



## Amygdala functioning during threat acquisition and extinction differentiates antisocial subtypes

Kostas A. Fanti<sup>1\*</sup> , Katerina Konikou<sup>1</sup>, Moran Cohn<sup>2</sup>,  
Arne Popma<sup>2,3</sup> and Inti A. Brazil<sup>4,5,6,7</sup>

<sup>1</sup>University of Cyprus, Nicosia, Cyprus

<sup>2</sup>VU University Medical Center, Amsterdam, The Netherlands

<sup>3</sup>Leiden University, Leiden, The Netherlands

<sup>4</sup>Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands

<sup>5</sup>Division Diagnostics, Research & Education, Forensic Psychiatric Centre Pompestichting, Nijmegen, The Netherlands

<sup>6</sup>Collaborative Antwerp Psychiatric Research Institute, University of Antwerp, Belgium

<sup>7</sup>Centre for Advances in Behavioural Science, Coventry University, UK

Extensive work implicates abnormal amygdala response during threatening stimuli in youth with antisocial behaviour. However, no research has examined whether youth identified in Primary and Secondary psychopathy subtypes would show differences in amygdala activity in response to threat acquisition and extinction. Latent profile analysis (LPA) was used to identify distinct antisocial groups based on participants' scores on callous–unemotional (CU) traits, anxiety, and familial abuse in a sample of 136 high-risk adolescents (mean age = 17.7, *SD* = 1.6; 86% male). Functional MRI was then used to assess amygdala activation patterns during a classical differential delay threat-conditioning task. In addition to the Primary and Secondary subtypes, we identified groups mainly high on anxiety and others who were mainly high on abuse. Participants in the Primary group showed lower right amygdala activity in response to neutral male faces compared to the low, Anxious, and Secondary groups, whereas participants in the group with history of abuse exhibited higher right amygdala activity during threat acquisition compared to the rest of the groups. During threat extinction, the Primary group showed lower right amygdala activity compared to the Secondary and abuse groups. This is the first study to reveal amygdala activation in identified psychopathy-related variants during threat conditioning. We found that stratifying the sample based on the identified variants revealed amygdala functioning patterns that furthered our understanding of emotion-based deficits among high-risk adolescents.

Antisocial behaviour is a worldwide phenomenon characterized by persistent displays of defiant behaviour, aggression, and disregard for the emotions of others (Hinshaw & Lee, 2003). Influential theories, starting from Karpman's theory (1941, 1948), suggest that individuals with persistent antisocial behaviour and psychopathic characteristics can be

\*Correspondence should be addressed to Kostas A. Fanti, Ph.D., Department of Psychology, University of Cyprus, P.O. Box 20537, CY 1678 Nicosia, Cyprus (email: kfanti@ucy.ac.cy).

divided into those with Primary (i.e., low anxiety and low emotional reactivity) and Secondary (i.e., high anxiety and emotional hyper-reactivity) psychopathy. The two subtypes are also differentiated on environmental experiences, with individuals in the Secondary subtype experiencing familial abuse and maltreatment. In the last decade, research has verified these subtypes among antisocial youth based on different risk factors, such as callous–unemotional traits (CU: lack of empathy or remorse and blunted affect), which is associated with the affective dimension of psychopathy, anxiety, and history of abuse (Cicchetti & Toth, 2014; Fanti & Kimonis, 2017). Moreover, neuroimaging studies have started to provide empirical evidence for deficient amygdala activation in response to threat conditioning among youth and adults with CU and psychopathic traits (Birbaumer *et al.*, 2005; Cohn *et al.*, 2013; Raine & Yang, 2006). However, the limited neuroimaging studies comparing adults identified in Primary and Secondary subtypes provide contradicting findings in terms of their amygdala responsiveness to threat detection (Schultz, Balderston, Baskin-Sommers, Larson, & Helmstetter, 2016; Van Honk & Schutter, 2006). Accordingly, the current study was focused on laying a foundation for differentiating the amygdala abnormalities underlying threat conditioning between Primary and Secondary variants within a sample of youth at risk of antisocial development (Van Domburgh, Vermeiren, Blokland, & Doreleijers, 2009).

Threat conditioning generally describes a learning strategy for predicting danger from previous experiences (Dayan & Niv, 2008). Standard learning paradigms use aversive events to study phases during which associations with threats are learned (i.e., threat acquisition) and are unlearned (i.e., threat extinction). During threat acquisition, contingencies are learned when a neutral stimulus becomes a conditioned stimulus (CS+) through its association with an unconditioned stimulus (US, e.g., electric shock). During threat extinction, responses to the CS+ decline following its presentation without the US. The amygdala is a brain structure that is hypothesized to play a critical role in threat conditioning (Davis, 1992). Neuroimaging studies have repeatedly shown that amygdala activity is observed during the early stages of conditioned threat acquisition (Büchel & Dolan, 2000; Labar, Gatenby, Gore, LeDoux, & Phelps, 1998), with lesioning or pharmacological disruption of the amygdala interfering with threat conditioning (Kim & Jung, 2006). Also, extinction processes during associative emotional learning tasks were found to engage activation of the amygdala/periamygdaloid cortex (Labar *et al.*, 1998). These findings led to a number of studies investigating associations between amygdala structure and activity with psychopathic traits to understand deficits in learning from aversive events, observed in antisocial individuals (for a review, see Hoppenbrouwers, Bulten, & Brazil, 2016).

