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Genetic covariance between psychopathic traits and anticipatory skin conductance responses to threat: Evidence for a potential endophenotype

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Abstract

The genetic architecture of the association between psychopathic traits and reduced skin conductance responses (SCRs) is poorly understood. By using 752 twins aged 9–10 years, this study investigated the heritability of two SCR measures (*anticipatory* SCRs to impending aversive stimuli and *unconditioned* SCRs to the aversive stimuli themselves) in a countdown task. The study also investigated the genetic and environmental sources of the covariance between these SCR measures and two psychopathic personality traits: impulsive/disinhibited (reflecting impulsive–antisocial tendencies) and manipulative/deceitful (reflecting the affective–interpersonal features). For anticipatory SCRs, 27%, 14%, and 59% of the variation was due to genetic, shared environmental, and nonshared environmental effects, respectively, while the percentages for unconditioned SCRs were 44%, 2%, and 54%. The manipulative/deceitful (not impulsive/disinhibited) traits were negatively associated with both anticipatory SCRs ($r = -.14, p < .05$) and unconditioned SCRs ($r = -.17, p < .05$) in males only, with the former association significantly accounted for by genetic influences ($r_g = -.72$). Reduced anticipatory SCRs represent a candidate endophenotype for the affective–interpersonal facets of psychopathic traits in males.

Efforts have recently been made to identify the endophenotypic markers of psychopathic personality, a multidimensional construct encompassing a cluster of distinct personality traits: callous–unemotional affective traits, arrogant–deceitful interpersonal traits, and impulsive–irresponsible behavioral traits (Hare, 1991; Lynam, 1997). The *endophenotype*, referring to some “intermediate” phenotype on the pathway from distal genotype to mental disorder of interest, has received increasing attention in the etiological studies of psychopathology (Gottesman & Gould, 2003). An endophenotype can be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature, but it must also (a) be heritable, (b) be reliably associated with

the disorder, and (c) share genetic covariance with the disorder (Rijsdijk et al., 2010). The concept of endophenotype represents an effort to decompose or deconstruct the complex disorder or syndrome into more basic elements, which are more proximal to the genetic predispositions than the disorder per se and, thus, may help advance our understanding of the etiology of the disorder.

Psychopathic traits show moderate to strong heritability (Bezdjian, Raine, Baker, & Lynam, 2011; see reviews by Viding & Larsson, 2010; Waldman & Rhee, 2006), and this genetic vulnerability is likely to be reflected at a physiological level. One of the primary physiological constructs that has been found to be reliably associated with psychopathic traits is attenuated anticipatory skin conductance responses (SCRs) to aversive stimuli in conditioning or quasi-conditioning paradigms (Arnett, 1997; Hare, Frazelle, & Cox, 1978). For example, using a (quasi-conditioning) countdown paradigm in which participants are presented with numbers counting down from 12 to 0 signaling a loud noise burst, we among others have found reduced anticipatory SCRs in children and adolescents with psychopathic tendencies (Fung et al., 2005; Wang, Baker, Gao, Raine, & Lozano, 2012) as well as in college students with antisocial personality features (Sylvers, Brubaker, Alden, Brennan, & Lilienfeld, 2008). Using various conditioning paradigms, other studies have reliably demonstrated the link between reduced anticipatory SCRs and psychopathic traits in clinical and community samples (Fairchild, Van Goozen, Stollery, & Goodyer, 2008; Flor, Birbaumer, Hermann, Ziegler, & Patrick, 2002; Rothmund et al., 2012). This attenuated SCR may reflect psychopathic individuals' lack of fear or anxiety prior to the aversive event or their insensitivity or lack of concern about the impending punishment (Hare, 1978; Hare & Thorvaldson, 1970; Lykken, 1957). The amygdala and ventromedial prefrontal cortex (vmPFC), regions closely involved in moral reasoning and emotional processing, may serve as important neural bases underlying reduced anticipatory SCRs in psychopaths (Bechara et al., 1995; Blair, 2007; La-Bar, LeDoux, Spencer, & Phelps, 1995).

