

Deficient Fear Conditioning in Psychopathy

A Functional Magnetic Resonance Imaging Study

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Context: Psychopaths belong to a larger group of persons with antisocial personality disorder and are characterized by an inability to have emotional involvement and by the repeated violation of the rights of others. It was hypothesized that this behavior might be the consequence of deficient fear conditioning.

Objective: To study the cerebral, peripheral, and subjective correlates of fear conditioning in criminal psychopaths and healthy control subjects.

Design: An aversive differential pavlovian delay conditioning paradigm with slides of neutral faces serving as conditioned and painful pressure as unconditioned stimuli.

Setting: The Department of Medical Psychology at the University of Tübingen, Tübingen, Germany.

Participants: Ten male psychopaths as defined by the Hare Psychopathy Checklist–Revised and 10 age- and education-matched healthy male controls. The psychopaths were criminal offenders on bail and waiting for their

trial or were on parole. The healthy controls were recruited from the community.

Main Outcome Measures: Brain activation based on functional magnetic resonance imaging, electrodermal responses, emotional valence, arousal, and contingency ratings.

Results: The healthy controls showed enhanced differential activation in the limbic-prefrontal circuit (amygdala, orbitofrontal cortex, insula, and anterior cingulate) during the acquisition of fear and successful verbal and autonomic conditioning. The psychopaths displayed no significant activity in this circuit and failed to show conditioned skin conductance and emotional valence ratings, although contingency and arousal ratings were normal.

Conclusion: This dissociation of emotional and cognitive processing may be the neural basis of the lack of anticipation of aversive events in criminal psychopaths.

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PSYCHOPATHIC BEHAVIOR IS characterized by an inability to have emotional involvement with others and by repeated violation of the rights of others.¹ Psychopaths, who are part of a wider group of persons with antisocial personality disorder, seem to lack the ability to anticipate punishment and are deficient in autonomic responding, eg, skin conductance responses (SCRs), in anticipation of threatening events.² High intelligence and high socioeconomic status may protect psychopaths from developing a criminal career and turn them into successful psychopaths who display a high incidence of reckless, risk-taking, and emotionally insensitive behavior patterns.³ Most psychopaths seem to lack the ability to predict impending harm from signals of threat and may thus show defi-

cient fear conditioning where a formerly neutral stimulus (conditioned stimulus [CS]) comes to predict a fear-eliciting stimulus (unconditioned stimulus [US]) after they have been paired several times.⁴⁻⁶

The brain circuits underlying the acquisition and maintenance of conditioned fear in humans have been the focus of major research efforts. Imaging studies using positron emission tomography or functional magnetic resonance imaging (fMRI) revealed that the amygdala, anterior cingulate, insula, and—less consistently—prefrontal and cerebellar areas are activated during the acquisition of a conditioned aversive response in a delay paradigm.⁷⁻¹⁰ Lesions of the orbitofrontal cortex (OFC), which is part of this frontolimbic circuitry, lead to behavioral manifestations designated “acquired sociopathy,”^{11,12} characterized by socially inadequate choices and

irresponsible behavior. This prefrontal-limbic circuit mediates anticipatory planning and emotion regulation and adjustment, particularly in social contexts, whereas the unconditioned responses to diverse aversive stimuli and abstract knowledge about correct responses are largely preserved after lesions form in the described circuit. Overactivity of the described neuronal structures should lead to pathological fear and avoidance of social situations, and underactivity should lead to behaviors comparable to those observed after these structures have been lesioned.

