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Fear conditioning in psychopaths: Event-related potentials and peripheral measures

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ABSTRACT

Aversive pavlovian delay conditioning was investigated in a sample of 11 criminal psychopaths as identified by using the Psychopathy Checklist-Revised and 11 matched healthy controls. A painful electric stimulus served as unconditioned stimulus and neutral faces as conditioned stimuli. Event-related potentials, startle response potentiation, skin conductance response, corrugator activity, and heart rate were assessed, along with valence, arousal, and contingency ratings of the CS and US. Compared to healthy controls, psychopathic subjects failed to differentiate between the CS+/CS− as shown by an absence of a conditioned response in startle potentiation and skin conductance measures. Through use of a fear-eliciting US, these data confirm previous findings of a deficient capacity to form associations between neutral and aversive events in psychopathy that appears unrelated to cognitive deficits and is consistent with hypothesized frontolimbic deficits in the disorder.

1. Introduction

Previous research indicates that psychopathy as indexed by Hare's (1991, 2003) Psychopathy Checklist-Revised (PCL-R) encompasses two distinguishable symptomatic components (factors)—emotional detachment and antisocial deviance (cf. Hare et al., 1991; Patrick et al., 1993)—that can be further partitioned into affective, interpersonal, lifestyle, and behavioral facets (Cooke and Michie, 2001; Hare, 2003; Hare and Neumann, 2005; Vitacco et al., 2006). In contrast with healthy controls, high psychopathic individuals appear deficient in the capacity to form appropriate associations between a cue and an aversive (Hare et al., 1978; Flor et al., 2002) or fear-evoking event (Patrick et al., 1994; Birbaumer et al., 2005)—despite intact cognitive processing of stimuli (Flor et al., 2002; Birbaumer et al., 2005; Kiehl, 2006).

In healthy individuals, aversive or threatening cues result in the mobilization of defensive actions, which can be measured by fear-associated responses such as the startle reflex that increase during presentation of aversive stimuli (Davis, 1989; Lang et al., 1990; Patrick et al., 1996). In psychopathic individuals, who are theorized to lack the ability to anticipate and learn from punishment (Lykken, 1957; Hare and Quinn, 1971; Hare et al., 1978; Veit et al., 2002; Blair, 2004; Birbaumer et al., 2005; Mitchell et al., 2006), the fear-associated startle reflex has been found to be diminished or absent (Patrick et al., 1993; Levenston et al., 2000; Pastor et al., 2003; Benning et al., 2005). Startle potentiation in response to aversive events (Davis, 1992; Angrilli et al., 1996; Pissiota et al., 2003) as well as an anticipatory skin conductance response (Bechara et al., 1999) are known to be mediated by amygdalar connections, suggesting a deficit in the amygdala or affiliated structures in psychopathic individuals. Consistent with this, recent imaging studies have revealed reduced activity in limbic circuits including the amygdala in individuals with psychopathy (Kiehl et al., 2001; Birbaumer et al., 2005; Mitchell et al., 2006). Other imaging work focusing on functional or structural frontal brain abnormalities has yielded evidence of decreased activity in orbito-frontal and limbic regions (Veit et al., 2002; Birbaumer et al., 2005) and reduced prefrontal volume of gray matter (Raine et al., 2000; Yang et al., 2005), indicating decreased activity in emotion processing circuits in high psychopathic individuals.

In contrast with these apparent deficits, cognitive processing of affective stimuli in psychopaths appears to be intact as

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demonstrated by studies showing overactivation in frontotemporal areas (Kiehl et al., 2001) and an enhanced P300 brain response at frontal electrode sites (Flor et al., 2002). Taken together, these findings support the theory of psychopathy as involving a specific type of emotional dysfunction as proposed by Blair (2004). According to Blair's model, altered activation in the amygdala as well as the ventrolateral and orbitofrontal cortex leads to deficiencies in basic emotional activation to stimuli that have motivational significance (cf. Lang et al., 1997). The cognitive evaluation of stimulus contingencies, however, should be unimpaired.

Newman et al. (1997) proposed the response modulation model which posits that psychopaths' deficient emotional responses may be a consequence of a dysfunction in attentional control. According to this model, the processing of emotional information is proposed to be diminished in situations where this information is not necessary for the ongoing task, resulting in differences between psychopaths and healthy controls that have been misinterpreted as innate fearlessness in psychopaths. An advantage of this model is that it yields testable hypotheses on the influences of situational variables on task performance (Newman et al., 2010). Empirical support for the model comes from studies reporting reduced interference in psychopaths in the Stroop task under certain conditions (e.g., Blair et al., 2006), which is not readily explained by models based on emotion dysfunction (Blair et al., 2005). However, the specific reduction of interference in certain Stroop test paradigms has been identified as a challenge to Newman's response modulation model (Blair and Mitchell, 2009). In addition, the ability of this model to accommodate other empirical findings of psychopathy remains a topic of debate (Blair and Mitchell, 2009).

In a previous conditioning study (Flor et al., 2002) we used aversive odors rather than painful stimulation in studying evoked responses and peripheral psychophysiological responses in psychopaths. However, this was not a true fear conditioning study, as unpleasant odors may evoke disgust rather than fear and may be more related to activations of the anterior insula and the anterior cingulate cortex (Wicker et al., 2003). For the study of fear conditioning, a painful electric shock has traditionally been used as an unconditioned stimulus (Hamm and Weike, 2005). However, findings on altered pain perception in psychopaths have been mixed, with a heightened threshold for pain reported in one study (Fedora and Reddon, 1993), but not in others (e.g., Hare, 1968). In a follow-up functional magnetic resonance imaging (fMRI) study that used painful shock as the unconditioned stimulus (US) Birbaumer et al. (2005) found a lack of conditionability in high psychopathic individuals along with deficient activation of a frontolimbic circuit comprising the orbitofrontal cortex, the amygdala, the insula, and the anterior cingulate cortex, in conjunction with regional activations indicating normal perception of the US.

The purpose of the present study was to examine peripheral and central correlates of fear conditioning in high psychopathic individuals using the same unconditioned and conditioned (CS) stimuli (i.e., painful shock and neutral face images) that were used in the aforementioned fMRI study. Since in that study, the processing of the CSs and the US as well as the processing of CS-US consistency did not seem to be compromised in psychopathic individuals, we hypothesized that psychopathic participants would show intact information processing as indexed by normal event-related potential (ERP) responses to the CS and US, as well as contingency ratings comparable to those of control subjects. The ERP components investigated in the current study were based on our previous conditioning study (Flor et al., 2002): there, the N100 component showed significant CS+/CS− differentiation in individuals with psychopathy, but not in the healthy controls, during periods of the acquisition phase. The psychopathic group also displayed an increased P200 amplitude to the CS+ during the acquisition phase, which is considered to reflect increased stimulus intake (Siegel, 1997). This pattern of results was interpreted as evidence for a specific emotional deficit in psychopathy, unrelated to alterations in attentional processing. The P300 response, which has been found to be enhanced in amplitude for psychopaths in some studies (Raine, 1992) and decreased in others (Kiehl et al., 1999a), displayed differential conditioning in frontal regions only, supporting the assumption that attentional processing in frontal areas is intact in psychopathic individuals (Kiehl et al., 1999b). One additional brain potential response that is known to reflect stimulus expectancy (Rosahl and Knight, 1995; Mnatsakanian and Tarkka, 2002), the contingent negative variation (CNV) has been shown to be altered in psychopaths during anticipation of aversive stimuli (Forth and Hare, 1989). Since the initial and terminal components of the CNV (iCNV, tCNV) differed between the groups and across phases in our previous study, we examined these components separately in the current study. Also, as in Flor et al. (2002), we investigated the late positive complex (LPC), which prior has shown to differentiate the reactions of psychopathic subjects and healthy controls to affective stimuli versus neutral (e.g., Williamson et al., 1991; Kiehl et al., 1999a,b).