Despite the large amount of evidence demonstrating the association between psychopathic traits and anticipatory SCRs, little is known about the heritability of the latter. Hettrema, Annas, Neale, Kendler, and Fredrikson (2003) reported that individual differences in SCRs at all phases of fear conditioning (e.g., habituation, acquisition, and extinction) were mainly due to genetic (26%–53%) and nonshared environmental (47%–74%) influences, while environmental effects shared by twins were nonsignificant. Using a loud tone (105 db) as aversive stimulus, Lykken, Iacono, Haroian, McGue, and Bouchard (1988) found that genetic (40%–70%) and non-shared environmental (30%–60%) effects were significant for almost all components of SCR habituation (e.g., slope, intercept, maximum magnitude, number of trials before habituation). Further, studies examining the heritability of skin conductance orienting responses, that is, responses to neutral but innovative stimuli in the environment, also reported significant genetic and nonshared environmental effects (but no significant shared environmental influences; Crider et al., 2004; Isen, Iacono, Malone, & McGue, 2012; Tuvblad et al., 2012). Taken together, evidence suggests that SCR measures in general are moderately heritable. It is therefore predicted that for anticipatory SCRs, there would be appreciable effects due to genetic and nonshared environmental but negligible influences due to shared environment.

Another physiological measure that is often linked to psychopathic traits in a conditioning or quasi-conditioning paradigm is autonomic reactivity to the aversive or punishment stimulus itself, for example, the unconditioned stimulus (UCS). Psychopathic individuals have shown reduced SCRs to the UCS (Fairchild, Stobbe, Van Goozen, Calder, & Goodyer 2010; Fung et al., 2005; Hare et al., 1978) compared to nonpsychopathic groups, although some studies have failed to find group differences (Fairchild et al., 2008; Flor et al., 2002; López, Poy, Patrick, & Moltó 2013; Rothmund et al., 2012). Prior research has been done on adults and adolescents, and to date no study has examined the association in children younger than 14 years.

Therefore, we attempted to fill the above-mentioned research gaps by examining two physiological correlates of psychopathic traits, namely, anticipatory SCRs and the SCRs to the aversive stimulus itself, in a sample of 9- to 10-year-old twins. We have previously demonstrated that psychopathic traits are substantially accounted for by genetic (46%–64%) and nonshared environmental influences (36%–54%; Bezdjian et al., 2011), and that reduced anticipatory SCRs are associated with high psychopathic traits in boys but not in girls (Wang et al., 2012). In the current study, we expand on these findings by investigating: (a) if both SCRs (anticipatory SCR and SCR to the UCS) are heritable; (b) whether SCR to the UCS bears significant phenotypic association with psychopathic traits; and (c) should there be significant association between psychopathic traits and SCRs, whether common genetic influences can explain this association. Finally, we also attempted to compare the genetic etiology of these associations between boys and girls. In summary, the primary objective of this study was to investigate whether anticipatory SCR and SCR to the UCS meet the criteria for candidate endophenotypes for psychopathy. To our knowledge, no previous multivariate twin study has conducted such analyses, and our study will be among the first to examine the genetic covariance between these physiological markers and psychopathic traits in both males and females.

Method

Participants

The present study was based on 616 sets of twins and triplets (1,241 subjects in total; 49% males, mean age = 9.6, $SD = 0.58$) who participated in the first wave of an ongoing Twin Study of Risk Factors for Antisocial Behavior at the University of Southern California (Baker et al., 2013). Twins were mainly recruited through public schools in the Greater Los Angeles area around 2000–2001, and the ethnic distribution (36.74% Hispanic, 27.4% Caucasian, 14.02% Black, 4.35% Asian, 0.16% Native American, and 17.32% mixed) was comparable to that of the Southern California urban community. Among them, 139 twin pairs were monozygotic males, 147 were monozygotic females, 88 were dizygotic males, 93 were dizygotic females, and the remaining 149 were dizygotic opposite sex.

