Supplementary Material and Suppl. Figure 1. After the experiment, debriefing revealed that all participants believed to play against a real opponent.

Mechanical aversive stimuli

The mechanical aversive stimuli were applied using a plastic cylinder (diameter of 7 mm) moved by air pressure modulated by a pneumatic device (Dokoh-Pneu, Erlangen; velocities: 2 m/s to 20 m/s). The individual pain threshold was determined by increasing and decreasing pressure velocities of the plastic cylinder. Prior to the experiment the participants were asked to rate the stimulation intensity on a scale from one (only touch) over three (uncomfortable) to five (very unbearable) on a visual analogue scale. A rating of four was used as the individual pain threshold. This procedure was repeated until the pain threshold was consistently in a range of four.

fMRI acquisition and functional imaging procedure

All subjects were investigated with a 3 Tesla MR-scanner (Siemens Trio) using T2*-weighted echo-planar imaging (EPI, TE = 30 ms; TR = 1.5 s; 22 slices of 3 + 1 mm thickness in a tilted transversal orientation; matrix size 64 × 64) and a T1-anatomy (MP-Rage; 176 slices, 1 × 1 × 1 mm). In addition we acquired a static field map after the second functional session to unwarp geometrically distorted EPIs. Four sessions with 305 scans each were conducted.

The scanning comprised four runs with 20 trials each. Each trial started with a written cue followed by a visual signal prompting the subject to press a button with the right index finger as quickly as possible. After 2–4 s a smiley symbol indicated trial outcome (the corner of the mouth–up or down–symbolized "win" or "lost" trials). After loosing trials, a visual five-point scale appeared for 3 s, showing the subject the intensity of the aversive stimulus he was about to receive (the subject saw an upwards moving bar on a scale pretending

a navigation on the scale by the opponent). This period was modeled as the "anticipation of pain". After a winning trial the same scale appeared (this period was modeled as the "retaliation"; note that anticipation and retaliation has exactly the same visual stimulus) and the subject was allowed to adjust with button presses of the right thumb the intensity of the stimulus for his alleged opponent. After stimulus adjustment a short pre-recorded video clip was shown. The video clip showed a recording of the alleged opponent 1 s before and 2 s after pain administration thus showing the opponent and his facial expressions triggered by the applied pain stimulus. This period was modeled as the "observation of the opponent." For lowest pain the facial expression was neutral; for pain level 5, when the pain was maximal, his face contorted with agony. Six different video clips were pre-recorded for each stimulus intensity and one of them was randomly chosen each time. To circumvent recognition of the video, the shown video clips were marked and not selected for the following trials. The alleged opponent was always enrobed with the same shirt as in the video clip to strengthen the subject's belief of a real social interaction. The number of "win" and "lose" trials was kept constant during the experiment. Furthermore, the intensity of the punishment given by the opponent was gradually increased during the experiment. To differentiate anticipatory and pain related responses the onsets of the pain stimuli was jittered relative to the written cue ("you will be now punished") from 2.5 to 4.5 s. The inter-trial-interval (ITI) varied between 8 and 16 s. After each run, lasting for 7.63 min, subjects verbally rated aggressive feelings, guilt and compassion towards their opponent on a five-point Likert-scale from no (zero) to high (five) presented visually on the screen. Aggressive behavior was operationalized as the average shock intensities selected by the subjects over trials.

Peripheral physiological data acquisition

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). Standard Ag/AgCl electrodes filled with unibase electrolyte affixed to the left hand were used. Peripheral physiological data were processed in a Matlab environment (Matlab 6.5.1, The Mathworks Inc., Natick, Massachusetts) and 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 lowest value in the interval. Skin conductance responses (SCRs) were log transformed ($\log(SCR+1)\mu S$) for statistical analysis. For all inference statistical analyses the Statistical Package for the Social Sciences (SPSS 12) were used.

Analysis of the imaging data

Spatial preprocessing and data analysis were performed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/spm2.html). Each time-series were realigned and resliced. Unwarping of geometrically distorted EPIs was performed using the FieldMap Toolbox available for SPM2. The anatomical image was corrected for intensity inhomogeneities and then normalization in MNI-space was performed. The same parameter-file was used for the normalization of the functional images (3 mm isotrop voxel size). Finally the echoplanar images were Gaussian smoothed with 15 mm (full width at half maximum; FWHM). Data were high-pass (cut off 128 s) and low-pass filtered (autoregression model AR(1)).