In the case of recognizing and processing threatening events, it is necessary to keep in mind that youth samples may differ from adult populations in their cognitive and affective abilities, and that these differences may have a significant impact on neural activation. Marsh *et al.* (2008) found that youth with psychopathic traits have reduced amygdala responsiveness to distress cues. In at-risk adolescents, a more recent fMRI study showed increased activation of the threat circuit in response to conditioned shocks, which was positively associated with impulsive traits yet negatively associated with CU traits (Cohn *et al.*, 2013). Regarding threat extinction, one neuroimaging study found hyper-activity of the threat circuit in the brain during extinction learning (Cohn *et al.*, 2015). In short, the pattern of findings in antisocial youth on processing cues signalling threat, point to both hypo- or hyper-responsiveness, and accounting for heterogeneity in antisocial behaviour might explain differences in the level of recruitment of the amygdala. Another issue is that the majority of studies only reported differences in threat acquisition and not in threat extinction. However, investigating how antisocial subtypes may differ in amygdala

activation during threat acquisition and extinction may help uncover groups of consistently hypo-responsive or hyper-responsive antisocial individuals, which could have important implications for future prevention of conduct disorders and associated conditions, such as substance abuse and aggressiveness in juvenile youth.

### **Current study**

We probed for the existence of latent groups in relation to amygdala responses during threat conditioning. The pattern of results obtained in previous studies suggests that functional brain abnormalities related to threat acquisition and extinction might differentiate Primary from Secondary variants of psychopathy. Amygdala was chosen as the region of interest because: (1) This region has been identified as being central to threat conditioning (e.g., Baxter & Murray, 2002), (2) adolescents with CU traits display amygdalar structural abnormalities and hypo-reactivity in fMRI studies in response to aversive stimuli (Glenn, Raine, & Schug, 2009; Harenski, Edwards, Harenski, & Kiehl, 2014; Viding *et al.*, 2012), and (3) activation of the amygdala has been observed in response to threat conditions across studies (Hoppenbrouwers *et al.*, 2016).

Specifically, the present study aimed to extend prior work by examining differences in amygdala activity during threat acquisition and extinction between Primary and Secondary variants. Despite similar levels of CU traits, these two variants are differentiated on levels of anxiety and their responsiveness to fear (Fanti, Kyranides, Petridou, Demetriou, & Georgiou, 2018; for a review see Fanti, 2018). Recent research on psychopathy subtypes has identified groups of youth with either CU traits accompanied by low levels of anxiety (Primary group), CU traits accompanied by high levels of anxiety and history of abuse (Secondary group), or solely high anxiety (Anxious group) (Cicchetti & Toth, 2014; Fanti & Kimonis, 2017; Kimonis, Fanti, Goulter, & Hall, 2017). We expected to replicate these subtypes in a sample of juvenile delinquent youth. Individuals in the Secondary and the Anxious subgroups tend to show neural hyper-arousal and a hyper-vigilant state primarily originating from previous abusive and traumatic social experiences that can lead to anticipatory anxieties, fear, and reactive aggression (Fanti *et al.*, 2018; Stein, Dukes, & Warren, 2006). Individuals in the Primary subgroups show amygdala hypo-activity rooted in intrinsic and idiopathic deficits (Jones, Laurens, Herba, Barker, & Viding, 2009). Based on prior neuroscientific work, we expected antisocial youth in the Primary subgroup to exhibit hypo-responsiveness during threat acquisition and possibly hyper-responsiveness during extinction, while the opposite associations were expected with Secondary groups and groups showing high levels of anxiety or abuse.

Another aim of the study was to investigate whether amygdala activation during threat conditioning is lateralized to the left or the right, since left and right amygdalae have different roles in emotional processing (Baas, Aleman, & Kahn, 2004; Costafreda, Brammer, David, & Fu, 2008). A meta-analysis of 385 studies provided evidence that hemispheric specialization in the right amygdala has a high-speed detection role for unconscious pictorial emotional stimuli, similar to the threat-conditioning task used in the current study, whereas the left amygdala is recruited for the evaluation of language-related stimuli (Costafreda *et al.*, 2008). Thus, we expected to identify stronger right than left amygdala dysfunctions as a result of threat conditioning. In addition, Sterzer, Stadler, Krebs, Kleinschmidt, and Poustka (2005) provided evidence that adolescents with conduct disorder showed reduced left amygdala activation to emotional stimuli, after accounting for internalizing problems. In contrast, Jones *et al.* (2009) and Viding *et al.* (2012) suggested that boys high on both conduct problems and CU traits showed

decreased right amygdala reactivity to fearful faces. Importantly, Viding *et al.* (2012) also provided evidence for high right amygdala reactivity among boys high on conduct problems but low on callous–unemotional traits. To inform prior controversies and extend this line of work, we aim to compare Primary and Secondary antisocial subtypes on both left and right amygdala activation.