Measures

To assess psychopathic traits, Lynam's (1997) Childhood Psychopathy Scale (CPS) was completed separately for each child by a caregiver. The CPS comprises 58 items rated on a 2-point scale (1 = *yes*, 2 = *no*). Two moderately correlated factors ($r = .45$, $p < .01$) were

derived from these 58 items (Bezdjian et al., 2011): the first factor included seven subscales (unreliability, lack of planning, boredom susceptibility, impulsivity, behavioral dyscontrol, poverty of affect, and callousness), reflecting impulsive–antisocial tendencies of psychopathy and thus labeled “impulsive/disinhibited”¹ in the current study; and the second factor loaded on six subscales (manipulativeness, parasitic lifestyle,² glibness, untruthfulness, failure to accept responsibility, and lack of guilt), reflecting the affective–interpersonal features of psychopathy and thus labeled “manipulative/deceitful.” Psychometric details of the CPS and formation of these two factors as their genetic analyses can be found in Bezdjian et al. (2011) and Wang et al. (2012).

The countdown task

The task was composed of three signaled trials and two unsignaled trials. In each of the signaled trials, participants watched numbers count down from 12 to 0 (at a rate of 1 s each) on the computer screen. They were told that a loud noise (1-s burst of 105 dB white noise) would be delivered when the number reached 0. For the unsignaled trials, the same loud noise burst was also presented, but no numeric countdown was visually presented; instead, participants viewed a blank screen, and thus they were unaware of when the trial began or the noise occurred. The 12 s prior to the unsignaled noise were examined for these unsignaled trials as a comparison condition in order to evaluate the efficacy of the countdown in the signaled trials in eliciting anticipatory fear (Fung et al., 2005). More details on the task can be found in Wang et al. (2012).

Psychophysiological data attainment

All psychophysiological data were collected with equipment and software from the James Long Company (Caroga Lake, NY). Skin conductance activity was recorded from bipolar leads on the distal phalanges of the index and middle fingers of the nondominant hand using Ag-AgCl electrodes (8 mm in diameter). A SCR was defined as an increase in conductivity exceeding 0.05 microsiemens in amplitude and the number of nonspecific SCRs (NS-SCRs) was scored manually (Fung et al., 2005; Wang et al., 2012).

¹This factor was labeled “callous/disinhibited” in Bezdjian et al. (2011) because the subscales “poverty of affect” (POE) and “callousness” were considered to reflect the affective aspects of psychopathy. This point of view, however, is no longer held in the current study upon careful examination of items included in these two subscales. First, POE has been found to reflect emotional lability/instability (e.g., feelings change often/quickly, moods unpredictable, and feelings come/go quickly) and emotional sensitivity/insensitivity (e.g., warm/kind person, reversed [R], open with feelings [R], and feelings seem fake). That it clustered together with those impulsive–disinhibited subscales in factor analysis pointed to the possibility that POE may index more emotional dysregulation than poverty of affect. This hypothesis was supported by a negative correlation between POE and the subscale “grandiosity” (measuring presence vs. absence of self-confidence; $r = -.20, p < .05$), because emotional instability or dysregulation was expected to cohere with low self-confidence. Second, “callousness” contained four items reflecting presence/absence of aggressiveness (mean to others, tease/pick on others, kind/thoughtful [R], and tries not to hurt others [R]) and one item reflecting emotional sensitivity (able to tell how others feel). Its grouping with impulsive–disinhibited subscales in factor analysis might thus arise from these aggressive contents. However, its correlations with “behavioral dyscontrol” ($r = .30, p < .05$) were only comparable in magnitude to that with “impulsiveness” ($r = .34, p < .05$) and “unreliable” ($r = .32, p < .05$), indicating that the aggression-oriented items in “callousness” are indexing impulsive–disinhibitory tendencies more so than callous–aggressiveness.