METHODS

PARTICIPANTS

We compared 10 emotionally detached psychopaths with criminal records with 10 healthy control subjects matched for age and education (all men). The mean age of the psychopaths was 35.30 years (SD, 5.79 years; age range, 23-41 years) and for the healthy controls, 31.50 years (SD, 7.58 years; age range, 21-41 years). This difference was not significant ($t_{18} = -1.49$; $P = .16$). The mean years of education were 12.80 (SD, 1.69 years; range, 10-15 years) for the psychopaths and 12.60 (SD, 2.37 years; range, 10-18 years) for the healthy controls. This difference was also not significant ($t_{18} = -0.22$; $P = .83$). The psychopaths consisted of offenders out on bail and waiting for their trial or those out of jail and on parole; both types were screened from a larger sample using the Psychopathy Checklist-Revised (PCL-R).¹³ We included only psychopaths with (1) a cutoff score of at least 10.5 on the emotional detachment scale of the PCL-R because we expected more deficient conditioning in this subgroup than in that with antisocial characteristics and (2) no comorbid disorder on Axis I of the DSM-IV¹⁴ as assessed by the Structured Clinical Interview for DSM-IV.¹⁵ The mean emotional detachment score was 11.63 (SD, 3.60; range, 10.5-14); mean antisocial behavior score, 10.87 (SD, 5.23; range, 3-13); and overall PCL-R score, 24.89 (SD, 5.23; range, 15-31). This is much lower than the values reported for American populations of psychopaths but in accordance with the lower values for the German norms.¹⁶ Six of the psychopaths also met DSM-IV criteria for antisocial personality disorder as assessed by the Structured Clinical Interview for DSM-IV. The healthy controls were recruited by newspaper advertisements and posters in public places and had to be free of any mental disorder. They had scores of less than 2 on both scales of the PCL-R. None of the participants was taking psychoactive medication or had a previous head injury. The healthy controls were paid €30 and the psychopaths were paid €100 to ensure participation of this difficult-to-recruit group. All participants signed informed consent. The study was approved by the local institutional review board and adhered to the Declaration of Helsinki. German law does not permit the testing of prison inmates. Because of this constraint and the very stringent inclusion criteria, the data acquisition spanned more than 2 years.

EXPERIMENTAL DESIGN

Neuroimaging was performed during classic aversive differential delay conditioning. Photographs of 4 male neutral faces (2 with and 2 without a mustache) served as the CS, with random assignment of the mustached and mustacheless faces to the CS followed by the US (CS+) and to the CS never followed by the US (CS-) (**Figure 1**). The conditioning procedure consisted of the following 3 phases: habituation (8 CS+ and CS- presentations in random order), acquisition (16 trials

with paired presentations of CS+ and US and 16 trials of CS-alone), and extinction (like habituation) that occurred successively. The CS was presented for 7.05 seconds; the US (painful pressure) lasted for 10 milliseconds and was terminated together with the CS+. The US was applied using a plastic cylinder with a 7-mm diameter and a 12-mm length that was placed in a small plastic tube and moved by air pressure. A pneumatic device (Dokoh-Pneu, Erlangen, Germany) was used to adjust the pressure applied on the mechanical stimulator with pressure velocities ranging from 2 to 20 m/s. The apparatus was placed outside the scanner, and a flexible tube was connected to the rigid plastic tube. Stimulation intensity was determined before the conditioning procedure by increasing the pressure velocity to a point where the subjects estimated the stimulus as moderately unpleasant (4 on a scale in which 1 indicates not at all unpleasant and 5, extremely unpleasant). The pressure velocities were not significantly different between the groups ($t_{18} = 0.50$; $P = .75$). Before each CS, a gray square was displayed for 3.5 or 7 seconds to keep the attention constant and fixed on the CS. Intertrial intervals were random, with a mean of 24.5 seconds and a range from 21 to 27 seconds. As a peripheral physiological measure of conditioning, SCRs were obtained. They were measured at the left foot from the skin above the abductor hallucis muscle about midway between the proximal phalanx of the first toe and a point below the ankle medial to the sole of the left foot. Silver-silver chloride electrodes and unibase electrolyte were used. The signal was recorded in an alternating current mode with an ambulatory digital recorder (Vitaport II; Becker Meditec, Karlsruhe, Germany) using a sampling rate of 16 Hz. The data were bandpass filtered off-line (cut-off frequencies, 0.05 and 10 Hz) to reduce signal drifts and MRI artifacts. The SCRs were defined as the maximum of the SCR signal from 1 to 5 seconds (first-interval response) after CS onset relative to baseline (mean value 1 second before CS onset). For statistical analysis, SCRs were logarithm transformed ($\log[\text{SCR} + 1]$). Emotional valence and arousal (values ranging from 1-9; Figure 1) related to the CS were rated after the habituation, first and second half of the acquisition, and extinction phases using the Self-Assessment Manikin.¹⁷ The Self-Assessment Manikin is a nonverbal measure of emotional responses based on pictograms that were displayed on a video screen. Contingency of the CS and US was assessed after the acquisition phase using a 9-point scale (ranging from completely certain [1] that pain will not follow to uncertain [5] to completely certain [9] that pain will follow subsequent to the presentation of the CS). These 3 measures served as self-report indices of conditioning.