## Method

### *Participants and procedure*

Participants were recruited from a cohort of 364 adolescents who were first arrested by the police before the age of 12. In total, 150 adolescents participated in the current study with a mean age of 17.60 ( $SD = 1.6$ ). Fourteen participants were excluded from analyses due to invalid MRI data, missing questionnaire data, or drug use prior to scanning. Analyses were performed on the remaining 136 participants (mean age = 17.7,  $SD = 1.6$ ; 86% male).

This study was approved by the Institutional Review Board of the VU University Medical Center, Amsterdam. All participants and their parents/custodians (if the participant's age was below 18) signed for informed consent. Participants underwent a neuroimaging protocol in a Philips 3T Intera MRI Scanner at the Academic Medical Center. All participants were instructed to refrain from using alcohol, cannabis, or psychostimulant medication for at least 24 hr before the MRI scan.

### *Assessment*

#### *Callous–unemotional traits*

The Youth Psychopathic traits Inventory (YPI; Andershed, Hodgins, & Tengström, 2007) was used for the assessment of CU traits. The YPI is a 50-item self-report instrument, which was developed in order to study personality traits associated with adult psychopathy in juvenile community samples. To ensure that all participants would understand the questions, the Dutch child version of the YPI was used (Baardewijk *et al.*, 2008), which has been shown to exhibit good 6-month test–retest reliability (ICC range 0.61–0.76). This version uses the same questions as the adolescent YPI in simplified wordings. Only the CU dimension was used in the current study, which had good internal consistency (Cronbach's  $\alpha = .85$ ).

#### *Anxiety*

Clinical characteristics of adolescents were assessed using reports on the Child Behavior Checklist (CBCL; Achenbach, 2011) and Youth Self Report (YSR; Achenbach, 2011). Adolescents and their parents rated how well each of the items described them or their child, respectively, over the past 6 months on a three-point scale (0 'not true' to 2 'very true or often true'). For the present study, only the 13-item anxiety subscale was used. Parent and self-reports were averaged to obtain reliable estimates. The CBCL and YSR have been used widely with community and incarcerated samples of youth, and have shown adequate reliability and validity in assessing behavioural and emotional problems.

#### *Childhood history of abuse*

The Childhood Trauma Questionnaire (CTQ; Bernstein *et al.*, 1994) is a 28-item self-report measure that captures different types of abuse: physical (i.e., 'I was punished with a

belt, a board, a cord, or some other hard object'), sexual (i.e., 'Someone tried to make me do sexual things or watch sexual things'), and emotional abuse (i.e., 'People in my family said hurtful or insulting things to me'), as well as physical (i.e., 'I didn't have enough to eat') and emotional neglect (i.e., 'People in my family looked out for each other'-reverse scored). Items, rated between 1 (never true) and 5 (very often true), were summed to compute a CTQ total score to be used in analyses. There is adequate support for the reliability and validity of CTQ total scores (Bernstein *et al.*, 2003). CTQ total scores demonstrated a test-retest correlation of .88 and convergence with the Childhood Trauma Interview. In the present study, the CTQ total score, related to familial abuse, was internally consistent ( $\alpha = .86$ ).

### **Threat-conditioning task**

A classical differential delay threat-conditioning task was employed (Birbaumer *et al.*, 2005). Pictures of two neutral male faces served as conditioned stimuli (CS), one of which (chosen at random during each experiment) was consistently paired with an aversive electric unconditioned stimulus (US) at the end of a 10-s viewing period (CS+; i.e., 100% reinforcement) during the acquisition period, while the other picture (CS-) was never followed by an US. The acquisition period, which consisted of 8 trials of each CS, was preceded by a habituation phase, in which CSs were presented 4 times each for 3.5 sec without an US and was followed by an extinction phase in which CSs were presented 4 times each for 7 sec and were not followed by an US either.

### **Electrical stimulation**

We used a Digitimer DS7A for 20-ms duration electrical stimulation to the right lower leg, at the lateral malleolus. Stimulus intensity was calibrated to a level that was rated as 'aversive but not painful' for each participant individually (mean stimulus intensity = 36.3 mA,  $SD = 11.4$ ).