²It is worth noting that the label for the “parasitic lifestyle” (PL) subscale may be problematic. First, this scale in its adult counterpart, Hare’s Psychopathy Checklist, intended to measure unwarranted reliance on others for support and sustenance. This is a concept obviously not applicable to children or adolescents because reliance on parents/guardians is necessary for them. Second, items in this subscale reflected selfishness or disregard toward others rather than parasitic tendencies (i.e., takes a lot without giving in return, gives/shares things [R], usually returns things he/she borrows [R], and tries to see how much he/she can get away with). This reinforced its role in indexing the affective–interpersonal features of psychopathy. Clarification of the parasitic lifestyle subscale, together with the revised interpretation of our impulsive/disinhibited factor, served to reconcile our findings with the broad literature adopting a classical distinction between impulsive–antisocial (“externalizing”) and affective–interpersonal features of psychopathy.

Skin conductance data during the 12 s before and 12 s after the white noise burst were examined. To test our hypotheses, two SCR measures were derived: the prenoise response averaged across three signaled trials (anticipatory NS-SCRs, indicating anticipatory fear responses to aversive stimuli), and the postnoise response averaged across all five trials (aversive NS-SCRs, three signaled and two unsignaled conditions combined, representing unconditioned responses to aversive event). Finally, the prenoise responses averaged across the two unsignaled trials was only included as a baseline to test the efficacy of countdown in eliciting anticipatory responses, because no significant associations were found for them with any factor of CPS scores in Wang et al. (2012).

Due to equipment error, all the SCR data from the count-down task before September 2001 was contaminated and thus removed. Only 752 subjects (45% boys) were retained for the NS-SCR data. This sample showed similar characteristics to those subjects excluded on almost all aspects except that there were fewer Caucasians in the current sample (for more details, see Wang et al., 2012).

Statistical analysis

To evaluate the efficacy of the countdown number in the signaled condition, mean difference in prenoise NS-SCRs between signaled and unsignaled conditions was examined using paired-sample *t* tests. The classical twin design was utilized to estimate the genetic and environmental influences on individual differences in the observed phenotypes. The variance–covariance structure in the classical twin design is usually attributed to three sources: the additive genes (A), the shared environment common to twins within a family (C), and the nonshared environment (E), including individual-specific environmental factor or experiences (e.g., peer relationships) and measurement errors. There are several important assumptions in the classical twin design: (a) monozygotic twins are assumed to share 100% of their genes such that the genetic correlation between both twins is set to 1, whereas it is only 0.5 for dizygotic twins because they are assumed to only share about 50% of genes; (b) the correlation of shared environment is set to 1 for both monozygotic and dizygotic twins if they are reared up together; and (c) the non-shared environment of a twin is independent of those of the other twin, such that the correlation of nonshared environment is set to be 0 (Evans, Gillespie, & Martin, 2002).

To examine how genetic and environmental influences contributed to variations in anticipatory NS-SCRs and aversive NS-SCRs, separate univariate genetic analyses were conducted. To test potential sex differences, three genetic models were fit to the data: Model 1 allowed sex differences on mean levels of the observed phenotype as well as the magnitudes of ACE components; Model 2 was a constrained model that equated magnitudes of ACE components; and Model 3 was a further constrained model that equated both means and ACE components between males and females. A saturated model with all parameters freely estimated (Model 0) served as a baseline model to derive chi-square statistics (a difference between $-2 \log$ likelihood of the saturated model and that of the assessed model) and degree of freedom (a difference between the number of free parameters and that of the assessed model) for each model. Goodness of model fits was mainly determined using the differences in the chi-square statistics. In addition, the suitability of the models were also

assessed by comparing the Akaike information criterion (Akaike, 1987) and the Bayesian information criterion, with smaller values indicating better fit (Raftery, 1995).