FUNCTIONAL MRI

One hundred twenty-seven T2*-weighted echoplanar images (32 coronary slices; slice thickness, 4-mm + 1-mm gap; 48×64 voxels; in-plane resolution, 3×3 mm; field of view, 192 mm; echo time, 36 milliseconds; acquisition time, 2.97 seconds; effective repetition time, 3.58 seconds) were acquired during each measurement block. The short echo time and the coronal orientation were chosen to minimize susceptibility artifacts in the orbitofrontal and temporal regions. Four blocks were measured for each subject. In addition, a T1-weighted 3-dimensional data set consisting of 128 sagittal slices (slice thickness, 1.5 mm; matrix, 224×256 ; field of view, 250 mm; repetition time, 9.7 milliseconds) was acquired.

During each CS+ and CS- presentation, the entire brain was scanned twice, and 1 scan was performed during the US presentation using a 1.5-T Vision whole-body MRI (Siemens AG, Erlangen) equipped with a head coil. During the scans, the faces were presented on a liquid crystal display video projector. An

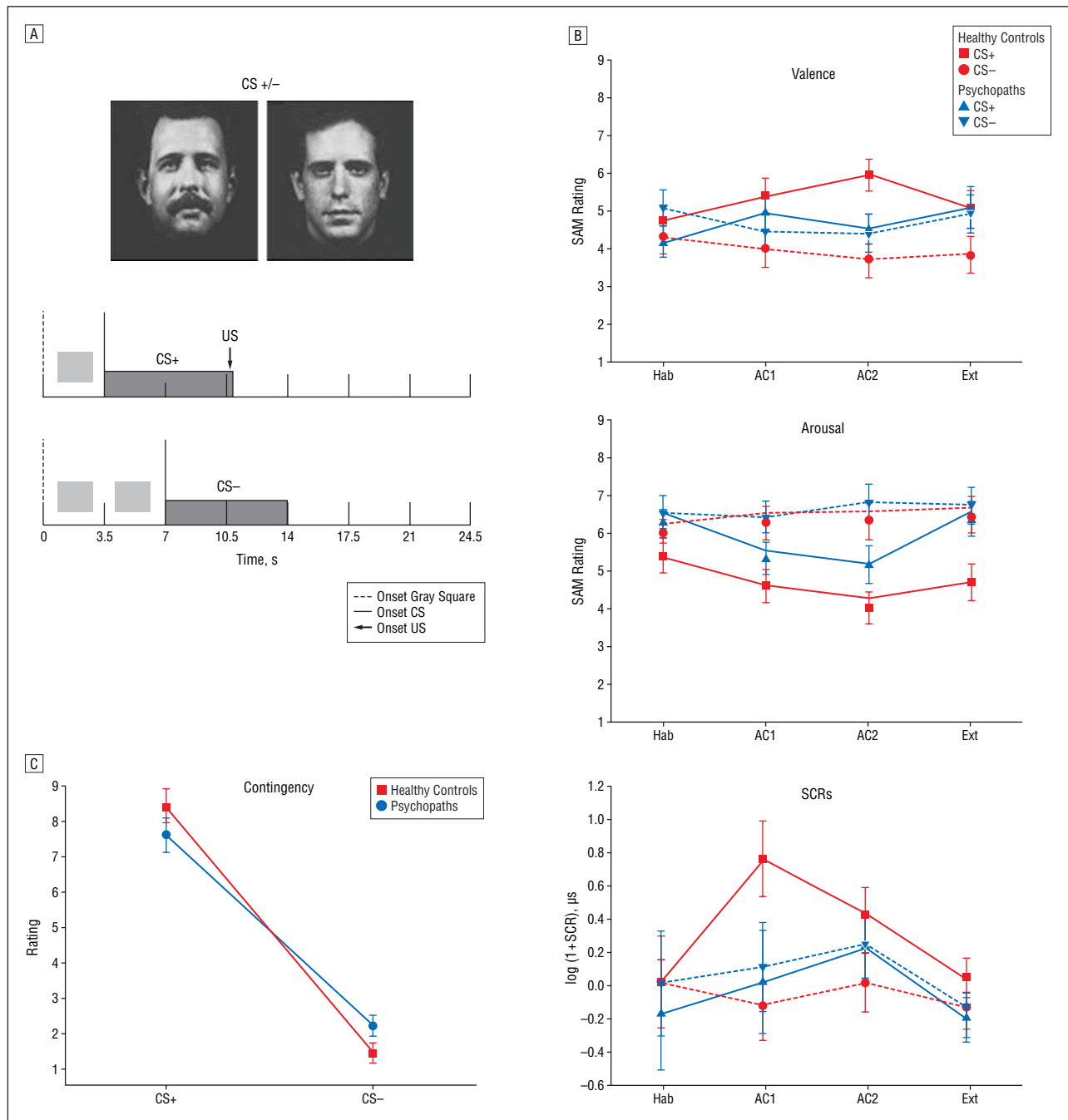


Figure 1. A, Schematic illustration of the experimental design showing 2 different trials. Each scan lasted for 3.5 seconds. The onset of each trial (time 0, onset gray square) was synchronized with the scanner. One presented face (mustached or mustacheless) served as the conditioned stimulus (CS) followed by the unconditioned stimulus (US) (CS+ condition) or as the CS never followed by the US (CS- condition). During the acquisition phase, half of the CSs (CS+) were followed by the US in a pseudorandomized order (100% reinforcement). The US terminated together with the CS+ 50 milliseconds after the beginning of the third scan relative to CS onset. Before the presentation of each face, a gray square was displayed for 3.5 to 7.0 seconds to keep the attention of the subjects focused. B, Subjective ratings to the CS+ and CS- for valence, arousal, and skin conductance responses (SCRs) across all phases (habituation [Hab], early acquisition [AC1], late acquisition [AC2], and extinction [Ext]) for both groups. The data indicated successful conditioning on the subjective and peripheral level in healthy control subjects but not in the psychopaths. SAM indicates Self-Assessment Manikin. For the valence rating scale, 1 indicates pleasant; 9, unpleasant. For the arousal rating scale, 1 indicates arousing; 9, calm. C, Contingency ratings to the CS+ minus the CS- for the 2 groups. For the contingency rating scale, 1 indicates completely certain that pain will not follow the presentation of the CS; 9, completely certain that pain will follow the presentation of the CS. Both groups were able to differentiate between CS+ and CS-.