At the same time, in line with the results of Flor et al. (2002), we hypothesized that psychopathic participants would show deficient emotional conditioning as indexed by a failure to differentiate between CS+ and CS− in valence and arousal ratings. We further hypothesized a lack of differentiation in response to CS+ versus CS− for startle potentiation, corrugator EMG reactivity, heart rate (HR), and skin conductance response (SCR), and in anticipation of US delivery for CNV. Regarding skin conductance, we hypothesized a lack of responsivity in the psychopathy group on the basis of prior findings (Hare and Quinn, 1971; Flor et al., 2002), but not necessarily in conjunction with altered self-reported arousal ratings as would be expected for healthy controls (Flor et al., 2002; Cleckley, 1955). The hypothesized lack of startle potentiation to the CS is considered to be a more specific indicator of impaired defensive activation than lack of SCR differentiation (Lang et al., 1990) and has been demonstrated specifically in relation to the emotional detachment ('Factor 1') component of psychopathy (Patrick, 1994). In the case of HR, our previous results contradicted earlier findings (e.g., Hare and Craigen, 1974; Hare et al., 1978), precluding clear a priori hypotheses.

2. Methods

2.1. Participants

Eleven psychopathic men (PPs) with prior criminal records and 11 healthy male controls (HCs) participated in the study. The PPs consisted of offenders either on bail and awaiting trial or on parole who were selected from a larger sample on the basis of scores on a screening version of the PCL-R (PCL-SV; Hart et al., 1995). The control subjects were recruited by signs posted in the university and local supermarkets. Exclusion criteria for the study were as follows: (a) age below 18 or over 45, (b) left-handedness, (c) history of cardiovascular or mental disorder, (d) history of drug or alcohol dependence, and (e) intake of alcohol or drugs within the previous 12 h. The mean age was 31 years ($SD = 6.4$, range = 22–40) for the PPs and 28 years ($SD = 6.7$, range = 22–43) for the HCs ($t(20) = 1.2$; n.s.; $d = 0.54$). The groups were matched in terms of employment status (categories: unemployed, employed, training/apprenticeship and student; $Z = -0.92$; n.s.). Procedures for the study were approved by the local Human Subjects Committee and adhered to the Human Subjects Guidelines of the Declaration of Helsinki. All participants were informed about the nature of the study and provided written informed consent prior to participation. The psychopathic participants received 80 Euros, and the controls 40 Euros, for their participation.

The overall mean PCL-SV score for individuals screened for inclusion in the PP group was 15.45 ($SD = 2.54$; range = 12–21), with Ms of 9.55 ($SD = 1.29$; range = 8–12) for Factor 1 and 5.90 ($SD = 1.81$; range = 2–9) for Factor 2. Subjects with Factor 1 scores of 8 or higher were included in the PP group, without regard to scores on Factor 2. We emphasized Factor 1 of the PCL-SV (Emotional Detachment) in the selection of participants over Factor 2 (Antisocial Behavior) because (a) scores on Factor 1 are more predictive of deficits in emotional reactivity (e.g., Patrick, 1994; Verona et al., 2004; Vanman et al., 2003; Vaidyanathan et al., 2011), and (b) scores on Factor 2 were expected to be generally lower for non-incarcerated individuals with criminal records than for incarcerated offenders. Control subjects had an overall

Table 1
Comparison of PPs and HCs with respect to US characteristics prior to the experiment.

US characteristic	PPs *M* (*SD*)	HCs *M* (*SD*)	*t*-Value	*p*-Value
Stimulus intensity	4.83 (2.82)	4.47 (1.96)	0.34	ns
Sensory threshold	2.87 (2.07)	2.65 (1.82)	0.25	ns
Pain threshold	4.31 (2.74)	3.89 (1.81)	0.41	ns
Pain tolerance	5.33 (2.82)	4.90 (2.09)	0.40	ns

Note: Units of measurement for all stimulus characteristic values are mA.

score of 2.09 (*SD* = 1.14; range = 1–4) on the PCL-SV, with values of 0.64 (*SD* = 0.67; range = 0–2) for Factor 1 and 1.45 (*SD* = 1.13; range = 0–4) for Factor 2.

Individuals screened for inclusion in the PP group were administered the full PCL-R at the time of testing, along with the German Version (Margraf et al., 1991) of the Anxiety Disorders Interview Schedule (ADIS, Di Nardo et al., 1983; Barlow et al., 1986), which assesses for symptoms of anxiety disorders and related diagnostic conditions. The mean overall PCL-R score for the PP group was 24.7 (*SD* = 4.45; range = 15–31), which is lower than values typically reported for high-psychopathic samples in American studies, but in the high-psychopathic range according to the German norms for the PCL-R (Ullrich et al., 2003). Importantly, all individuals in the PP group received scores of 10 or higher on Factor 1 of the PCL-R (*M* = 12.0; *SD* = 1.1; range = 10–14), which approximates 2/3 of the maximum possible score of 16. Scores on PCL-R Factor 2 were generally lower (*M* = 8.7; *SD* = 3.26; range = 3–13). Nonetheless, all individuals in the PP group met full criteria for a diagnosis of antisocial personality disorder according to DSM-IV-TR criteria (American Psychiatric Association, 2000).

All participants also completed the German version of the Positive and Negative Affect Schedule (PANAS, Watson et al., 1988). The groups did not differ on the Positive Affect scale of the PANAS [$t(20) = 0.70$; n.s.; $d = 0.31$], but PPs scored significantly higher than HCs on the Negative Affect scale [$M_{PP} = 22.27$, $SD = 4.80$; $M_{HC} = 14.36$, $SD = 2.73$; $t(16) = 4.75$; $p < 0.001$; $d = 2.38$]. The PPs also scored significantly higher on the Sensation Seeking Scale [Zuckerman, 1984; $M_{PP} = 24.18$, $SD = 4.4$; $M_{HC} = 19.27$, $SD = 5.73$; $t(20) = 2.25$; $p = 0.04$; $d = 1.01$]. The two groups did not differ with respect to either state [$t(20) = 1.44$; n.s.] or trait anxiety [$t(20) = 0.75$; n.s.; $d = 0.34$] as measured by the German version of the State Trait Anxiety Inventory (STAI; Laux et al., 1981).

2.2. Experimental design

The design of the study closely resembled that used by Flor et al. (2002). The subjects participated in an aversive differential conditioning experiment, which lasted about 2 h. Two neutral faces (black and white, 18 cm × 23 cm) of a male person (Schneider et al., 1994) were presented on a PC monitor and served as CS+ (CS paired with US) and CS− (nonreinforced CS), respectively. CS+ and CS− were pseudorandomly presented with the constraint of a maximum of 3 consecutive presentations of each CS type. The type of face serving as CS+ or CS− was counterbalanced across subjects. For all phases of the experiment the mean intertrial interval (ITI) was 18 + 2 s. The CS was presented for 6 s, with the US occurring during the final 20 ms of the CS, such that the CS and US coterminated. The shock stimulus was a 20-ms bipolar electrical pulse delivered via an intracutaneous gold electrode placed on the left middle finger (Bromm and Meier, 1984). Stimulus intensity was adjusted on an individual basis through a pre-experimental procedure in which detection and pain thresholds were determined along with pain tolerance level. Stimulus intensity was chosen such that it was perceived as moderately painful. The PP and HC groups did not differ with regard to stimulus characteristics (Table 1).