### **fMRI protocol and analyses**

T1-weighted anatomical scans (180 slices, 1 mm<sup>3</sup> voxels, FOV 256 × 256 mm, TR 9.0 ms, TE 3.5 ms) were acquired using an 8-channel SENSE head coil. Furthermore, 400 T2\*-weighted axial echo-planar images (EPI) were acquired during threat conditioning (38 slices, 3 mm thickness, 2.29 × 2.29 in-plane resolution, FOV 220 × 220 mm, TR 2300, TE 30 msec). Functional MRI data were processed using SPM8, including realignment, unwarping, slice-time correction, normalization to MNI space based on the segmented anatomical scan, and 8 mm FWHM smoothing. First-level models included separate regressors for CS+/- and CS- during habituation, acquisition, and extinction; US; and rating blocks. Furthermore, during acquisition the first 5-s of each trial was modelled separately from the remainder of the trial (5s for acquisition) to account for fast within-trial habituation of threat neurocircuitry, focusing analyses on the first epoch only during acquisition. Fast within-trial habituation of the fear neurocircuitry has been reported elsewhere (e.g., Cohn *et al.*, 2013; Quirk, Armony, & LeDoux, 1997) and was evident from inspection of our own data. As such, anticipation was modelled as multiple epochs, similar to previous studies assessing amygdala reactivity (e.g., Phelps *et al.*, 2001). Realignment parameters were also included in first-level models to account for movement effects. Next, average neural response estimates for each region of interest (ROI) were extracted

using the MarsBaR toolbox for SPM (Brett, Anton, Valabregue, & Poline, 2002). Similar to our previous work and consistent with a recent meta-analysis of brain regions involved in threat conditioning, we focused analyses on the amygdala (Mechias, Etkin, & Kalisch, 2010). Amygdala was anatomically defined using the Automated Anatomical Labeling atlas (Tzourio-Mazoyer *et al.*, 2002).

### **Plan of analyses**

Latent profile analysis (LPA) in Mplus 8 (Asparouhov & Muthén, 2010) was used to identify distinct groups based on participants scores on callous–unemotional (CU) traits, anxiety, and abuse. LPA identifies different latent classes by decomposing the covariance matrix to highlight relationships among individuals and clusters individuals that are similar on the constellation of indicators into latent classes (Bauer & Curran, 2003). Models that specify different numbers of classes are tested. The Bayesian information criterion (BIC) and Lo–Mendell–Rubin (LMR) statistics are used as statistical criteria to compare models to identify the optimal number of groups to retain (Nylund, Asparouhov, & Muthén, 2007). The model with the lowest BIC value is preferred. A non-significant chi-square value ( $p > .05$ ) for the LMR statistic suggests that a model with one fewer class is preferred. Finally, the average posterior probabilities and the entropy value were taken under consideration. The average posterior probabilities can be used to check for the precision of classification and therefore indicate the degree to which the classes are distinguishable (Nagin, 2005). In addition, the entropy value was used to judge the classification accuracy of placing participants into classes and the degree of separation between classes. Entropy can range from zero to one, and a higher entropy value is preferred (Muthén, 2000). Average posterior probabilities and entropy values equal to or greater than .80 indicate clear classification and greater power to predict class membership (Clark & Muthén, 2009). The goal of latent profile analysis is to classify individuals in homogenous subgroups based on probabilistic assessments of the likelihood of each participant belonging to any of the identified latent classes. Every participant in the data set has his/her own probabilities calculated for his/her membership in all of the latent classes estimated (when summed they equal 1). Latent classes are based on these probabilities, and each individual is allowed fractional membership in all classes to reflect the varying degrees of certainty and precision of classification. By adjusting for uncertainty and measurement error, these classes become *latent* resulting in the ultimate class membership that each respondent would assume (Asparouhov & Muthén, 2010).

We then used repeated measures analysis of variance (ANOVA) in IBM SPSS 20.0 to compare the identified groups' (between-subject variable) in terms of amygdala functioning during threat conditioning. Two separate ANOVAs were tested to examine differences during acquisition (first and second part) and extinction phases. In both ANOVAs, CS type (CS+ and CS–) was used as a within-subject measure. Greenhouse–Geisser corrected effects, partial eta-square values ( $\eta^2 = .01$ –.06 small effect size,  $\eta^2 = .06$ –.14 medium effect size,  $\eta^2 > .14$  large effect size; Cohen, 1988), and standardized mean difference effect sizes (Cohen's  $d = .20$  small,  $d = .50$  medium,  $d = .80$  large; Cohen, 1992) are reported in the text. Significant interactions are depicted in figures, along with standard error bars. In order to correct for the fact that we ran analyses separately for right and left amygdala, we have used an adapted Bonferroni correction taking into account the correlation between right and left amygdala ( $r = .77$ ). The adjusted threshold of  $p$  that we used equals to  $0.05/k^{(1-r)}$ , where  $k$  is the number of comparisons and  $r$  their correlation, which takes into account the interdependence of

outcome variables (similar to Cohn *et al.*, 2013). This correction resulted to a threshold of 0.043 [ $p = 0.05/2^{(1-0.77)}$ ].