For each subject a design matrix was created with the following condition types: reaction time task, smiley good (response for winning the task), smiley bad (response for loosing the task), anticipation of pain, punishment, retaliation, and observing the opponent. For each condition a separate regressor was modeled. Each condition was convolved with a hemodynamic response function. On a first level analysis contrast images were calculated independent of the stimulus intensity in order to analyze the main activations for each condition. Each subject's contrast images were entered in a random effects one-sample *t*-test separately for all condition types. Main effects were considered significant using a whole-brain false discovery rate (FDR) of $p<0.05$.

To investigate areas showing a response-related modulation, parameter estimates of hemodynamic response amplitudes were calculated using separate regressors for each single trial for all critical conditions. On the first level, contrast images were calculated combining all single trials corresponding to low punishment (levels 1 and 2) and high punishment (levels 4 and 5) adjustments levels. A paired *t*-test with sphericity correction between high- and low-stimulus intensities was computed. Effects were considered significant using a FDR of $p<0.05$.

ROI-analyses

In addition to the whole brain analyses we conducted an ROI-analyses based on the findings of our previous study (Lotze et al., 2007). We defined anatomical ROIs for the condition "retaliation" as well the "watching the opponent" condition (dorsal mPFC, ventral mPFC, ventrolateral PFC (BA 47), amygdala). Those predefined ROIs were created with the WFU-pickatlas (Maldjian et al., 2003)) implemented as a toolbox in SPM2. This atlas includes Brodmann areas and anatomical labels (Automated Anatomical Labelling; (Tzourio-Mazoyer et al., 2002)) which can be used for creating different masks. Those masks can then be used to correct the *p*-value for volume of interests (small volume correction). The ventrolateral PFC was defined as BA 47. Unfortunately there is no clear-cut description of the boarders of the dorsal and ventral subdivisions of the medial PFC. For the dorsal mPFC, we created a mask covering the medial part of BA 8 and BA 9. The exact boundaries were $x=20$ to -20 mm, $y=+39$ to $+69$ mm and $z=+5$ to $+60$ mm. For the ventral mPFC, we used the same boundaries in *x* and *y* direction, but lower boundaries in the axial direction ($z=+5$ to -27). Effects were considered significant using a FDR of $p<0.05$ for the whole brain volume but also within the predefined regions (indicated with a star in Tables 2 and 3).

Finally, the parameter estimates of the highest activated voxel in the ventral and dorsal mPFC were correlated with the psychopathy scores, whether the two factors in the PCL:SV and the LSRS contribute to different activations. We therefore conducted four regression analyses (2 areas, 2 scales) and found two significant correlations between the factor 2 of the LSRS and the activation in the ventral and dorsal mPFC. We used a sequential Bonferroni correction (Rice, 1989) for the significant results (p1 compared to 0.05, p2 compared to 0.05/2). One subject was excluded from the factorial analyses of the conditions retaliation and watching the opponent, because he pressed throughout the experiment always the lowest level which allowed no modulation of high and low punishment settings.

Results

Behavioral and peripheral data

An ANOVA with repeated measurements revealed a significant linear increase in intensity of administered punishment for the opponent over the four sessions of the experiment ($F(3,21)=11.96$; $p<0.001$). Exploratory post-hoc paired *t*-tests showed that the difference was most prominent between the first and third session ($t=4.81$, $p<0.01$) but also significant between the first and last session ($t=3.46$, $p<0.05$). Patients developed an increase in ratings of anger towards the opponent over measurement-time ($F(3,21)=3.30$;