The experiment was conducted in three phases. In an initial habituation phase, the subjects received 12 presentations of CS+, CS−, and US in random order. The acquisition phase consisted of 96 conditioning trials (48 CS+, 48 CS−). The CS+ was always followed by the aversive painful electric shock, whereas the CS− never was. The extinction phase comprised a total of 48 (24 CS+, 24 CS−) trials without US presentation. The startle stimulus consisted of a 50-ms, 95-dB broadband ("white") noise burst delivered binaurally through headphones. Six startle stimuli were presented during the habituation phase, two each during ITIs following each of the 3 stimulus categories (CS+, CS−, US). During acquisition, 12 startle stimuli were administered for each stimulus category, and during extinction, 8 were administered for each. For the CS, startle stimuli were presented randomly within 2–3 s after CS onset (Bradley et al., 1993). For the US, the startle stimulus occurred 150 ms after stimulus onset. Startle stimuli were presented during ITI periods in all three phases. The startle stimulus was presented at the earliest 4 s after CS offset and at the latest 4 s prior to CS onset.

Using an animated ratings display, the Self Assessment Manikin (SAM, Bradley and Lang, 1994), ratings of valence (from 1, indicating "pleasant" to 9, indicating "unpleasant") and arousal (from 1, indicating "arousing" to 9, indicating "calm") were obtained for the CSs and the US at mid-habituation, at the end of habituation, and after every 12th acquisition and extinction trial. In addition, subjects rated the CS-US contingency ("How likely is it that the electric stimulus will follow now?") on a visual analogue scale ranging from −100 (="US will absolutely certainly not follow") to +100 (="US will absolutely certainly follow") at these same points during the procedure.

2.3. Physiological recordings

Physiological data were sampled at a rate of 251 Hz in a continuous recording mode. Except for skin conductance sites, the skin at each electrode site was treated during the hookup process with alcohol and abraded with Omniprep paste or fine-grained sand paper to ensure electrode impedances below 5 kΩ. Integrated EMG activity was measured from the m. corrugator supercilii bilaterally and from the left m. orbicularis oculi, using the placement described by Blumenthal et al. (2005), to record 'frown' response and startle blink reflex, respectively. Signals were recorded using Coulbourn V75-01 bioamplifiers (Coulbourn Instruments, Allentown, PA, USA) set to a band width of 90–1000 Hz. Ag–AgCl electrodes (4 mm in diameter) filled with TECA electrolyte were used for the recordings. Skin conductance response (SCR) was recorded using 11 mm Ag–AgCl electrodes filled with KY jelly and placed on the thenar and hypothenar eminences of the non-dominant hand as described by Fowles et al. (1981). To record SCR, a Rimkus Medizintechnik bioamplifier (Rimkus Medizintechnik, Parsdorf, Germany) with a bandwidth of 0.25–10 Hz was employed. The electrocardiogram was recorded from electrodes placed bilaterally on the lower rib cage. Signal amplification was achieved by a neonatal monitor 303A (Biomedical Systems Inc.). R-waves were detected by a Schmitt trigger.

The electroencephalogram (EEG) was recorded from 9 scalp electrodes (F3, F4, C3, C4, P3, P4, Fz, Cz, Pz) positioned according to the International 10–20 system and referenced to linked mastoids, using Neuroscan SynAmps (Neuroscan, Neurosoft Inc., Sterling, VA, USA) DC amplifiers. The continuous EEG signal was filtered from DC to 30 Hz. The Electro-Cap System (Electro-Cap International Inc. [ECI], Eaton, OH, USA) with tin electrodes of 10 mm diameter filled with ECI electro gel was used. Horizontal and vertical electrooculographic activity was also recorded for purposes of ocular artifact correction.

2.4. Data reduction and analysis

2.4.1. Peripheral measures

A computer program developed by Globisch et al. (1993) was used for scoring the SCR. The conditioned SCR was defined as the maximum response in the time window from 1 to 4 s after CS onset (Prokasy and Kumpfer, 1973). SCR amplitudes below 0.05 μS were classified as zero responses. A log10(1 + SCR) transformation was employed to normalize the SCR data.

The same computer program used for SCR scoring (Globisch et al., 1993) was used to score startle eyeblink amplitude within a time window of 30–120 ms after the onset of the acoustic ("white noise") startle stimulus. The amplitude of the startle response was defined as the difference between the footpoint and peak of the blink response within the above-mentioned time window. Startle response latency was defined as the time between the onset of the startle stimulus and the footpoint of the startle blink. If a blink response was not evident during the scoring window, the value of the startle amplitude was set to zero.

For EMG, averages were computed for every 0.5 s of the 6 s CS presentation and for 1 s after CS offset, and these average values were baseline-corrected by subtracting from each the mean EMG activity level during the 1-s period preceding onset of the CS. Then, based on previous findings (Flor et al., 1996, 2002), the mean EMG level during the 500 ms preceding the onset of the US was defined as the conditioned response. The unconditioned response was defined as the mean EMG amplitude occurring in a time window of 1–1.5 s after US offset. For heart rate (HR), interbeat intervals were computed offline from the R-wave data and converted to beats-per-minute values for each 500 ms segment of the 3-s baseline preceding CS onset, the 6-s CS interval, and the 5-s recovery period following CS offset by weighting each beat according to the proportion of the interval it occupied. For statistical analysis, 1-s averages were computed for the 5 s of CS presentation prior to US delivery.

2.4.2. EEG activity

All data from trials in which EEG signal activity fell outside the measurement range of the amplifier (+200 mV) for more than 1 s were excluded. Eye movement correction was performed using the method described by Berg (1986). Analyses of N100, P200, P300, LPC, and CNV measures for the acquisition and extinction phases were based on the grand averages of all trials for each phase. ERP baseline correction was carried out using a baseline of 100 ms except for CNV, for which a baseline of 500 ms prior to CS onset was employed. N100, P200 and P300 peaks were identified by visual inspection within a time window of 80–180 ms (N1), 180–250 ms (P2), and 250–800 ms (P3) post-CS onset. iCNV was determined as the area under the curve during the time interval of 0.5–1.5 s following CS onset and tCNV was measured as area under the curve for the time interval of 5–6 s after CS onset.

2.5. Statistical analyses

Separate analyses were performed for each response parameter within each phase of the conditioning procedure. Unless otherwise specified, group (PP vs. HC) × CS type (CS+ vs. CS−) × time (block of trials) repeated measures ANOVAs were computed. Startle responses were analyzed by collapsing the responses for the CS+ and CS− during the acquisition and extinction into four and two trial blocks,

respectively. SCR was compared across 8 trial blocks during acquisition and 4 trial blocks during extinction. For corrugator and HR, the four blocks of trials during acquisition and the two during extinction were averaged. The seconds comprising the interval from CS onset to US onset were added as a Time factor into the analyses for corrugator and HR, and hence for these measures, 12 time points each comprising the four averaged trial blocks for acquisition and the two for extinction were analyzed. Otherwise, the first and second halves of the acquisition and extinction phases were compared. In addition to factors of Group, CS type, and Time, for the ERP components and slow cortical potentials, hemisphere (right vs. left) and topography (frontal vs. central vs. parietal) were included as additional within-subject factors in the repeated measures ANOVAs. Valence, arousal, and CS-US contingency ratings were analyzed across all 8 rating times during acquisition, across the 4 ratings obtained during extinction, and across the 2 ratings obtained during habituation.