Next, phenotypic correlations of the two SCR variables with two factors of CPS (impulsive/disinhibited and manipulative/deceitful) were examined separately in males and females. In case of significant phenotypic correlations, a bivariate genetic analysis with a correlated factors solution was employed to investigate the genetic and environmental architecture of that correlation. This correlated factors solution decomposes the variance of each phenotype as well as the covariances between two measures into genetic, shared environmental, and nonshared environmental factors. A genetic correlation (r_g) indicates the extent to which genetic effects on one measure overlap with genetic effects on another measure. Similarly, shared (r_c) and nonshared (r_e) environmental correlations indicate the extent to which environmental effects on one measure overlap with environmental effects on another. These statistics vary from -1.0 and $+1.0$, and are independent of the magnitudes of genetic influences (or heritability) for each set of measures (Posthuma et al., 2003).

We also calculated the proportion of the phenotypic correlation that was due to genetic (i.e., bivariate heritability [BH]), shared environmental (i.e., bivariate shared environment [BSE]), and nonshared environmental (i.e., bivariate nonshared environment [BNSE]) influences through the following equations:

$$BH = \frac{\sqrt{A_{SCR}} \times r_g \times \sqrt{A_{CPS}}}{\sqrt{A_{SCR}} \times r_g \times \sqrt{A_{CPS}} + \sqrt{C_{SCR}} \times r_c \times \sqrt{C_{CPS}} + \sqrt{E_{SCR}} \times r_e \times \sqrt{E_{CPS}}}, \quad (1)$$

$$BSE = \frac{\sqrt{C_{SCR}} \times r_c \times \sqrt{C_{CPS}}}{\sqrt{A_{SCR}} \times r_g \times \sqrt{A_{CPS}} + \sqrt{C_{SCR}} \times r_c \times \sqrt{C_{CPS}} + \sqrt{E_{SCR}} \times r_e \times \sqrt{E_{CPS}}}, \quad (2)$$

$$BNSE = \frac{\sqrt{E_{SCR}} \times r_e \times \sqrt{E_{CPS}}}{\sqrt{A_{SCR}} \times r_g \times \sqrt{A_{CPS}} + \sqrt{C_{SCR}} \times r_c \times \sqrt{C_{CPS}} + \sqrt{E_{SCR}} \times r_e \times \sqrt{E_{CPS}}}. \quad (3)$$

Bivariate heritability is a measure of the extent to which shared genetic influence generates a correlation between two traits and varies from 0 to 1. The bivariate statistics sum to the phenotypic correlation and are only informative when r_g , r_c , and r_e are in the same direction (Plomin, DeFries, McClearn, & McGuffin, 2008).

Phenotypic correlations between SCR measures and CPS factors were conducted in SAS 9.2 (SAS, 2008). All genetic models based on the raw data (rather than the covariance matrix) were implemented in Mplus 5.2 (Muthén & Muthén, 2007). Prior to all the analyses, CPS and SCR were first ranked (PROC RANK; Blom, 1958) and then normalized (PROC STANDARD) in SAS to decrease the skewness and kurtosis in their distributions. According to a simulation study by van den Oord et al. (2000) for behavior genetic analysis with psychiatric symptom count data, this transformation procedure performed best in identifying the true genetic model among a set of alternative models.

Results

The paired-sample t test showed significantly fewer prenoise NS-SCRs under unsigned conditions ($M = 0.54$, $SD = 0.66$) than those under signaled conditions ($M = 0.76$, $SD = 0.79$), $t(757) = 8.03$, $p < .01$, indicating the validity of the signaled countdown in eliciting anticipatory fear to impending aversive stimuli. About 70% of the sample (i.e., 540 participants out of the 758 cases with usable SCR data) showed one or more prenoise NS-SCRs in any of the three signaled trials.