adjustable mirror above the eyes allowed direct view. Data pre-processing and statistical evaluation were performed using SPM99 software (Wellcome Department of Imaging Neuroscience, London, England). The first 5 scans were excluded from the analyses to eliminate T1 saturation effects. The remaining 122 scans were realigned to the first image of the session using

a rigid body spatial transformation (head movements were smaller than 1.5 mm in all subjects). Preprocessing included spatial realignment, slice time correction, normalization into Montreal Neurological Institute space, and spatial (full-width at half-maximum, 15-mm) smoothing. Normalization was performed in 2 steps (using default values in SPM99). First, the

Table 1. Differential Activations (CS+ vs CS-) During Conditioning in Healthy Control Subjects and Psychopaths

Region	MNI Coordinates	T Contrasts	P Value
Healthy controls*			
Habituation	No differential activations		
Acquisition			
Insula left	-36, 3, -12	6.01	.01†
Anterior insula right	36, 12, -15	5.38	.01†
Caudal anterior cingulate	-3, 9, 39	6.55	.03†
Rostral anterior cingulate	-3, 33, -3	4.97	.03†
Posterior cingulate	3, 18, 39	9.32	.003†
Anteromedial orbitofrontal left	-24, 30, -12	5.98	.04†
SII left	-60, -27, 33	6.52	.002†
SII right	51, -42, 24	11.23	.001†
SMA	12, 3, 69	6.18	.02†
Amygdala left	-27, 3, -18	4.46	.03†
Interaction (CS type × early/late acquisition) effect			
Amygdala right	27, 3, -27	5.79	.004‡
Anterolateral left OFC	-36, 57, -3	5.05	.008‡
Ventromedial OFC	0, 57, -9	4.05	.01‡
Extinction	No differential activations		
Psychopaths			
Habituation	No differential activations		
Acquisition			
Amygdala right	21, 6, -18	5.27	.02†
Extinction	No differential activations		

Abbreviations: AC1, early acquisition; AC2, late acquisition; CS, conditioned stimulus; CS-, CS never followed by the unconditioned stimulus; CS+, CS followed by the unconditioned stimulus; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; SII, secondary somatosensory cortex; SMA, supplementary motor area.