For all analyses, a Greenhouse-Geisser correction was applied if the sphericity assumption was not met. In addition, unless otherwise noted, the level of significance for post hoc tests was Bonferroni-adjusted to yield a family-wise alpha level of $p = 0.05$. Demographic and questionnaire data for the two groups were compared using two-tailed t-tests for independent samples, or, where appropriate, Mann–Whitney U-tests. Effect sizes were calculated for all group comparisons between psychopaths and healthy controls, using Cohen's d for the calculation of effect size for independent t-tests and η^2 for multivariate comparisons. The SPSS software package was used for all statistical analyses.

3. Results

3.1. Ratings

3.1.1. Valence

During habituation, there were no significant group differences between PPs and HCs. CS+ and CS− were rated similarly in the two groups (Fig. 1). During acquisition, the valence ratings showed a significant main effect for CS type [$F(1,19) = 7.6$; $p = 0.01$; $\eta^2 = 0.23$], indicating successful CS+/− differentiation across both groups, and a significant Time effect [$F(7,133) = 5.9$; $p = 0.003$; $\eta^2 = 0.08$] indicating a general increase in unpleasantness ratings over trials. A significant CS type × Time interaction [$F(7,133) = 3.56$; $p = 0.03$; $\eta^2 = 0.05$] was also observed, indicating that ratings of CS+ versus CS− unpleasantness increased over time. No significant group [$F(1,19) = 3.05$; n.s.] or group-related interaction effects were evident during acquisition. During extinction, a significant CS type × Time interaction [$F(3,60) = 4.55$; $p = 0.01$; $\eta^2 = 0.04$] was found, indicating a decrease in CS+ unpleasantness ratings over time.

3.1.2. Arousal

During habituation, no significant differences between the two groups and no significant effect of CS type were observed, indicating similar initial levels of arousal for the two CSs in both groups (Fig. 1). During the acquisition phase, CS type became significant [$F(1,19) = 26.67$; $p < 0.001$; $\eta^2 = 0.22$], indicating CS+/− differentiation in both groups. There were no significant effects involving group during acquisition. During extinction significant CS type [$F(1,20) = 6.08$; $p = 0.02$; $\eta^2 = 0.01$] and CS type × Group × Time [$F(3,60) = 2.98$; $p = 0.04$; $\eta^2 = 0.01$] effects were found, reflecting a reduction in CS+/CS− differentiation in arousal ratings for the PPs (mean CS+ vs. CS−: $t(10) = 0.99$; n.s.; $d = 0.63$) compared to the HCs (mean CS+ vs. CS−: $t(10) = 2.61$; $p = 0.03$; $d = 1.65$) that became more pronounced over time.

3.1.3. Contingency

During habituation, none of the effects for contingency ratings reached significance, indicating equal US expectancy in the two groups. During the acquisition phase, a significant CS type effect [$F(1,19) = 421.81$; $p < 0.001$; $\eta^2 = 0.96$] was found, indicating overall good CS+/− differentiation. In addition, a significant CS type × Time interaction was evident [$F(7,133) = 6.46$; $p = 0.005$; $\eta^2 = 0.25$], indicating an increase in US expectancy to the CS+ and a decrease in US expectancy to the CS− across acquisition trials (Fig. 1).

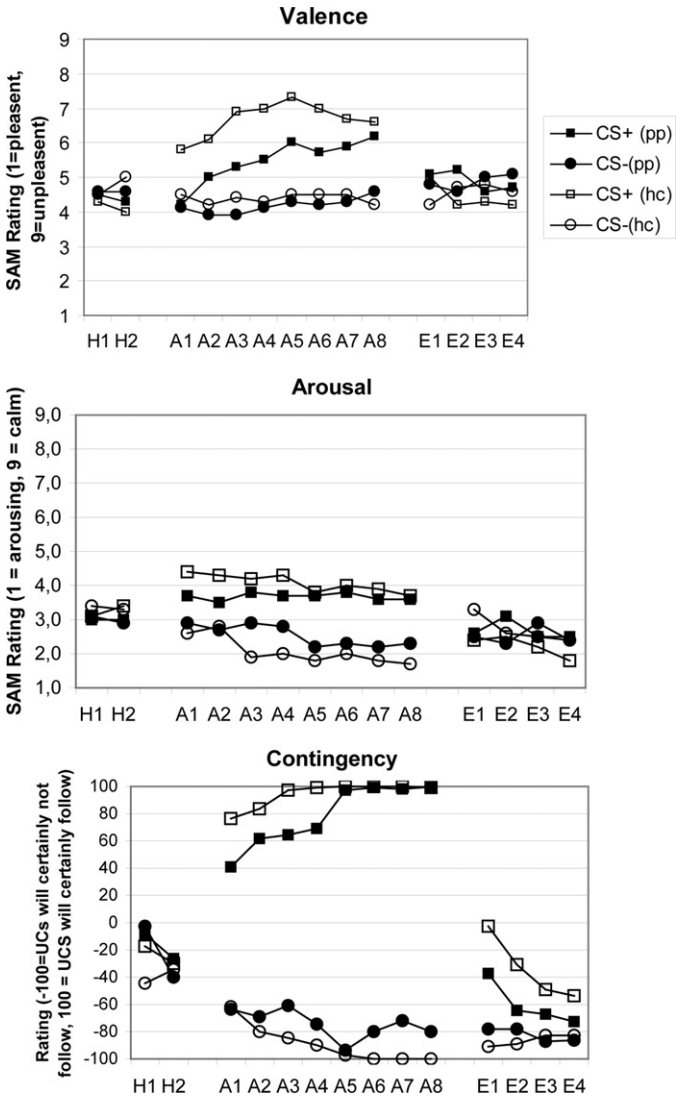

Fig. 1. Valence rating (SAM) for CS+ and CS− across all three experimental phases for the psychopaths (PP) and healthy controls (HC). During acquisition both groups differentiate the CS+/−. Ratings of CS+ unpleasantness increase significantly over time. Arousal rating (SAM) for CS+ and CS− across all three experimental phases for the psychopaths (PP) and healthy controls (HC). During the acquisition phase both groups differentiate the CS+/−. Contingency rating (SAM) for CS+ and CS− across all three experimental phases for the psychopaths (PP) and healthy controls (HC). During acquisition both groups differentiate the CS+/−. Furthermore, the US expectancy to the CS+ increases significantly over time whereas US expectancy to the CS− decreases over trial time.

3.1.4. Valence and arousal ratings of the US

The two groups differed with respect to valence ratings of the US during habituation [$F(1,20) = 4.67$; $p = 0.04$], indicating higher unpleasantness ratings of the US in the HCs although pain ratings did not significantly differ. No other group differences in valence or arousal ratings of the US or of non-painful electrical stimulation were evident during habituation, acquisition, or extinction.