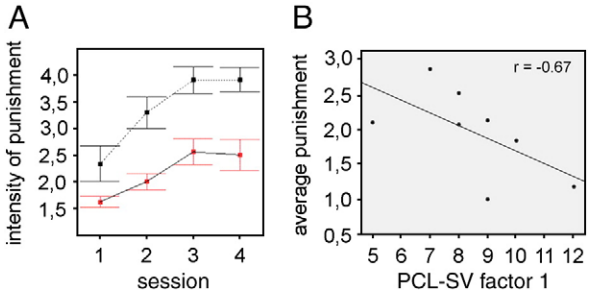

Fig. 1. (A) Mean intensity of administered (solid line with red error bars) and received (dotted line with black error bars) punishment over 4 sessions. An ANOVA with repeated measurements revealed a significant increase of stimulus intensity over the course of the experiment. (B) Inverse relationship between the average amount of punishment intensity applied over the whole experiment (*y*-axes) and scores in the PCL-SV factor 1 (*x*-axes) of psychopathy ($r=-0.67$).

$p<0.05$; see Fig. 1B). However, there were no significant differences in reported feelings of aggression towards the opponent with increasing level of provocation over the course of the experiment.

Regression analysis of PCL:SV, LSRS, aggression scores (Buss-Perry) and total amount of applied punishment revealed that factor 1 of PCL:SV was inversely related with the mean punishment intensities ($r=-0.67$, $p=0.05$; "less callous unemotional more punishment"). On the other hand scores of anger ($r=0.67$, $p=0.05$) showed a positive relation to the averaged applied stimulus intensities (Fig. 2), whereas for physical aggression ($r=0.03$, $p=0.95$) no correlation was found.

SCR amplitudes in anticipation of the punishment showed no correlation with the intensity of the applied stimulus ($r=-0.07$). However, we observed an increase in skin conductance activity during actual punishment of highest intensity level (level 5: 0.35 ± 0.08 μS) in comparison to lower levels (level 4: 0.24 ± 0.05 μS; $t=2.76$, $p<0.05$ one-tailed; level 3 (0.26 ± 0.04 μS; $t=2.39$ $p<0.05$ one-tailed).

fMRI-results

During anticipation of pain patients showed significant activations in the right superior temporal lobe (MNI-coordinates: 69, −42, 21; $t=9.75$), the right postcentral gyrus (60, −18, 30; $t=7.38$), the left middle temporal lobe (−48, −63, 0; $t=5.83$) and the right pars triangularis of the inferior frontal gyrus (51, 27, 9; $t=4.23$). Anticipation of higher pain events compared to low was associated with activation in bilateral occipital lobe, bilateral inferior orbitofrontal cortex, precentral gyrus, postcentral gyrus, pallidum, thalamus, SMA and right secondary somatosensory cortex (Table 1).

During retaliation (subjects adjusted stimulus intensities for their opponent) significant activations were found in the right middle occipital lobe (42, −75, 6; $t=8.79$), right superior temporal gyrus (66, −36, 18; $t=5.69$), right inferior temporal gyrus (51, −51, −21; $t=13.36$), bilateral inferior parietal lobe (right: 57, −36, 45; $t=6.64$; left: −45, −54, 42; $t=4.40$) bilateral fusiform gyrus (right: 27, −42, 12; $t=6.79$; left: −30, −36, −18; $t=8.40$), right supramarginal gyrus (66, −33, 30; $t=7.39$), left hippocampus (−21, −21, −18; $t=8.57$) and in the right angular gyrus (45, −60, 45; $t=6.59$).

Comparison of high- versus low-intensity adjustments yielded significant activations in hypothalamus and midbrain (extending to dorsal periaqueductal gray (PAG)), left inferior frontal gyrus pars triangularis, posterior cingulate cortex and left amygdala (Table 2 and Fig. 1A). There was a strong positive covariation between scores in the BP "physical aggression" subscale and blood-oxygen-level dependent