Univariate analyses

The intrafamily correlations for the two SCR measures stratified by zygosity are presented in Table 1. For each measure, the correlations in monozygotic twins were larger than those in dizygotic twins, indicating genetic influences.

Univariate genetic model comparisons suggested that, for anticipatory NS-SCRs, although males and females differed significantly on means, the proportion of variance due to genetic, shared environmental, and nonshared environmental influences were comparable between sexes (Model 2, $\chi^2 = 0.68$, $df = 3$, $p = .88$). There was no significant sex difference for aversive NS-SCRs in either means or variance due to genetic and environmental influences (Model 3, $\chi^2 = 3.39$, $df = 1$, $p = .07$). Table 2 summarizes the details of model comparisons as well as parameter estimates with their 95% confidence intervals (CIs) based on the best-fitting model. As expected, the contribution of shared environmental effects was nonsignificant for both SCR measures.

Bivariate analysis

For both males and females, impulsive/disinhibited was not significantly correlated with either SCR measure (Table 1). In contrast, manipulative/deceitful was negatively associated with both anticipatory NS-SCRs ($r = -.14$, $p < .05$) and aversive NS-SCRs ($r = -.17$, $p < .05$) in males, but not in females. A Steiger t test (Steiger, 1980) showed that the association for manipulative/deceitful with aversive NS-SCR was significantly larger than that for impulsive/disinhibited ($t = 2.36$, $p < .05$) in males. No other significant differences were found.

As a result of this, two sets of bivariate genetic analyses were conducted in boys only: anticipatory NS-SCR with manipulative/deceitful and aversive NS-SCR with manipulative/deceitful. This male-only sample ($n = 341$) could potentially decrease the statistical power in differentiating genetic and shared environmental influences. Therefore, only full ACE models were fitted to data and no further model comparisons (i.e., comparing reduced models by dropping A or C components) were conducted.

Figure 1 presents the correlated factor solutions for these two full ACE models, along with parameter estimates and 95% CIs. Anticipatory NS-SCRs and aversive NS-SCRs exhibited divergent patterns. Specifically, there was a significant genetic correlation between anticipatory NS-SCR and manipulative/deceitful ($r_g = -.72$, 95% CI = -1 to -0.12), whereas for the covariation between aversive NS-SCR and manipulative/deceitful only the nonshared environmental correlation was significant ($r_e = -.22$, 95% CI = -0.43 to -0.05).

Further calculation indicated that 35% (see Equation 1 for how to derive this proportion) of the phenotypic correlation between aversive NS-SCR and CPS manipulative/deceitful was explained by genetic influences, almost none were accounted for by shared environmental influences (see Equation 2) and the remaining 65% (see Equation 3) was explained by nonshared environmental influences. Bivariate statistics were not calculated for the relationship between anticipatory NS-SCR and manipulative/deceitful because r_g and r_c were in opposite directions.

Discussion

This study aimed to investigate the heritability of anticipatory SCRs and SCRs to aversive stimuli, and more importantly the genetic and environmental sources of the covariance between these two measures and psychopathic personality traits in children. The main findings were the following:

1. significant phenotypic relationships between manipulative/deceitful (but not impulsive/disinhibited) and the two types of SCRs were found in males only;
2. genetic and nonshared environmental effects were important for both types of SCRs, whereas the contribution of the shared environment was negligible;
3. for males there was significant genetic correlation between anticipatory SCRs and manipulative/deceitful, suggesting an overlap between genetic influences in anticipatory SCRs and manipulative/deceitful, whereas for aversive SCRs and manipulative/deceitful there was a significant nonshared environmental correlation; and
4. the phenotypic correlation between anticipatory SCRs and manipulative/deceitful was mediated by common genetic influences.

These findings together suggest that reduced anticipatory SCRs may be a candidate endophenotype for the interpersonal aspects of psychopathic traits in males.