3.2. EMG reactivity

3.2.1. Left corrugator

During habituation, no group or CS type effects were significant. During the acquisition phase, a significant CS type effect [$F(1,20) = 5.16$; $p = 0.03$; $\eta^2 = 0.04$] indicated overall successful CS+/− differentiation (Fig. 2). During extinction, a significant

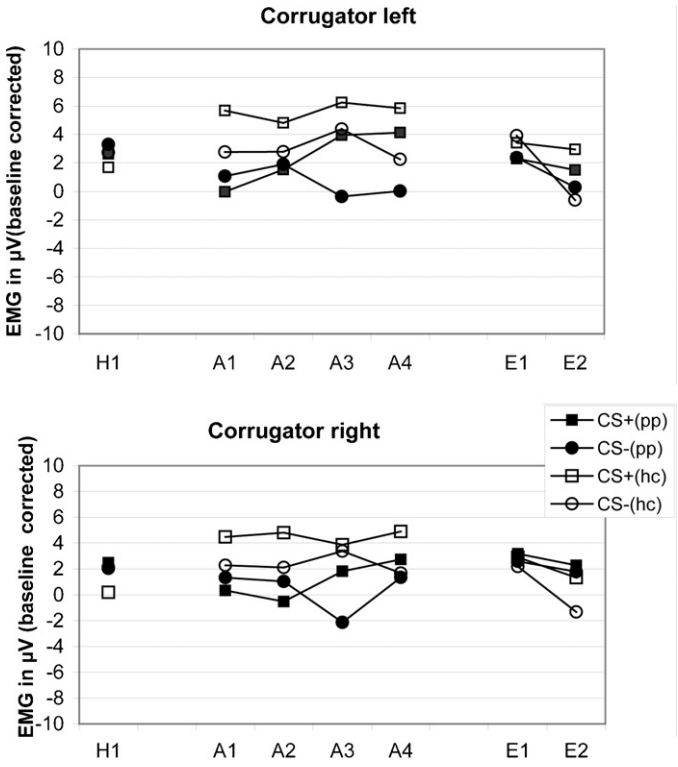

Fig. 2. Conditioned response of the left and right corrugator muscles for CS+ and CS− across all three experimental phases for the psychopaths (PP) and healthy controls (HC). During acquisition, the left corrugator indicates overall successful CS+/− differentiation.

CS type × Time interaction [$F(1,20) = 8.72$; $p = 0.008$; $\eta^2 = 0.04$] indicated a decrease in corrugator activity over trials.

3.2.2. Right corrugator

For the right corrugator, no significant group, time, or CS type effects were observed during the acquisition, habituation or extinction phases (Fig. 2).

3.3. Startle reflex modulation

During habituation, a significant group effect was observed [$F(1,20) = 6.25$; $p = 0.02$], indicating significantly higher startle amplitudes in the HC group to both CSs (CS+; HC vs. PP: $t(20) = -2.34$; $p = 0.03$; $d = -1.05$; CS−, HC vs. PP: $t(20) = -2.55$; $p = 0.02$; $d = -1.14$). During acquisition, significant group [$F(1,20) = 7.09$; $p = 0.02$] and CS type [$F(1,20) = 10.69$; $p = 0.004$; $\eta^2 = 0.03$] effects were found (Fig. 3). In addition, a significant CS type × Group interaction [$F(1,20) = 9.28$; $p = 0.006$; $\eta^2 = 0.03$] was evident, indicating a lack of emergence of startle potentiation for CS+ versus CS− in the PP group (all blocks of trials CS+ vs. CS−: n.s.) compared with robust potentiation in the control group (first block CS+ vs. CS−: $p = 0.05$, all other blocks $2.34 < t(10) < 3.20$; $0.01 < p < 0.04$). During the extinction phase, significant effects were evident for group [$F(1,20) = 4.76$; $p = 0.04$], CS type [$F(1,20) = 5.45$; $p = 0.03$; $\eta^2 = 0.02$], CS type × Time [$F(1,20) = 5.57$; $p = 0.03$; $\eta^2 = 0.01$], and Group × Time [$F(1,20) = 6.98$; $p = 0.02$; $\eta^2 = 0.03$], indicating a reduction in startle reactivity for the PPs (CS+: $M = 221.4$; $SD = 306.1$; CS−: $M = 182.8$; $SD = 266.5$) as compared to the HCs (CS+: $M = 557.5$; $SD = 413.7$; CS−: $M = 436.6$; $SD = 302.9$) that was especially pronounced in the first part of the extinction phase (Fig. 3).

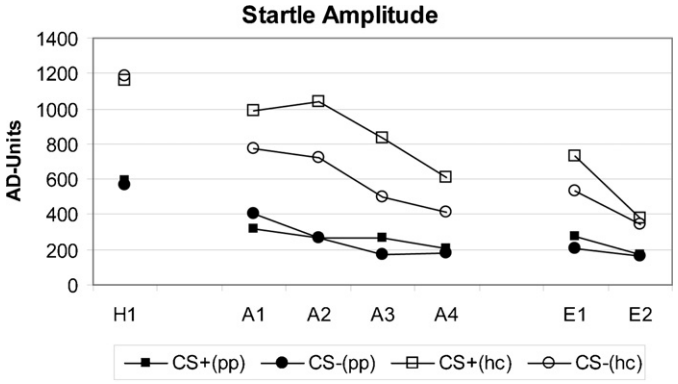

Fig. 3. Startle reflex amplitude (EMG activity of the left m. orbicularis oculi) for CS+ and CS− across all three experimental phases for the psychopaths (PP) and healthy controls (HC).

3.4. Skin conductance responses

During habituation, a significant group effect was observed [$F(1,20) = 8.39$; $p = 0.009$], with the PPs showing generally lower SCRs than the HCs. This group effect was also evident during acquisition [$F(1,20) = 14.54$; $p = 0.001$; see Fig. 4], along with a significant effect of CS type [$F(1,20) = 14.72$; $p = 0.001$; $\eta^2 = 0.18$], indicating robust CS+/− differentiation across groups. During the extinction phase, a significant group effect was also found [$F(1,20) = 5.68$; $p = 0.03$], again indicating generally lower SCR in the PPs than the HCs.

3.5. Heart rate

During the habituation phase, no significant effects were observed for HR. During the acquisition phase, a significant constant decline in HR level was evident from CS onset to CS offset, and from CS onset to US onset (linear trend $F(1,20) = 28.24$, $p < 0.001$; see Fig. 5). During the extinction phase, no significant CS type or Group effects were found.

3.6. Physiological responses to the US

Analyses evaluating group differences in responses to the US during the acquisition phase yielded a significant effect for the startle response only [HCs > PPs; $F(1,20) = 5.62$; $p = 0.03$]. No significant group difference in response to the US was evident for any other peripheral physiological measure or any rating measure (all n.s.).

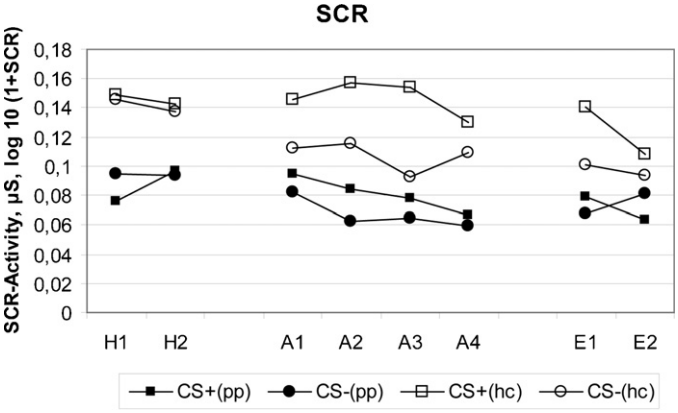

Fig. 4. Skin conductance response (SCR) for CS+ and CS− across all three experimental phases for the psychopaths (PP) and healthy controls (HC).