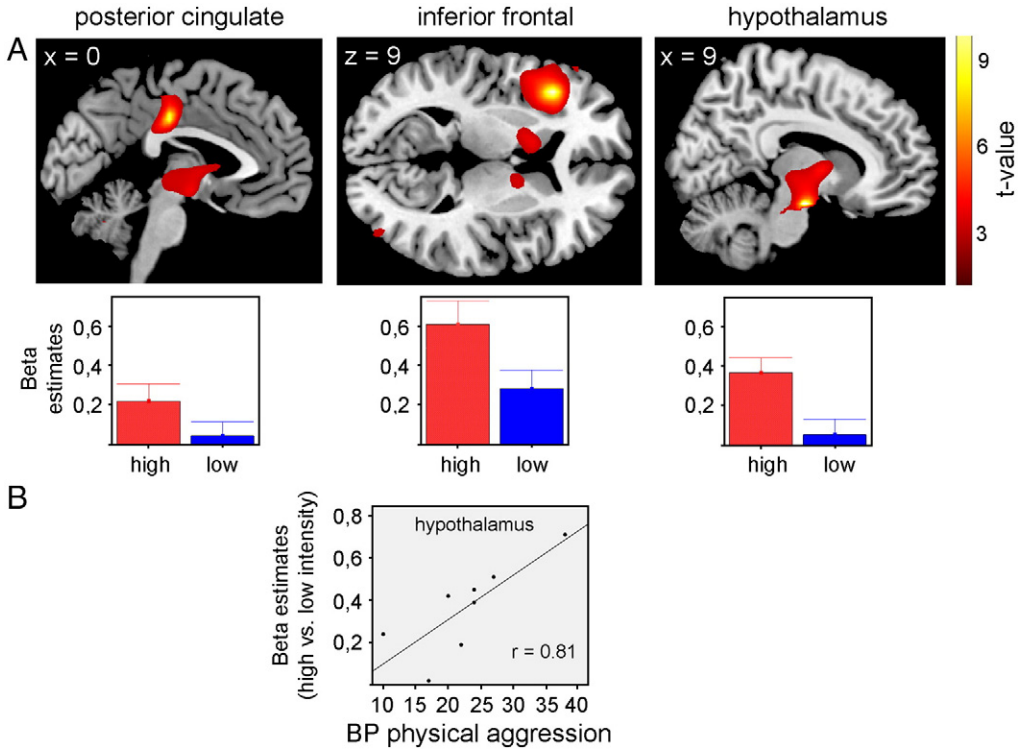

Fig. 2. (A) Group activation maps during retaliation projected on the MNI single subject brain ($p<0.001$, uncorrected). Direct statistical comparison between high and low punishment adjustment revealed different activations in the posterior cingulate (left, coordinates: 0, −21, 39), the inferior frontal gyrus triangularis (middle, coordinates: −42, 24, 9) and the medial hypothalamus (right, coordinates: 9, −12, −18). The corresponding contrast values (±SD) for high (red) and low (blue) intensity adjustments are displayed on the bottom right of each activation map. The *t*-value of the differential activation is given in the adjacent colour bar. (B) Positive correlation between the differential activation in the medial hypothalamus and Buss-Perry physical aggression scores ($r=0.81$, $p=0.01$).

Table 1
Regions with differential activation during anticipation of the pain between high in comparison to low punishment intensities.

Region (Brodmann's area)	*t*-value	MNI coordinates		
		x	*y*	*z*
Occipital Lobe R (BA 18)	8.94	12	−84	−12
Occipital Lobe L (BA 18)	8.78	−48	−87	−6
Inferior orbitofrontal R (BA 47)	6.78	60	21	−6
Inferior orbitofrontal L (BA 47)	5.31	−33	24	−21
Postcentral gyrus L (BA 1, 2, 3)	5.26	−57	12	45
Thalamus L	4.74	−9	−9	6
Precentral gyrus L (BA 4)	4.73	−45	0	54
Precentral gyrus R (BA 4)	5.06	51	−6	48
SMA (BA 6)	5.13	0	15	60
Secondary somatosensory R (BA 40)	4.65	66	−24	30
Inferior orbitofrontal L (BA 44)	4.95	−60	12	6
Frontal inferior triangular. L (BA 45)	4.17	−39	24	9
Pallidum R	4.52	15	3	3
Pallidum L	4.48	−12	3	3

FDR<0.05 corrected for the whole brain.

Table 3
Regions with differential activation during observation of the opponent between high in comparison to low punishment intensities.