## Results

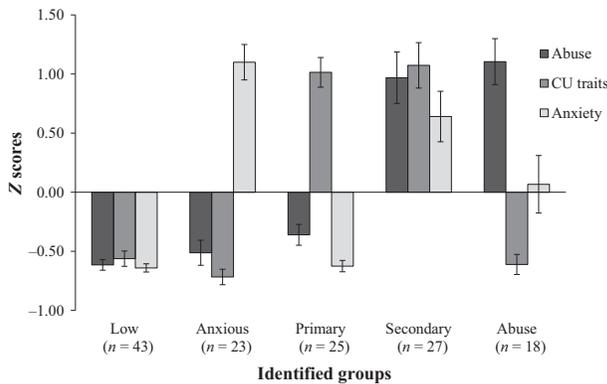
### LPA findings

To identify the optimal number of groups to retain, models with one to six classes were estimated using LPA. Model fit information is presented in Table 1. The BIC statistic increased from Class 5 to Class 6 and decreased from Class 4 to Class 5. In addition, the LMR statistic fell out of significance for the six-class model ( $p = .27$ ). Thus, the 5-class model better represented the data based on the BIC and LMR statistics. The mean posterior probability scores ranged from .90 to .97 and the entropy value was .92, suggesting that the identified classes were well separated.

Figure 1 shows standardized scores (z-scores) by identified classes on each grouping variable. The majority of the sample scored below average (low-risk group) on all the measures under investigation. Youth in the Anxious group scored > 1 standard deviation (SD) above the mean on anxiety, but below average on measures of abuse and CU traits. Youth in the Primary group scored below average on anxiety/abuse and approximately 1 SD above the mean on CU traits. Youth in the Secondary group scored above the mean on all LPA measures, whereas youth in the Abuse group scored > 1 SD above the mean on abuse, at average levels of anxiety, and below average on CU traits.

**Table 1.** Model fit statistics

Classes	BIC	Entropy	LMR
2	2,896.17	.93	$p < .001$
3	2,840.34	.93	$p < .001$
4	2,780.84	.92	$p < .001$
5	2,720.09	.92	$p < .01$
6	2,791.38	.90	$p = .27$