First, the phenotypic relationships found only between manipulative/deceitful (not impulsive/disinhibited) and SCRs were consistent with previous findings (Fowles & Dindo, 2009; Patrick & Bernat, 2009) and indicated that reduced affective-physiological responses were unique to the affective-interpersonal aspects of psychopathy. This provided further support for divergent etiologies for different facets of psychopathy and the importance in differentiating them (Patrick, Fowles, & Krueger, 2009; Patrick, Hicks, Nichol, & Krueger, 2007). Second, as predicted, we demonstrated that genetic and nonshared environmental effects, but not shared environmental influences, contributed significantly to the variations of both anticipatory SCRs and aversive SCRs. Furthermore, each measure was under a similar amount of genetic and environmental influences in both sexes.

However, although males with high manipulative/deceitful traits showed significantly fewer anticipatory NS-SCRs and aversive NS-SCRs, a significant phenotypic correlation was not found for females. This discrepancy provides further evidence that there may be distinctive genotype–phenotype pathways for the development of psychopathy for these two sexes (Isen et al., 2010). Consistent with this finding, other recent studies have demonstrated the

sexually dimorphic effect of catechol-*O*-methyltransferase and monoamine oxidase A, two candidate genes implicated in fear processing (Montag et al., 2008; Williams et al., 2009), on genetic susceptibility to an array of psychiatric disorders, including major depression (Åberg, Fandiño-Losada, Sjöholm, Forsell, & Lavebratt, 2011), obsessive-compulsive disorder (Karayiorgou et al., 1999) and attention-deficit/hyperactivity disorder (Biederman et al., 2008). Evidence from brain imaging studies (Tranel, Damasio, Denburg, & Bechara, 2005) has also shown sex-specific patterns for functional asymmetry of the vmPFC, a brain region implicated in reduced fear responses of psychopaths (Blair, 2007). For example, defects in emotional processing and decision making arose from damages to the unilateral right vmPFC in men but the left vmPFC in women (Tranel et al., 2005). It is possible that this functional asymmetry of the vmPFC may be a neurophysiological expression of those sexually dimorphic genes. Given the scarcity of research investigating psychopathy at the molecular level (Blair, Peschardt, Budhani, Mitchell, & Pine, 2006), we must await more evidence to elucidate the sex-specific genotype-phenotype pathways involved in emotion learning and the development of psychopathic traits.

Despite significant genetic influences found for both SCR measures and for the two CPS factors, only the anticipatory SCRs were found to share a significant genetic covariance with manipulative/deceitful, and thus considered to be a potential endophenotype in males. This differential relationship may be partly due to the different neurobiological mechanisms underlying the two types of physiological responses. In one study, LaBar et al. (1995) used a classical fear conditioning paradigm to investigate the SCRs to the conditioned stimulus (CS +), CS-, and UCS in human subjects with lesions to the amygdala, and they found that the temporal lobectomy group and the nonepileptic control group differed significantly on responses to the CS+, but not to the CS- or the UCS. A significant amount of animal research on amygdala and fear has also suggested that there are different neurocircuitries for conditioned and unconditioned fears (see a review by Rosen, 2004; Walker & Davis, 1997): the former involves more cognitive processes like learning and memory than the latter. In addition, the early growth response gene 1, a type of gene implicated in learning and memory, has been found to play dissociative roles in conditioned and unconditioned fears (Malkani, Wallace, Donley, & Rosen, 2004). Enlightened by findings from animal research and the hypothesis that psychopaths' reduced NS-SCRs in anticipation of an aversive stimulus reflect a lack of cognitive activity, specifically a deficit in the ability to imagine future consequences (Öhman & Mineka, 2001; Schalling, 1978), a tentative explanation would thus be that the common genes underlying anticipatory fear responses and psychopathy exert influences on the relevant phenotypes through cognitive appraisal of the impending negative stimuli. In contrast, nonshared environmental factors contribute more to the association between psychopathic traits and an emotional appraisal of the threatening stimuli. Future behavioral genetic research examining the mediating effect of cognitive processes such as learning/memory and their related brain activities are needed to test this hypothesis.