*Early/late interaction corresponds to the contrast $[(CS+_{AC1}) - (CS-_{AC1})] - [(CS+_{AC2}) - (CS-_{AC2})]$.

†Corrected for the expected amount of false-positive findings among suprathreshold voxels of the predefined regions using the atlas of Tzourio-Mazoyer et al.¹⁹

‡Corrected for the expected amount of false-positive findings among suprathreshold voxels in a sphere of 10 mm around the maximally activated voxel within the predefined regions.

values of a 12-parameter affine transformation were determined followed by an iterative nonlinear parameter estimation using $7 \times 8 \times 7$ basis functions (T1 image to T1 template). The resulting parameters were then used to reslice the functional images.

DATA ANALYSIS

We chose a linear model approach to estimate hemodynamic response amplitudes. Boxcar functions convolved with a synthetic hemodynamic response function were used to model hemodynamic responses to the visual and pain stimuli. The derivative of the hemodynamic response and the (first-order) rigid body transformation parameters (translation and rotation) were used as additional regressors. The following 3 different event types were defined: CS+ and CS- as covariates of interest and the gray squares as confound. The epoch lengths for CS+ and CS- were 2 scans. During acquisition, the US presentation was used as an additional regressor. We performed *t* contrasts between CS+ and CS- to identify regions with a greater response to the CS+ as compared with the CS- separately for each phase and group. Based on publications^{7,8,18} demonstrating a rapid habituation of the responses in the amygdala during conditioning, we investigated the early (first-half) and late (second-half) acquisition phases and the interaction between early and late acquisition for all brain regions separately. Each subject's data set was high-pass filtered (cutoff period, 151 seconds) to remove low-frequency drifts. We performed random-effects analyses by computing a mean subject-specific functional image for the CS+/CS- contrast in each conditioning phase (habituation, acquisition, and extinction). These individual contrast images were then entered into a second-level

analysis using a 1-sample *t* test. Comparisons between groups were performed using a 2-sample *t* test.

Based on a priori anatomical hypotheses,^{7,8} the cingulate cortex, insular cortex, supplementary motor area, amygdala, OFC, and secondary somatosensory cortex were analyzed. *P* values are corrected for the regions of interest using a mask based on the anatomical borders of the atlas of Tzourio-Mazoyer et al.¹⁹ in case of the within-subject analyses for both groups. For the between-subject comparison, we used a less conservative criterion, choosing a spherical region of interest (10 mm) located on the highest activated voxel within these predefined regions. To reduce type I error, a method that corrects for the false discovery rate²⁰ was applied to suprathreshold voxels (**Table 1** and **Table 2**). Statistical maps were thresholded at $P < .05$.

The self-report and SCR data were analyzed by means of repeated-measures analyses of variance (ANOVA) with the groups (psychopaths and healthy controls) as between-group factors and the phases (habituation, acquisition, and extinction) and CS type (CS+ vs CS-) as within-group factors. Because of the varying scanner artifact, SCRs were available for 5 psychopaths and 7 healthy controls.

RESULTS

SELF-REPORT INDICES OF CONDITIONING

Both groups displayed a conditioned response for arousal and contingency ratings and clearly differentiated CS+ and CS- (Figure 1B). However, the psychopathic group

failed to show a differential response in the emotional valence ratings. For valence, CS type ($F_{1,18}=4.72$; $P=.04$), CS type \times phase ($F_{3,16}=5.91$; $P=.006$), and CS type \times group ($F_{1,18}=5.06$; $P=.04$) were significant, indicating that the CS+ was rated as significantly more aversive specifically in the acquisition phase only by the healthy controls ($P=.01$) and not by the psychopaths ($P=.53$). The arousal ratings yielded a significant CS type ($F_{1,18}=14.76$; $P<.001$), phase ($F_{3,16}=5.70$; $P=.008$), and CS type \times phase effect ($F_{3,16}=3.60$; $P=.04$) with arousal ratings being significantly higher in the CS+ condition in the early ($P=.005$) and the late ($P=.03$) acquisition phase. Contingency yielded a significant CS type effect ($F_{1,18}=250.98$; $P<.001$), with the CS+ eliciting higher contingency ratings than the CS- without a significant group difference. A marginally significant group \times CS type effect ($F_{1,18}=4.25$, $P=.05$) emerged, which, however, was not accounted for by significant group differences in perceived contingency for either CS+ ($P=.3$) or CS- ($P=.07$).