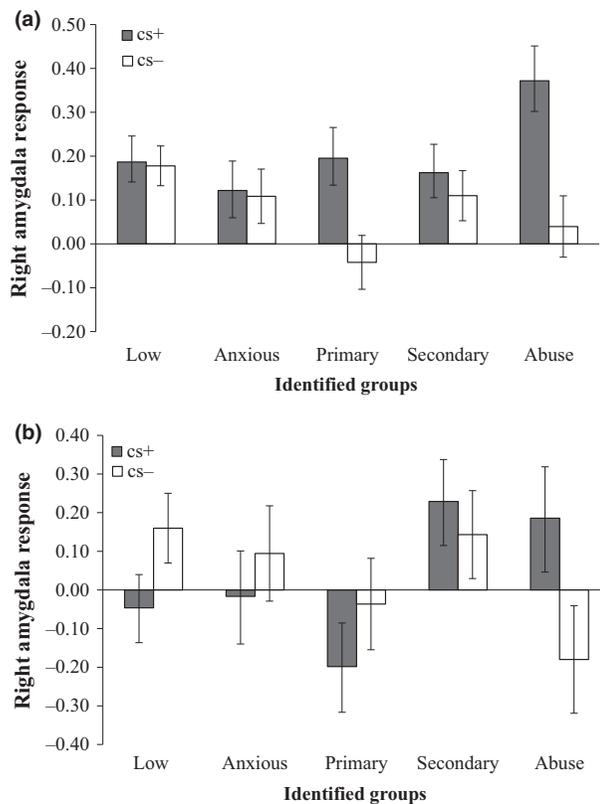


**Figure 1.** Groups identified using latent profile analysis.

## Comparing the identified groups during the acquisition phase

### Right amygdala

Findings from the repeated measures ANOVA suggested that activity in the right amygdala during the first and second acquisition phase was similar across participants,  $F(1, 131) = 0.05$ ,  $p = .82$ ,  $\eta^2 = .0$ , although on average participants showed lower responses to CS- ( $M = .08$ ,  $SE = .03$ ) compared to CS+ ( $M = .21$ ,  $SE = .03$ ,  $p < .001$ ) conditions,  $F(1, 131) = 11.62$ ,  $p < .001$ ,  $\eta^2 = .08$ . Beyond the basic CS differences, we found that stratifying the sample based on the identified groups revealed patterns that help clarify the threat-processing deficits of individuals with these characteristics. Specifically, we identified an interaction between CS type and groups,  $F(4, 131) = 2.84$ ,  $p < .043$ ,  $\eta^2 = .08$ ,  $\varepsilon = 1.00$ . This interaction is depicted in Figure 2a. Participants in the Primary group showed lower right amygdala activity in the CS- condition (in response to neutral faces) compared to the low ( $d = .79$ ), Anxious ( $d = .51$ ), and Secondary ( $d = .55$ ) groups, whereas the difference with the abuse group was small ( $d = .27$ ). Participants in the abuse group exhibited higher right amygdala activity in the CS+ condition compared to the rest of the groups ( $d$  ranged from .53 to .83). The Primary ( $d = .72$ ) and abuse ( $d = .99$ ) groups were the ones showing the higher CS differentiation.



**Figure 2.** (a) Conditioned stimuli (CS) by group interaction during the acquisition phase. (b) Conditioned stimuli (CS) by group interaction during the extinction phase. We refer to CS paired with an aversive electric unconditioned stimulus during threat acquisition as CS+ and as CS- when not paired with the electric stimulus. Values represent average neural response estimates.

*Left amygdala*

Similar to right amygdala, we did not identify an effect of acquisition phase in relation to left amygdala activity,  $F(1, 131) = 0.64$ ,  $p = .43$ ,  $\eta^2 = .01$ , although on average participants showed lower responses to CS- ( $M = .07$ ,  $SE = .03$ ) compared to CS+ ( $M = .25$ ,  $SE = .04$ ,  $p < .001$ ) conditions,  $F(1, 131) = 16.26$ ,  $p < .001$ ,  $\eta^2 = .11$ . However, no significant interaction between CS type and groups was identified,  $F(4, 131) = 1.82$ ,  $p = .12$ ,  $\eta^2 = .05$ ,  $\varepsilon = 1.00$ .

**Comparing the identified groups during the extinction phase***Right amygdala*

Findings from the repeated measures ANOVA testing differences in right amygdala activity during the extinction phase pointed to similar responses across CS conditions,  $F(1, 131) = 0.01$ ,  $p = .93$ ,  $\eta^2 = 0$ . Similar to the acquisition analysis, we identified an interaction between CS type and groups,  $F(4, 131) = 2.76$ ,  $p < .043$ ,  $\eta^2 = .08$ ,  $\varepsilon = 1.00$ . This interaction is depicted in Figure 2b. As shown in this figure, the Primary group showed lower activity compared to the Secondary ( $d = .81$ ) and abuse ( $d = .69$ ) groups during the CS+ condition, although the difference with the low ( $d = .30$ ) and Anxious ( $d = .34$ ) groups was smaller. The abuse group showed opposite responses during the CS- condition compared to the Secondary ( $d = .57$ ), Anxious ( $d = .47$ ), and low-risk ( $d = .60$ ) groups. Finally, the abuse group continued exhibiting similar CS differentiation ( $d = .63$ ) as during the acquisition phase.

*Left amygdala*

Regarding left amygdala activity during extinction, we did not identify an effect of CS condition,  $F(1, 131) = .67$ ,  $p = .42$ ,  $\eta^2 = .01$ . The interaction between CS type and groups only approached significance,  $F(4, 131) = 2.19$ ,  $p = .07$ ,  $\eta^2 = .06$ ,  $\varepsilon = 1.00$ .

**Discussion**

The present study set out to investigate heterogeneity in levels of CU traits, anxiety, and history of abuse in a sample of youth at risk for antisocial behaviour. We were particularly interested in whether Primary and Secondary subtypes, previously identified in community and incarcerated samples, would show differences in amygdala activity in response to threat acquisition and extinction. We identified five groups of youth based on measures of abuse, anxiety, and CU traits: a group scoring low on all three aspects ('Low' group), a group scoring low on abuse and CU traits but high on anxiety ('Anxiety group'), a third group scoring high on CU traits only ('Primary psychopathy group'), another one scoring high on all three variables ('Secondary psychopathy group'), and a group scoring high on familial abuse only ('Abuse group'). Therefore, the present findings provide evidence for significant heterogeneity in this high-risk sample and suggest that these unique groups of youth differ in their engagement of the amygdala during threat conditioning.

The groups identified are consistent with those found in previous studies focused on subtyping populations at risk of engaging in severe antisocial acts, which used questionnaires and psychophysiological measures (e.g., Dackis, Rogosch, & Cicchetti, 2015; Fanti & Kimonis, 2017; Fanti *et al.*, 2018; Kimonis, Fanti, Goulter, & Hall, 2017).