Region (Brodmann's area)	*t*-value	MNI coordinates		
		x	*y*	*z*
Inferior orbitofrontal R (BA 47)	9.89	60	27	−9
Precentral R (BA 4)	7.37	39	0	39
Inferior frontal triangularis R (BA 45)	6.85	51	30	21
Insula R (BA 13)	6.45	42	18	−6
Dorsal mPFC (BA 8)	9.30	9	42	51
Insula L (BA 13)	7.84	−33	15	−12
Middle temporal R (BA 21)	8.59	63	−9	−15
Middle temporal L (BA 39)	8.06	−54	−69	15
Inferior orbitofrontal L (BA 47)	6.79	−42	21	−9
Superior temporal sulcus (STS) R	6.98	66	−48	12
Superior temporal sulcus (STS) L	5.83	−63	−51	12
Inferior temporal R (BA 20)	5.72	51	−48	−18
Ventral mPFC (BA 10)[a]	5.21	−3	69	−6
Amygdala R[a]	4.97	30	−6	−15

FDR<0.05 corrected for the whole brain.
[a] FDR<0.05 corrected for predefined region of interest.

(BOLD) effect difference between high versus low punishment adjustments in the medial hypothalamus ($r=0.81$, $p=0.01$; Fig. 2B). However, there was no intensity-modulated activation in the dorsal or ventral mPFC.

During the observation of the opponent receiving the applied pain stimulus activation of right inferior (45, −63, −15; $t=12.24$) and right superior occipital lobe (15, −99, 18; $t=6.82$), middle temporal lobe (left: −66, −12, −24; $t=5.73$; right: 69, −18, −18; $t=7.20$), right inferior temporal lobe (45, −45, −15; $t=9.37$), right fusiform gyrus (21, −33, −18; $t=5.61$), right STS (66, −42, 12; $t=4.86$), right precuneus (12, −57, 27; $t=6.36$) and right supramarginal gyrus (45, −45, 27; $t=5.06$) were found. The comparison between high and low punishment intensities revealed increased activation in the bilateral inferior orbitofrontal cortex, bilateral insula, bilateral temporal areas, right precentral gyrus, and dorsal mPFC. ROI analyses indicated additional activations in the ventral mPFC and amygdala (Table 3; Fig. 3). Activations in the ventral and dorsal mPFC were inversely correlated with scores of factor 2 in the LSRS (ventral mPFC: $r=-0.76$, $p<0.05$; dorsal mPFC: $r=-0.70$, $p<0.05$), meaning that less antisocial behavior is accompanied with higher mPFC activation during observation of painful stimulation of the opponent. Similarly, factor 2 of the PCL:SV inversely covaried with dorsal mPFC activity ($r=-0.72$, $p<0.05$) but only marginally with ventral mPFC activation ($r=-0.59$, $p=0.12$). However, there was no significant correlation between dorsal or ventral mPFC activity and total scores in the PCL:SV (dorsal: $r=-0.55$, $p=0.16$; ventral: $r=-0.16$, $p=0.70$). Both results survived the Bonferroni correction.

Discussion

Inspired by the findings of our previous study on healthy volunteers using the modified Taylor aggression paradigm (Lotze et al., 2007) we conducted a follow-up investigation incorporating subjects high on clinical psychopathy measures. As a general finding subjects high on psychopathy revealed an aberrant social and cortical response pattern during the experiment. In our previous study, we found that healthy subjects with high scores in callous traits showed greater reactive aggression using the strongest increase in administered stimulus to the opponent. Furthermore, the magnitude of callous unemotional traits (factor 1) was positively related to a responsiveness differentiation in ventral mPFC during retaliation. Our results in the present study indicate no differential activation in the ventral mPFC during retaliation neither in relation to the intensity of punishment nor to psychopathy scores. However, there are substantial distinctions between the clinical group and the healthy volunteers on the behavioral level. For instance the mean punishment level selected by the psychopathic group was notably lower than those observed in the healthy group investigated before. This different behavior of the psychopathic population made it methodologically impossible to directly compare the activation maps of both subject groups within the conditions measured.

Table 2
Regions with differential activation during retaliation between high in comparison to low punishment intensities.