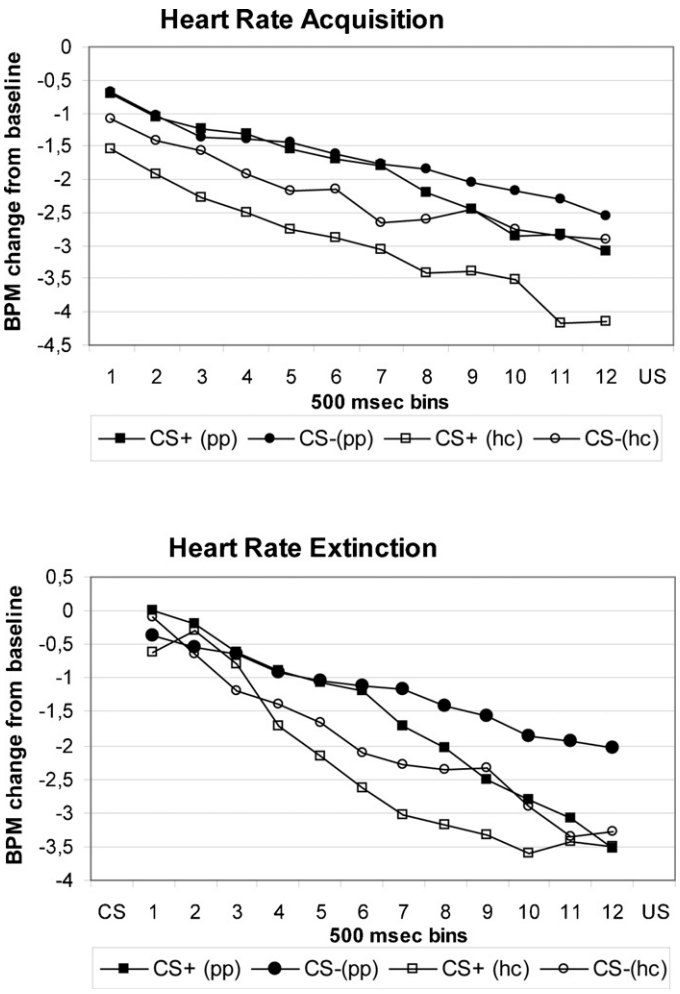

Fig. 5. Change in heart rate during the presentation of CS+ and CS− averaged across all acquisition trials and all extinction trials for the psychopaths (PP) and healthy controls (HC).

3.7. Event-related potential components

3.7.1. N100

During habituation, a significant effect was found for Location [$F(2,30) = 7.77$; $p = 0.007$; $\eta^2 = 0.12$]. In addition, significant CS type × Location × Group [$F(2,30) = 7.01$; $p = 0.003$; $\eta^2 = 0.06$] and Hemisphere × Location × Group [$F(2,30) = 3.51$; $p = 0.04$; $\eta^2 = 0.03$] interactions were found, along with a significant 4-way CS type × Hemisphere × Location × Group interaction [$F(2,30) = 4.27$; $p = 0.02$; $\eta^2 = 0.01$], indicating greater activity in the HC than the PP to the stimuli at central and parietal sites of the right hemisphere (Fig. 6). During acquisition, a significant group effect was observed [$F(1,16) = 10.51$; $p = 0.005$], indicating an overall lower N100 response in the PPs. During extinction, no significant effects for Group or CS type were observed.

3.7.2. P200

During habituation, no effects were significant. During the acquisition phase, significant effects were found for CS type [$F(1,16) = 7.96$; $p = 0.01$; $\eta^2 = 0.01$] and for CS type × Location × Group [$F(2,32) = 5.12$; $p = 0.02$; $\eta^2 < 0.01$], indicating larger P200 response to the CS+ in the PPs at frontal and central sites (Fig. 6). During the extinction phase, a significant CS type × Group effect was observed [$F(1,16) = 12.60$; $p = 0.003$; $\eta^2 = 0.02$], reflecting diminished P200 response to the CS+ versus the CS− in the PP group as compared to enhanced P200 for CS+ versus CS− for the HC group. In addition, a significant Time × CS type × Hemisphere × Group interaction was observed [$F(1,16) = 6.59$; $p = 0.02$; $\eta^2 < 0.01$], with the PPs showing enhanced P200 response to the CS− during the first block of extinction at frontal and central sites of the left hemisphere.

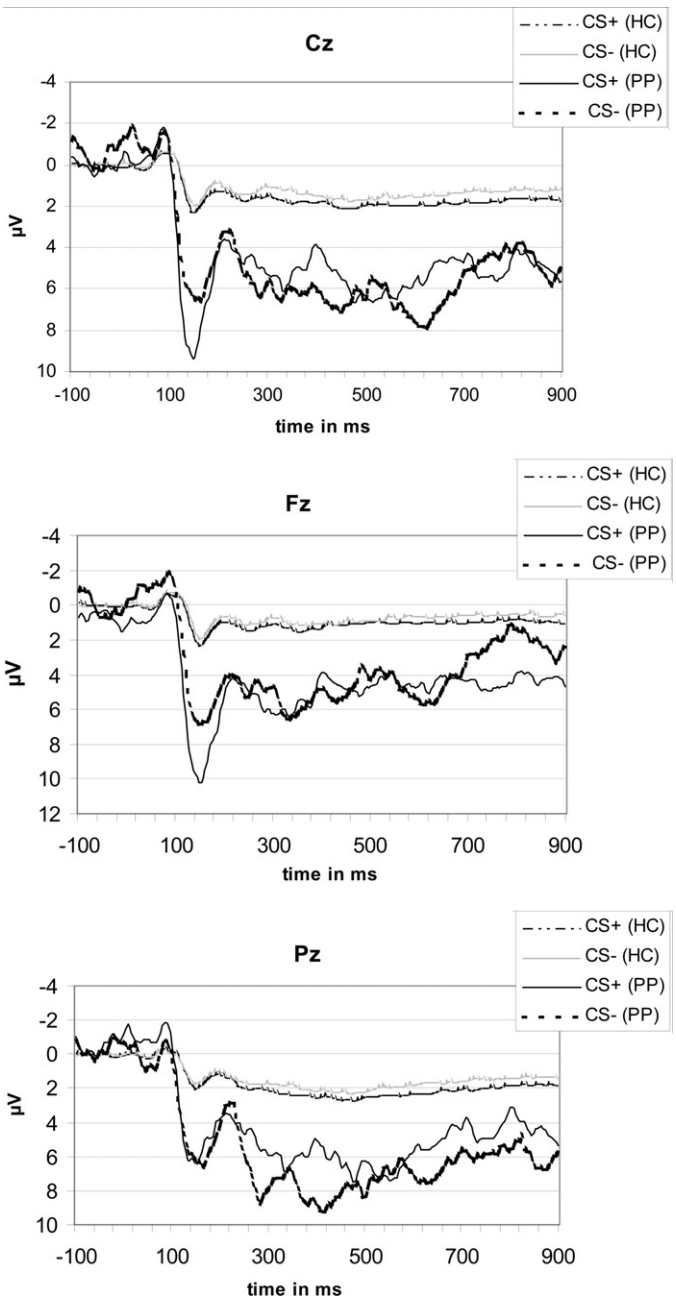

Fig. 6. Grand averages of event-related potentials (N100, P200, P300) of all acquisition and extinction trials from three electrode sites are shown for the psychopaths (PP) and the healthy controls (HC). CS onset starts at time zero.