According to prior work, youth characterized by anxiety, with or without CU traits, and youth exposed to familial abuse show similar deficits in emotional regulation and are characterized by physiological hyper-arousal, emotional hyper-reactivity, and heightened defensive responses to fear-inducing and threatening stimuli (Dackis *et al.*, 2015; Fanti *et al.*, 2018; Kimonis, Fanti, Goulter, & Hall, 2017). In contrast, low-anxious Primary variants not exposed to abuse are characterized by hypo-arousal and reduced responding to threat. These differences can be used to explain the current study findings, which extend this line of work by showing that some subgroups differ in the pattern of amygdala reactivity during threat conditioning as well.

Importantly, each group showed different patterns of amygdala responses to the CS+ and CS− during both threat acquisition and extinction learning, but these differences were only found in the right amygdala. The Low, Anxious, and Secondary psychopathy groups all had similar responses of the right amygdala to the CS+ and CS− during threat acquisition. In other words, at-risk youth in the Secondary psychopathy (which also scored relatively high on anxiety) and the Anxious groups showed normal activation during threat acquisition. These results are somewhat surprising, as high trait anxiety has been related to hyper-responsivity to threats in the amygdala (e.g., Indovina, Robbins, Núñez-Elizalde, Dunn, & Bishop, 2011). However, one study on the interaction between sex and anxiety in relation to amygdala responses found that only female participants showed a positive correlation between level of trait anxiety and amygdala responses to fearful faces, which are believed to signal the presence of a threat (Dickie & Armony, 2008). Our sample consisted predominantly of male participants, which could account for the pattern of results obtained in the Anxious group. It should be noted that even the group scoring lower on anxiety, abuse, and CU traits was at risk for antisocial behaviour, which might explain the similarities in amygdala threat reactivity during acquisition between the groups.

Similarly, our results for threat acquisition also contradict some prior reports of elevated (amygdala-dependent) autonomic responding during threat conditioning in adult offenders with Secondary psychopathy (e.g., Aniskiewicz, 1979). Note that our results are still consistent with other research pointing out that adult Secondary psychopathy is related to average levels of autonomic responsivity in anticipation of aversive outcomes (Lykken, 1995), and that youth in the Secondary group show normative physiological responding to negative stimuli (Dackis *et al.*, 2015). Our findings also agree with a recent fMRI study providing evidence that the Secondary group showed similar amygdala activity in response to fearful facial expressions (signalling the presence of a threat) as the comparison group (Sethi *et al.*, 2018). Interestingly, this group also showed a relative hyper-responsivity to the CS+ during threat extinction, which would be in agreement with the notion that the threat circuit is hyper-active in Secondary psychopathy. While all the other groups showed different amygdala responses to the CS+ versus CS− during the extinction phase relative to acquisition, the Secondary psychopathy group did not. It seems as if the Secondary psychopathy group had difficulties in learning that the CS+ does not lead to aversive outcomes anymore during threat extinction. In addition, the lack of differentiation between CS+ and CS− is consistent with prior brain research indicating that some groups of antisocial individuals do not differentiate well between different types of stimuli (Brazil *et al.*, 2012), and that psychopathic traits are related to the formation of inaccurate cognitive representations in the amygdala during threat conditioning (Brazil, Mathys, Popma, Hoppenbrouwers, & Cohn, 2017). Taken together, these findings seem to support the suggestion that individuals with personality types corresponding to Secondary psychopathy erroneously

perceive neutral events as threatening or ambiguous, leading to hostility and excessive aggressive behaviour (Hicks, Markon, Patrick, Krueger, & Newman, 2004; Karpman, 1941, 1948; Poythress, Skeem, & Lilienfeld, 2006). Moreover, our findings challenge the belief that individuals with relatively high trait anxiety, including those with a personality structure resembling Secondary psychopathy, tend to show a general hyper-responsivity to aversive stimuli. We suggest that there seem to be no impairments in threat processing in high-anxious youth at risk of engaging in antisocial behaviour, while the impairments are limited to the unlearning of associations to threatening events in the Secondary psychopathy group.

Interestingly, the Primary psychopathy group exhibited reduced responses to the CS–, but normal responses to the CS+ condition. Extant evidence suggests that, in general, psychopathy is linked to diminished engagement of the threat-processing circuit (see Hoppenbrouwers *et al.*, 2016). From this perspective, the reduced amygdala response to the CS– could reflect that hypo-activation is the default response to neutral events. In contrast, the amygdala response during the CS+ condition was significantly reduced during extinction in the Primary psychopathy group, more so than the reduction seen in the Low and the Anxious groups, respectively. Given the role of the amygdala in modulation of attention (see Moul, Killcross, & Dadds, 2012), we speculate that the pattern observed in the Primary psychopathy group could be linked to impairments in the modulation of attention allocation to the CS+ due to its enhanced saliency relative to the CS– (Cunningham & Brosch, 2012). During acquisition, the increased saliency of the CS+ is likely to have engaged auxiliary attentional resources that may have helped overcome the default state of hypo-activation in the amygdala in the Primary psychopathy group. The CS+ lost its saliency in the extinction phase, perhaps leading to an exaggerated disengagement of the attentional resources. Such an account would be consistent with the proposal that individuals with (adult) Primary psychopathy show an impairment in balancing the amount of attention they allocate to target relative to non-target stimuli (e.g., Newman & Kosson, 1986).