CONDITIONED SCRS

The overall ANOVA for SCRs yielded a significant CS type ($F_{1,10}=4.49$; $P=.05$) and a trend toward a significant phase \times CS type effect ($F_{3,8}=3.35$; $P=.06$) as well as a significant CS type \times group effect ($F_{1,10}=8.00$; $P=.02$), indicating that SCRs increased to the CS+ in the acquisition phase only in the healthy controls and not in the psychopaths (Figure 1C). When the healthy controls were entered into a separate analysis, a significant CS type effect emerged ($F_{1,6}=13.29$; $P=.01$); the CS+ compared with the CS- elicited a significantly higher SCR in the first half of the acquisition phase ($t_6=2.50$; $P=.05$). In addition, the increase in responding from the habituation to the acquisition phases was significant for CS+ ($t_6=2.83$; $P=.03$). None of these effects was significant for the psychopaths.

fMRI DATA IN THE HEALTHY CONTROLS AND PSYCHOPATHS

During acquisition, the healthy controls showed significant activation of the frontolimbic circuit involved in emotional learning (CS+/CS- differentiation; Table 1). The brain circuit involves the left amygdala, left anteromedial OFC, anterior and posterior cingulate, right anterior and left middle insula, supplementary motor area, and secondary somatosensory cortex bilaterally. A time-dependent CS+-related response showing more activation in the first compared with the second part of the acquisition phase was found in the right amygdala and in the medial and lateral OFC (early/late acquisition \times CS type [where early vs late corresponds to the contrast [(CS+_{AC1}) - (CS-_{AC1})] - [(CS+_{AC2}) - (CS-_{AC2})]. See asterisk footnote to Table 1.) (Figure 2 and Table 1). The psychopaths showed no significant changes related to differential conditioning in these brain regions except for a small activation in the right amygdala (Table 1). A direct comparison between the CS+/CS- differentiation of the psychopaths and healthy controls during acquisition showed significantly less activation in the left amygdala, left middle and right anterior insula, anterior cingulate, and right secondary somatosensory cortex

Table 2. Differential Activation to CS+ vs CS- in the Healthy Control Subjects Minus the Psychopaths*

Region	MNI Coordinates	T Contrast	P Value
Habituation		No differential activations	
Acquisition			
SII right	-51, -45, 15	5.46	.003†
Amygdala left	-18, 6, -24	3.76	.04†
Insula right	33, -6, 15	3.72	.03†
Rostral anterior cingulate	3, 30, 3	3.29	.045†
Acquisition 2nd half:			
Ventromedial orbitofrontal cortex	15, 24, -12	3.40	.04†
Extinction		No differential activations	

Abbreviations: CS, conditioned stimulus; CS-, CS never followed by the unconditioned stimulus; CS+, CS followed by the unconditioned stimulus; MNI, Montreal Neurological Institute; SII, secondary somatosensory cortex. *Tested by means of the 2-sample *t* test.

†Corrected for the expected amount of false-positive findings among suprathreshold voxels in a sphere of 10 mm around the maximally activated voxel within the predefined regions.

(Figure 2 and Table 2), as well as the right ventromedial OFC in the second half of the acquisition phase (early/late acquisition \times CS type; Table 2). An analysis of the self-reported, peripheral, and hemodynamic brain responses to the US indicated no significant group differences (all $P>.20$), suggesting that the response to biologically significant stimuli was equal for both groups.

COMMENT

The data from the healthy controls confirm that fear conditioning involves the amygdala, OFC, anterior cingulate, and anterior insula. Activation within the secondary somatosensory cortex may be related to the processing of painful stimulation and interoceptive signals,²¹⁻²³ and that of the supplementary motor area to a preparatory defense response.^{9,10} The psychopaths were significantly different from the healthy controls in their activation in all brain regions. The amygdala and the OFC^{11,24,25} have been implicated in deficits in emotional processing observed in psychopaths. In our study, the healthy controls showed sustained activation of the left amygdala throughout the acquisition phase, whereas the psychopaths displayed only right amygdala activation. In the direct comparison, the left amygdala of the psychopaths was significantly less active than that of the healthy controls when learning occurred. There have been suggestions of differential activations of the right and left amygdala related to different types of stimulus processing^{26,27}; however, methodological problems in most of the studies do not permit firm conclusions.²⁸ It is conceivable that the psychopaths acquired some knowledge about the association of the CS and US but never processed the emotional significance of the association, as seen in the lack of a conditioning effect in the emotional valence ratings and the deficient anticipatory SCRs. However, they showed intact cognitive stimulus processing as indi-