3.7.3. P300

For the habituation phase, no significant effects were found for Group or CS type. During acquisition, significant main effects were observed for CS type [$F(1,16) = 5.2$; $p = 0.04$; $\eta^2 = 0.07$], indicating successful CS+/− differentiation, and for Hemisphere and Location, reflecting larger overall P300 amplitude in the right hemisphere and at central and parietal sites (Fig. 6). No significant effect involving group was observed during acquisition. During the extinction phase, Hemisphere [$F(1,16) = 7.7$; $p = 0.01$; $\eta^2 = 0.07$] and

Location [$F(1,16) = 6.3$; $p = 0.02$; $\eta^2 = 0.18$] were significant, indicating a larger P300 amplitude in the right hemisphere and at central and parietal sites. Significant interaction effects were not observed.

3.7.4. Contingent negative variation

3.7.4.1. Initial CNV (iCNV). No significant effects were observed during habituation. During the acquisition phase, a significant Time × CS type × Hemisphere × Group interaction was found [$F(1,12) = 9.11$; $p = 0.01$; $\eta^2 = 0.01$], reflecting a larger iCNV to the CS+ during the second block of trials at the left hemisphere in PPs. In addition, a significant Time × Hemisphere × Location × Group interaction was evident [$F(2,24) = 4.5$; $p = 0.02$; $\eta^2 = 0.02$], indicative of larger iCNV during the second block of trials at the left hemisphere at central and parietal sites in PP subjects. During extinction, no significant effects were found involving CS type or Group.

3.7.4.2. Terminal CNV (tCNV). During habituation, no effect reached statistical significance. During the acquisition phase, a significant Location × Group interaction was observed [$F(2,24) = 3.6$, $p = 0.04$; $\eta^2 = 0.10$], indicating a lower tCNV at frontal and a larger tCNV at central sites in the PP group as compared to the HC group. Results for the two groups were similar at parietal sites. During extinction, a significant Time × Group interaction was present [$F(1,12) = 9.15$; $p = 0.01$; $\eta^2 = 0.11$], indicating a larger tCNV during the second block of trials versus the first in PP compared with a smaller tCNV during the second block versus the first for HC.

3.7.4.3. Late positive complex (LPC; 300–400 ms after stimulus onset). During habituation, no significant effect was observed for Group or CS type. During the acquisition phase, a significant main effect was found for CS type [$F(1,16) = 5.68$; $p = 0.03$; $\eta^2 = 0.08$], along with a significant CS type × Time × Location interaction [$F(2,32) = 3.86$; $p = 0.03$; $\eta^2 = 0.01$], indicating a larger LPC to the CS+ during the first part of the acquisition phase at central and parietal sites. During extinction, no significant effects were found for Group or CS type. However, main effects of Hemisphere and Location were evident, indicating increased reactivity in the right hemisphere at central and parietal sites.

4. Discussion

This study used peripheral measures, subjective ratings, and ERP components to investigate aversive fear conditioning in high psychopathic individuals. The results confirm that psychopaths are deficient in fear-conditioning as previously suggested (Lykken, 1957; Hare and Quinn, 1971; Hare et al., 1978; Veit et al., 2002; Birbaumer et al., 2005). The PP group showed associative learning deficits as indexed by a lack of differential startle response, lack of increased skin conductance, and a lack of increased corrugator activity to the CS+. These deficits do not appear to be attributable to insufficient evaluation of or reactivity to the noxious US stimulus itself, as indicated by a lack of significant group differences in valence and arousal ratings of the US, and SCR, HR, and corrugator responses to the US in the learning phase. Notably, the groups did differ (PP < HC) with respect to startle blink reactivity to the US during acquisition. However, a parallel group difference (PP < HC) in blink reactivity to startle noise stimuli was evident across habituation, acquisition, and extinction phases—indicating a group difference in general startle reactivity across varying conditions of the experiment. This group effect might conceivably reflect a difference in contextual fear related to the occurrence of shocks within the experimental situation (cf. Grillon and Davis, 1997), given that differences in general startle reactivity have not been reported for high versus low psychopathic groups in simple picture-viewing studies (e.g., Levenston et al., 2000; Patrick et al., 1993; Vanman et al., 2003).

In contrast with previous findings indicating higher levels of pain tolerance in high and low psychopathic prison inmates compared to normal controls (Fedora and Reddon, 1993), we found no difference between PP and HC groups in pain tolerance or pain threshold associated with the US. We also found no difference between PPs and HCs with respect to detection threshold for electric shock, which is consistent with findings reported by some previous investigators (Fedora and Reddon, 1993) but not others (e.g., Hare, 1968). However, we did find a group difference (PP < HC) with respect to valence ratings of the US during habituation suggesting that the same level of painful experience was viewed as less unpleasant in the PP.

Attentional processing of the conditioned stimuli as indexed by the P200, the P300, and also the anticipation-related CNV appeared equal or superior in the PP group. Contrary to our previous results (Flor et al., 2002), the initial CNV component indicated superior left-lateralized CS-type processing in PPs as compared to HCs. The terminal CNV, however, showed a lower magnitude at frontal and a larger magnitude at central sites in the PPs as compared to the HCs. Based on findings from neuroimaging studies, an explanation for the lower activity at frontal electrode sites in the PPs may be reduced activity in the limbic-prefrontal circuit (Birbaumer et al., 2005) associated with reduced volume in prefrontal gray matter (Yang et al., 2005).

Similar to our previous results (Flor et al., 2002), arousal ratings data indicated expected CS+ and CS− differentiation in both groups. In parallel with this, but in contrast with our earlier results indicating impaired CS+/− differentiation in the PPs (reflecting evaluation of the CS− as more aversive compared with the HCs; Flor et al., 2002), results for valence ratings suggested comparable CS+/− differentiation in both groups. However, a direct comparison of results across the current and earlier studies is complicated by the fact that different stimulus modalities (odor vs. electric shock) and different trial times (10 vs. 8 acquisition blocks) were used in the two studies. Unpleasantness ratings for the CS+ increased in both groups from the first to the second half of the acquisition phase. In addition, consistent with prior results (Birbaumer et al., 2005), contingency ratings evidenced a significant CS type effect with no significant group difference. Also in accordance with previous results (Hare and Quinn, 1971; Herpertz et al., 2001; Flor et al., 2002; Pastor et al., 2003; Benning et al., 2005; Birbaumer et al., 2005), skin conductance response was generally smaller for PPs as compared to HCs, and as reported earlier (Flor et al., 2002), did not relate to arousal ratings, which were similar in both groups.