Region (Brodmann's area)	*t*-value	MNI coordinates		
		x	*y*	*z*
Midbrain/hypothalamus	15.42	9	−12	−18
Frontal inferior triangular L (BA 44)	11.12	−42	24	9
Frontal inferior triangular L (BA 45)	10.15	−57	21	18
Posterior cingulate	9.80	0	−21	39
Amygdala L[a]	3.69	−21	−6	−12

FDR<0.05 corrected for the whole brain.
[a] FDR<0.05 corrected for predefined region of interest.

Instrumental and reactive aggression in psychopathy

Woodworth and Porter (2002) investigated the relationship between scores in the Psychopathy Checklist-Revised (PCL-R; 20) and the nature of committed homicides and found that over 90% of psychopathic offenders are characterized by instrumental violence whereas non-psychopathic inmates acted predominantly reactive. Similarly, Edens et al. (2006) found substantial correlations between PCL-R ratings and reports of aggression in male offenders. On the other hand, it has been shown that psychopathy is associated with an increased risk for both reactive and instrumental aggression (Cornell et al., 1996). Overall there is some evidence that instrumental aggression is more related to factor 1 of the PCL-R, which is measuring emotional deficiencies. Remarkably, in the present study, regression analysis of psychopathy scores and the total amount of applied punishment revealed that factor 1 in both psychopathy scales inversely covaried with the mean punishment levels. In other words, subjects with more callous unemotional traits applied less punishment intensity to the opponent. In fact, there are indications that subjects scoring high in psychopathy showed less reactive aggression in a laboratory aggression paradigm compared to low psychopathic individuals (Ciarkowska and Francek, 1986). Recently, it has been shown that factor 2 but not factor 1 of the LSRS predicted laboratory aggression in undergraduate males (Reidy et al., 2007). Similarly, Patrick and Zempolich (1998) pointed out that there is