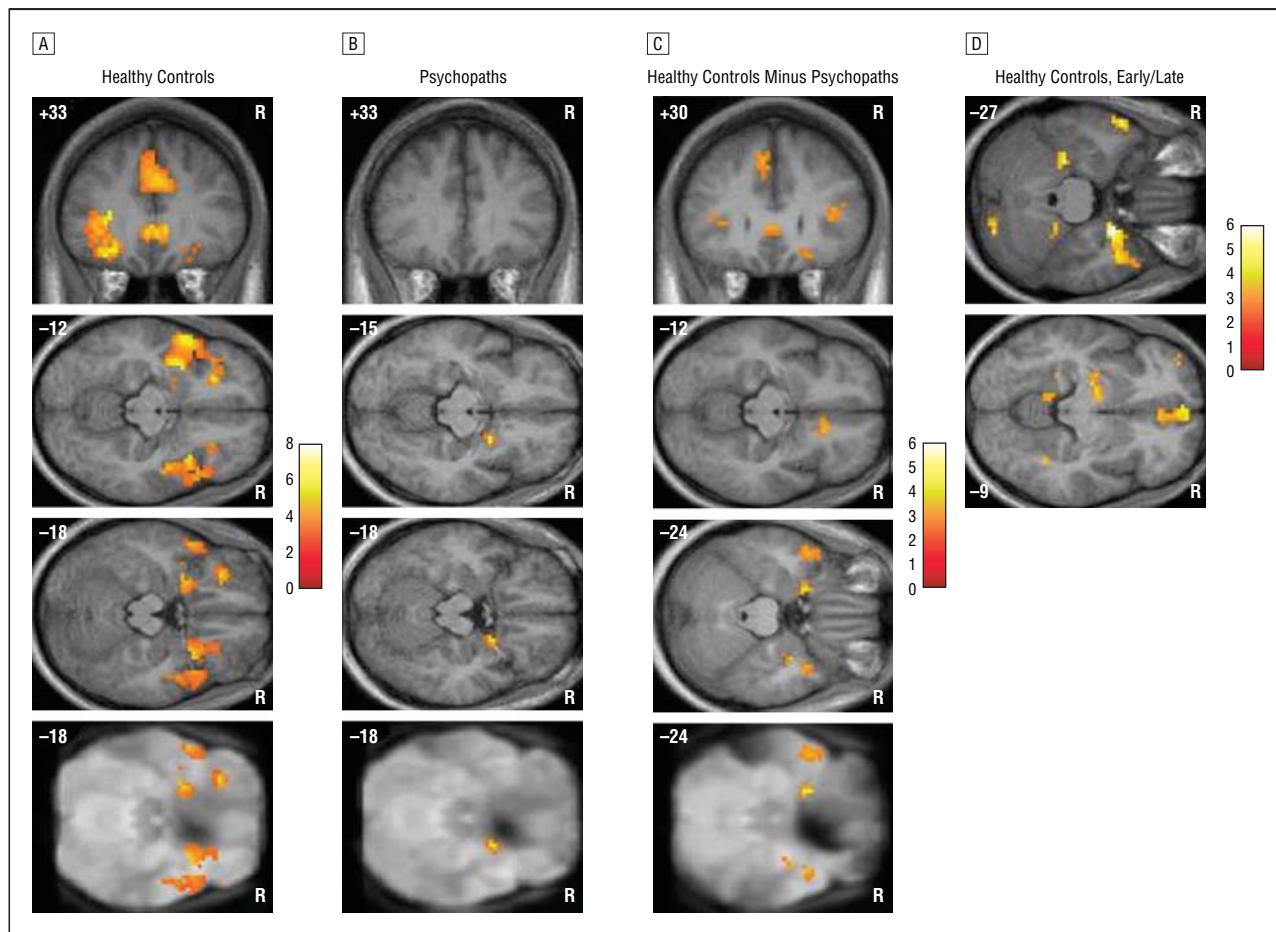


Figure 2. Activation clusters for the contrast conditioned stimulus (CS) followed by the unconditioned stimulus (US) (CS+ condition) minus the CS never followed by the US (CS- condition) during acquisition for the healthy control subjects (A), the psychopaths (B), the comparison of healthy controls minus psychopaths (C), and the comparison of early minus late acquisition in the healthy controls (D) projected on the normalized mean anatomical image of the corresponding group. All images were thresholded at $P < .01$ (uncorrected for visualization). A, Controls revealed differential conditioning in the anterior cingulate, anterior insula, and the left amygdala (as well as the secondary somatosensory cortex and supplementary motor area, not shown here). B, Psychopaths showed a small differential activation in the right amygdala only. C, The comparison healthy controls minus psychopaths revealed significant differences within the rostral anterior cingulate, anterior insula (top), and left amygdala (bottom). The ventromedial orbitofrontal cortex (middle) was differentially activated between groups during the second acquisition phase. D, The right amygdala (middle right) and the ventromedial orbitofrontal cortex (bottom right) were significantly more activated in the early compared with the late acquisition phase.

cated by the differential contingency ratings. This is in accordance with previous work supporting the notion of “cold” emotional processing devoid of true (emphatic) emotional involvement leading to “myopia for the future” in psychopaths.^{4,5,24,25,29-31}

Activation of the OFC has been associated with the anticipation of punishment and reward and the ability of reversal learning in the face of changing reinforcement contingencies as well as social cognition in general.^{24,25,29,30,32-34} The interaction of the amygdala and OFC seems to be crucial for encoding expected outcomes during learning as well as producing conditioned SCRs.^{33,35,36} Our data show that the psychopaths lack OFC activation, especially in the second half of the acquisition phase when the learned association needs to be translated into behavioral responding. Lesions in the ventromedial OFC have been associated with deficient somatic markers.^{11,12} The “somatic marker” hypothesis stands in the James-Langian tradition of ascribing feedback from the autonomic, musculoskeletal, and endocrine systems to the cortical somatosensory areas, limbic system, and OFC with a critical role