Notably, in accordance with previous work (Flor et al., 2002), right corrugator EMG activity and startle reflex amplitude showed a lack of CS+/CS− differentiation in the PP group. This pattern of results provides further support for the hypothesis of impaired emotional learning capacity in psychopaths. The current data also coincide with results from neuro-imaging studies demonstrating reduced activation of the amygdala (Kiehl et al., 2001; Birbaumer et al., 2005; Most et al., 2006; cf. Kiehl, 2006) and orbitofrontal cortex (OFC) during affective stimulus processing in psychopaths (Birbaumer et al., 2005). In view of evidence that intact amygdala function is crucial for developing anticipatory SCRs (Bechara et al., 1999) and that amygdala-OFC interaction is crucial for encoding expected outcomes during learning (Schoenbaum et al., 1998), our data provide further evidence that high psychopathic participants learn some of the CS-US association without processing the emotional significance of stimuli, as demonstrated by deficient anticipatory SCR and a failure to exhibit enhanced startle reactivity over the course of acquisition or during extinction.

In contrast with SCR and startle, HR did not differentiate between CS+ and CS− in either group during acquisition or extinction. This result matches with our previous report (Flor et al., 2002), although not with earlier work demonstrating enhanced HR acceleration during anticipation of aversive stimuli in psychopaths (cf. Hare and Craigen, 1974; Hare et al., 1978). Consistent with previous results (Levenston et al., 2000), a trend toward greater HR orienting to the CS was evident for PPs compared with HCs (Fig. 5), but this effect was not significant. Overall, in accordance with previous reports showing HR deceleration in response to pictures of facial expressions (Dimberg et al., 1986), HR decelerated as a function of time in both groups during acquisition.

In contrast with observed deficits in emotional stimulus processing, cognitive functions in the PP group appeared to be intact as suggested by differential contingency ratings for CS+ versus CS−, and equal or superior magnitudes of P200, P300, CNV, and LPC responses. Similar to our previous results (Flor et al., 2002), PPs exhibited increased P200 amplitude to the CS+ at frontal and central sites, which is in accordance with the literature indicating increased amplitude of this component as a function of stimulus intensity (Blenner and Yingling, 1994; Kiehl, 2006) and stimulus valence (Montoya and Sitges, 2006). However, PPs and HCs did not differ with respect to P300 in the current study. The literature concerning the P300 component in psychopaths is notably inconsistent. Whereas some studies have reported enhanced P300 amplitude in high psychopathic individuals (Raine and Venables, 1988; Raine, 1989, 1992; Flor et al., 2002), others have reported reduced P300 values (Kiehl et al., 1999a, 2000, 2006) or no difference between psychopaths and non-psychopaths (Jutai et al., 1987). However, these studies did not investigate aversive conditioning in psychopaths, but rather attention, orienting, and information processing using procedures such as go/no-go tasks, visual oddball paradigms, etc.

Contrary to previous results (Raine et al., 1990; Flor et al., 2002), N100 amplitude in the current study was significantly smaller in the PPs as compared to the HCs, suggesting some reduction in attentional processing in the PP group. However, in line with previous research results (Forth and Hare, 1989; Raine et al., 1990), the initial CNV to the CS+ (also known to reflect arousal and recruitment of attention) was found to be larger for PPs during the second block of trials in the left hemisphere at central and parietal sites, whereas HCs showed a larger iCNV to the CS+ during the first block of trials in the right hemisphere at central and parietal sites. In addition, the terminal CNV was found to be smaller at frontal and larger at central sites in PPs as compared to the HCs. Notwithstanding these effects, CS differentiation was similar in both groups.

The lower deflection of the tCNV at frontal sites for PPs is in accordance with results from imaging studies suggesting decreased activity in orbitofrontal cortex (Veit et al., 2002; Birbaumer et al., 2005) and reduced prefrontal volume (Raine et al., 1997, 2000; Yang et al., 2005) in psychopathic individuals. Evidence from combined EEG and fMRI studies points to the bilateral thalamus, anterior cingulate, and supplementary motor cortex (SMA) as generators of the CNV (Nagai et al., 2004), with the late component of the CNV maximal at the vertex as seen in the present study. This later component appears to be reflective of motor preparation (Birbaumer et al., 1990), whereas the earlier CNV appears to be more related to attentional processes and an anticipatory orienting response to the stimulus (Nagai et al., 2004). Related to this, the late positive complex (LPC), another component known to be associated with orienting, attention, stimulus evaluation, and memory (Courchesne et al., 1975; Donchin et al., 1984; Knight, 1996), was similar in both groups during acquisition. Both groups showed successful CS+/− differentiation in the LPC, indicating no difference in attention and orienting response between PPs and HCs. Taken together, these data suggest that attentional orienting as indexed by the CNV and LPC is undisturbed in psychopaths. However, it appears that the emotional modulation of these cognitive processes is disturbed, as evidenced by down-regulated activity in frontolimbic circuits among psychopaths. As a final point, in accordance with previous results (cf. Hare, 1998; Flor et al., 2002), ERP findings as a whole indicated superior right-hemisphere processing in psychopaths.

A recent study (Newman et al., 2010) demonstrated that, in psychopaths, the focus of attention modulated the startle response in an instructed fear paradigm. Specifically, participants in this study were instructed that red letters might be followed by an aversive electric shock, whereas green letters would not. Participants' attention was either focused on the threat information (pressing a key depending on the color of the letter) or on threat-irrelevant information (pressing a key depending on the letter being upper or lower case). Psychopathic individuals had a normal startle response in the threat-focused condition but a diminished one in the non threat-focused condition. Hence, the conditioning deficits documented previously in psychopathic individuals may be indicative of an attentional processing anomaly rather than a general fear deficit (cf. Newman et al., 1997). At first sight, these results seem to contradict the findings of the present study, which proposes frontolimbic deficiencies as the origin of deficient conditioning. However, it is conceivable that these divergent findings may reflect the use of quite different paradigms. In Newman et al.'s study, as described above, the instruction already contained explicit information about CS-US contingency. In the study described here, this connection had to be learned implicitly by the participants. This, combined with the finding that reactions to the US did not differ between PPs and HCs (with the exception of startle response), leads to the assumption that the PPs are deficient in their ability to connect emotionally relevant information, especially during an implicit learning process.

Additionally, Newman et al. (2010) pointed out that evidence for amygdala dysfunction may vary depending on the attentional requirements of a task procedure. In the current conditioning task, we observed equal or even better attentional processing as indicated by P200, P300 and CNV in the PP group compared to the healthy controls. Thus, we assume that our results are not influenced by differential attentional processes. The findings reported by Newman et al. may be a special case of attentional processing in psychopaths, elicited in a specific experimental setting. Accordingly, the question of attentional deficits in psychopaths thus warrants further investigation.

This study has some limitations that should be acknowledged. First, the number of participants was relatively small due to the fact that German law does not permit the study of incarcerated subjects. Although significant effects in line with prediction were obtained, replication with larger samples is needed to establish the generalizability of these effects. Additionally, the possibility that group differences may be due at least in part to differing prior experiences with painful stimuli for PPs as compared to HCs, leading to differing degrees of habituation to such stimuli, cannot be completely ruled out. In addition, intelligence was not assessed in the current sample, raising the possibility that this variable might have affected conditioning performance. One further limitation is that variations in incarceration experience were not systematically assessed, precluding us from evaluating possible effects of this variable on conditioning performance. Nonetheless, the findings of this study add to a growing body of data indicating that the syndrome of psychopathy entails basic deficits in emotional processing that are not readily attributable to cognitive or attentional impairments. Further research aimed at clarifying the precise neural bases of these emotional processing deficits is needed to advance conceptual understanding of this disorder and perspectives on effective prevention and treatment.

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