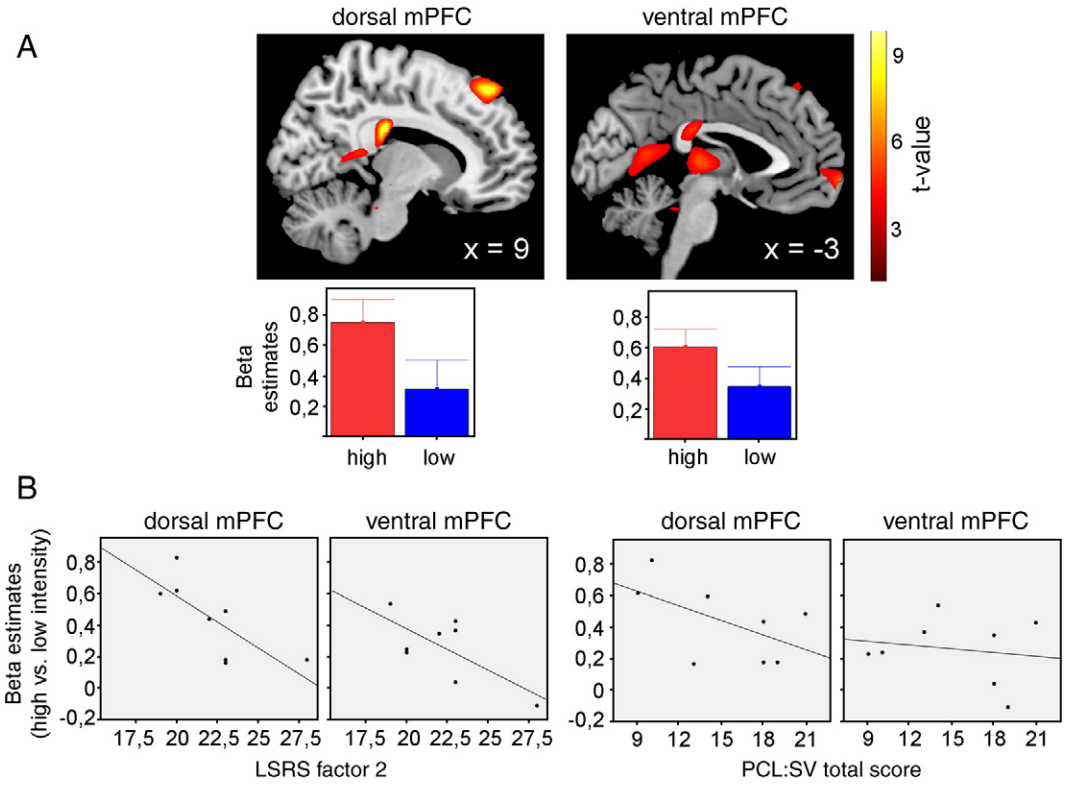

Fig. 3. (A) Group activation maps during observation of the opponent (high in comparison to low pain adjustments) projected on the MNI single subject brain ($p<0.01$, uncorrected). Direct statistical comparison between high and low punishment adjustment during opponent observation revealed different activation in the dorsal mPFC (middle row left, coordinates: 9, 42, 51) and the ventral mPFC (middle row right, coordinates: −3, 69, −6). The corresponding contrast values (±SD) for high (red) and low (blue) intensity adjustments are displayed on the bottom of each activation map. (B) Regression analyses between beta estimates (high versus low intensity) and LSRS factor 2 (left) or PCL-SV total score (right) during observation of the opponent. Activations in the ventral and dorsal mPFC covaried inversively with scores of factor 2 in the LSRS (dorsal mPFC: $r=-0.70$ $p<0.05$; ventral mPFC: $r=-0.76$ $p<0.05$), but not with total scores of the PCL-SV (dorsal mPFC: $r=-0.55$ $p=0.16$; ventral mPFC: $r=-0.16$ $p=0.70$).

some evidence that instrumental aggression is more related to core features of psychopathy (factor 1) and reactive aggression is linked to antisocial personality characteristics (factor 2).

fMRI-activation during anticipation of punishment

There were also remarkable differences in the peripheral and cortical response patterns during anticipation of punishment between the forensic group and healthy volunteers. In our previous study (Lotze et al., 2007) healthy controls showed a modulation in activation in bilateral areas associated with pain processing (affective; ACC, amygdala, hypothalamus; discriminative: S2, insula). In contrast, in psychopaths we found the most prominent differences between anticipation of high compared to low punishment levels in the inferior orbitofrontal cortex, the thalamus and the pallidum bilaterally. However, no ACC, amygdala or prefrontal activity was present in the anticipation period. Koyama et al. (2005) demonstrated that expectation of thermal pain without accompanied sympathetic arousal and hence no fear, elicited strong activations in the thalamus, putamen and globus pallidus. Congruently, thalamus, pallidum and putamen were active to most intensive stimuli in our study, too. The missing amygdala activation and the unchanged SCR support the assumption that anticipation of fear was weak or non-existing in psychopaths as found previously in a comparable sample (Birbaumer et al., 2005). The increasing SCR during actual pain stimulation but not during anticipation of pain further supports the assumption that psychopathic individuals are not impaired in sensory aspects of pain processing but only in its anticipation (Flor et al., 2002). Thus, the observed activations seem to represent a purely cognitive and not an emotional appraisal of the upcoming pain.

fMRI-activation during retaliation

One critical contrast in this study was the comparison between high and low retaliation levels. The most prominent difference was found in the medial hypothalamus extending to the midbrain. The hypothalamus is believed to play a regulatory role in aggression control (Gregg and Siegel, 2001). The strong correlation between scores in physical aggression and increased BOLD-response in the hypothalamus during high in comparison to low retaliation emphasizes their putative role during aggressive acts. Davidson et al. (2000) reported that several areas in the prefrontal cortex including the dorsal and ventral/orbital medial prefrontal cortex are involved in human aggression. Especially the OFC comprising BA 47 modulates reactive aggression (Blair, 2007). However, the exact role of the different prefrontal areas and their interaction with subcortical areas in aggression and aggression control in humans are still unclear. In our preceding study (Lotze et al., 2007) we found lower activity in the ventral mPFC in high callous compared to low callous subjects during retaliation, possibly reflecting increased moral concerns in more empathic individuals. In the present study there was no altered activation of the mPFC between high and low retaliation. The inability of psychopathic individuals to empathize with others is a major characteristic of the disorder and the ventral mPFC seems to play a key role in the circuit establishing and maintaining empathic behavior.