In contrast to the majority of the identified groups, the Abuse group showed heightened amygdala responses during threat acquisition. Prior work assessing physiological reactivity suggested that incarcerated and community samples of youth who mainly scored high on measures of familial abuse showed increased startle reactivity to aversive events compared to the Primary variant and also to youth high on CU traits scoring low on experiences of abuse (Dackis *et al.*, 2015; Kimonis *et al.*, 2017). Furthermore, individuals suffering long-term abuse show dysfunctional engagement of the amygdala and hyper-arousal to threatening experiences (see Glaser, 2000; McCrory, De Brito, & Viding, 2012 for reviews). These findings suggest that the threshold to reacting to stressful and negative events is lower among abused individuals, indicating greater sensitization to threatening cues. This suggestion might explain the greater amygdala response identified in the current study in response to threatening stimuli. Also, the strong right amygdalar response of the Abused group is similar to what is seen in patients suffering from post-traumatic stress disorder, who tend to show heightened activity in their right amygdala when presented with their own traumatic experiences (e.g., Rauch *et al.*, 1996). As a result, the right amygdala might be particularly important for processing threatening stimuli among individuals exposed to traumatic experiences. Furthermore, adolescents in the Abuse group showed similar deficits as those in the Secondary group during the extinction phase, pointing to impairments in the unlearning of associations to threatening events. Thus, the findings for both the acquisition and extinction phase point

to dysfunctional amygdala responses among individuals with a history of abuse, agreeing with prior work (Glaser, 2000; McCrory *et al.*, 2012).

Taken together, we found that the Primary and Abuse groups were different from the rest of the sample during threat acquisition, with the Abuse group showing higher right amygdala activity during the CD+ condition, and the Primary group showing lower amygdala activity during the CS- condition in response to neutral faces. During threat extinction, the Abuse group continued showing high right amygdala response, which was similar to the Secondary group, although the Abuse group showed lower amygdala response to the CS- condition compared to the rest of the groups. In contrast, the Primary group showed low amygdala response during both the CS+ and CS- conditions in the extinction phase. These results are the first to provide clear indications that subtypes of at-risk youth differ in how the amygdala is activated depending on the level of threat associated with a particular stimulus, and provide a more nuanced view of individual variations in brain responses to threat.

It is important to consider that our study mainly included adolescents, of which a portion had the legal age to be considered adults, while others did not. This introduces an additional challenge for generating claims on a group level. Therefore, it is important to remain cautious while extrapolating findings obtained in adult populations to developmental samples, especially considering the lack of previous studies comparing youth with Primary versus Secondary psychopathy personality types (Hoppenbrouwers *et al.*, 2016). The high level of brain plasticity during this developmental period of life increases the likelihood that the brain will adapt to cope with environmental influences, and both maturation and the emergence of protective factors can change an individual's developmental pathway (Brazil, 2015). Therefore, similarities in brain responses observed in adult offenders with psychopathy, who have often had more exposure to detrimental factors and are institutionalized, and those observed in non-institutionalized adolescents may not necessarily reflect the same underlying cognitive or neurobiological impairments. Much more longitudinal work is needed to examine the developmental stability of brain response measures in antisocial populations.

In conclusion, this is the first study showing discernible patterns of amygdala functioning during threat acquisition and extinction in antisocial youth differentiated on levels of abuse, CU traits, and anxiety. Importantly, findings extend work suggesting that left and right amygdala have different roles in emotional processing (Baas *et al.*, 2004), and agree with Costafreda *et al.* (2008) meta-analysis in that the right amygdala is involved during non-verbal conditioning tasks. Findings are also in agreement with work identifying right, but not left, amygdala dysfunction among boys differentiated on conduct problem and CU traits (Jones *et al.*, 2009; Viding *et al.*, 2012) and extends this work by identifying deficits among diverse antisocial subtypes during threat acquisition and extinction. The findings might inform research on pathways towards antisocial behaviour in that distinct combinations of abuse, anxiety, and CU traits might be differentially associated with brain responses to threat reactivity. Several theories propose that both high and low threat reactivity can predict engagement in antisocial behaviour (see Fanti, 2018 and Frick, 2012 for reviews), and our findings point to additional impairments in the ability to learn and appropriately react to threatening events. In addition to extending our knowledge regarding heterogeneity in antisocial behaviour, the findings can inform the development of individualized intervention and treatment strategies based on the underlying brain mechanisms associated with threat reactivity (Brazil, van Dongen, Maes, Mars, & Baskin-Sommers, 2018).

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