in emotional responses, ie, new decisions are possible by reviving the emotional somatic markers in the orbitofrontal-limbic-postcentral circuit. The lack of amygdalar, orbitofrontal, and limbic brain responses in the psychopaths is in accordance with the results of several positron emission tomography and fMRI studies in antisocial personality disorder or psychopathy that reported decreased prefrontal blood flow, or with those of structural MRI studies that showed reduced prefrontal volume.^{37,38}

Activation in the anterior and middle insula indicates emotional processing of anticipated pain and anticipatory anxiety and has been implicated especially in awareness of threat stimuli and associated body states.³⁹⁻⁴¹ These processes were absent in the psychopaths. The rostral and caudal anterior cingulate were also differentially active to CS+ and CS- and showed deficient activation in the psychopaths. Activation in the rostral anterior cingulate cortex, a region that is closely connected with the amygdala, has been associated with emotional stimulus content, and the dorsal anterior cingulate cortex has been connected to attentional processes and stimulus expectancy.^{42,43} Thus,

affective processing and emotional stimulus expectancy seem to be deficient in the psychopaths.

This study has several limitations. First, 10 subjects constitute a very small study population, and thus differential statements about subgroups of psychopaths were not possible. Second, the design of the study precluded a connectivity analysis on a neural level, which might have yielded more information about the dynamic interplay of the brain regions involved in conditioning. Third, we did not focus on extinction, which would have required a more extended test. A strength of the study is, however, its focus on the subgroup of emotionally detached psychopaths and the very strict exclusion criteria regarding comorbidity and medication use.

CONCLUSIONS

This imaging study of fear conditioning in emotionally detached persons with a psychopathy diagnosis revealed a failure of differential conditioned responses in the left amygdala, insula, anterior cingulate, OFC, and secondary somatosensory cortex. The psychopaths displayed intact responses to the US, however, as previously shown.³¹ The amygdala–anterior cingulate–orbitofrontal–parietal connection is critical for assigning emotional valence in an anticipatory fashion to social stimuli, particularly to human faces.⁴⁴ This inability to emotionally relate neutral and biologically significant events rather than a lack of response to biologically relevant stimuli in general may be at the core of psychopathy. The absence of emotional associative ability (“cold emotion”) may be crucial for psychopathic behavior and should be targeted by behavioral and somatic interventions.

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