Observing the opponent suffering from retaliation

During observing the opponent the psychopaths showed increased activation for a suffering compared to a neutral opponent in occipital areas, the inferior and middle temporal areas comprising the superior STS, the inferior orbitofrontal cortex (BA 47), the insula, the

dorsomedial PFC, the ventral mPFC and the right amygdala. Most of these areas have been described to be involved in social cognition and Theory of Mind (ToM) tasks (Gobbini et al., 2007). Völlm et al. (2006) found increased activation during ToM but not empathy related tasks in the ventrolateral PFC (BA 47), suggesting that this area is involved in cognitive appraisal of situational aspects. It is known that psychopathic individuals are not generally impaired in ToM tasks (Hare, 1993) at a cognitive level and can even adopt the perspective of others but disregard the emotional content and rely only on cognitive information. The missing change in SCR's during observing the high suffering opponent supports the assumption that no empathic feeling or compassion were elicited. Moreover, in healthy people a strong positive relationship between SCR amplitudes and the amount of suffering after higher pain application to others has been described (Lotze et al., 2007), indicating that distress cues (high suffering in others) evoke empathic concerns. Again, a comparable association was not seen in the present population. Additionally, the dorsal and the ventral mPFC was differentially activated between high and low intensity adjustments and replicate the results of our previous study (Lotze et al., 2007). More importantly, in the present study subjects with higher scores on the antisocial factor but not on the interpersonal emotional factor showed more dorsal mPFC activity during the observation of the video clips with the highly suffering opponent, pointing to a more emotional as well as cognitive involvement in criminal individuals scoring high in factor 2 but not in factor 1. The dorsal mPFC is often activated during tasks requiring mentalizing and person perception. It might be assumed that less antisocial participants reflected more about the opponent and the consequences of their own actions. In contrast, the activity in the ventral mPFC correlated negatively with factor 2 of the LSRS and there was also a tendency for less ventral mPFC activation with higher total PCL:SV score. The ventral mPFC is a key structure for moral reasoning and lesions in this area causes impairments in feeling of regret in a gambling task (Camille et al., 2004). Hynes et al. (2006) demonstrated that the ventral mPFC is predominantly active when participants engage in emotional as compared to cognitive perspective-taking, especially when perceivers make inferences about the affective aspects of another person's mental state. Developmental psychopathy shows significant impairments in moral reasoning and judgment and a deficit in mPFC activation (Blair, 2007).

Limitations of the study

The generalizability of our findings is undoubtedly limited by the rather small size of this exceptional sample. Since there are no functional imaging studies that address institutionalized, “unsuccessful” psychopathic subjects with the used methodology of a realistic scenario, it was impossible to judge whether previous findings apply to highly dangerous psychopathic samples.

Conclusion

Our findings are in line with recent assumptions (Porter and Woodworth, 2006) that reactive aggression seems to be rather related to the antisocial facet than to the affective or interpersonal aspect of psychopathy. The latter is found to be more related to forms of goal directed instrumental “cold” aggression. Furthermore, representation maps of all three conditions tested were remarkable: psychopaths showed a purely cognitive and not an emotional appraisal of the upcoming pain. They showed no modulation of the dorsal mPFC by different intensities of retaliation as it has been reported for healthy subjects. Although theory of mind areas were active during observation of the suffering opponent, ventral mPFC correlated negatively with factor 2 of the LSRS indication higher antisocial personality.

Appendix A. Supplementary data

Supplementary Figure 1. Illustration of the experimental design. Top row shows a winning trial, bottom row a loosing trial. The time course is displayed on the *x*-axes. Wins (top row): after the instruction, a start signal appeared which should be responded by a button hit 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 was controlled on a visual five-point scale. Thereafter, the subject was told to watch the opponent suffering via a video camera. In fact, but not known to the subject, a video of the opponent was shown selected from one out of six previously taped clips for each selected stimulus intensity. An example of two videos with low (Level 1) and high (Level 5) pain is shown on the top right. Losses (bottom row): the reaction time task was followed by a sad, negative facial expression as feedback. The subject was informed that the opponent now adjusts the intensity of the pain 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 participant received a mechanical aversive stimulus as symbolized with the red arrow.

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