It is worth noting that although the significant genetic correlation was found between manipulative/deceitful and anticipatory SCRs, the total variance of manipulative/deceitful that could be accounted for by anticipatory SCRs through shared genetic influences was

only about 3% ($0.13 \times [-0.72]^2 - 0.38$). Similar effect sizes have also been reported in studies on resting heart rate and antisocial behaviors (Baker et al., 2009), fear conditioning and self-reported fear (Hettema, Annas, Neale, Fredrikson, & Kendler, 2008), and gray matter and psychopathic traits (Rijsdijk et al., 2010). These relatively small percentages, on the one hand, were not able to provide strong support for the mediating effect of these endophenotypes in the pathway from genetic risks to full spectrum of psychopathology. It is yet to be tested, hopefully through experimental studies, whether these endophenotypes did play a direct, causal role as an intermediate phenotype in the pathophysiology (for a discussion about endophenotype vs. intermediate phenotype, see Lenzenweger, 2013).

On the other hand, however, we must also be cautious in taking these small variances as signs for discounting the importance of these endophenotypes in unraveling etiologies of complex traits or diseases, which are usually under the influences of multiple loci interacting with each other. The main purpose of detecting an endophenotype is to identify elementary and “downstream” phenotypes (as opposed to behavior macros) that are associated with fewer genes and might Mendelize in a predicted manner, which in turn may decrease the heterogeneity in traits or disease symptoms (Gottesman & Gould, 2003; Iacono, 1998). Future studies could benefit from adopting a multivariate endophenotype approach (i.e., combined use of multiple endophenotypes) to increase predictive power of the endophenotype for complex traits or disorders such as psychopathy (Iacono, Carlson, & Malone, 2000).

The conclusions of the current study are subject to several limitations. First, our subjects were 9- to 10-year-old boys and girls, and it thus remains a question as to whether our findings would also apply to older populations. Although we have found that the heritability of parent-reported CPS total scores is relatively stable from ages 9 to 20 (Tuvblad, Wang, Bezdjian, Raine, & Baker, 2014), the genetic influences on skin conductance orienting responses, which were found to be positively associated with skin conductance fear conditioning (Gao, Glenn, Schug, Yang, & Raine, 2009), were the largest at ages 11–14 (Tuvblad et al., 2012). Therefore, the next step is to see how the genetic architecture of the covariation between psychopathic traits and anticipatory fear responses varies with ages. Second, another limitation is related to sample size in the bivariate analyses, where only males were included. Typically, a small sample size lacks sufficient power to differentiate between genetic and shared environmental effects; as such, a full ACE model was presented. A decrease in the magnitude of heritability of anticipatory SCRs as well as a change from significance to nonsignificance arose (compared to univariate genetic analyses). Therefore, future replications with larger sample sizes are warranted. However, this finding did not contradict the overall conclusion that the association between anticipatory SCRs and CPS manipulative/deceitful is mainly accounted for by genetic influences given the negligible contribution of the shared environment in both CPS manipulative/deceitful and SCRs and the significant phenotypic correlation between these two measures. Third, although the factor structure of CPS reported in the current sample fit in the classical distinction of impulsive–antisocial and interpersonal–affective aspects of psychopathy, an independent replication of the same factor structure (especially the tentative labeling of the impulsive/disinhibited factor) would reinforce generalizability of conclusions in current study.

Conclusions

To summarize, this was the first study to demonstrate significant genetic covariance between anticipatory SCRs and the interpersonal–affective features of psychopathy, thus providing initial evidence that anticipatory SCRs may be an endophenotype of psychopathy. Reduced SCRs to aversive stimulus were also related to psychopathic traits, but this association was mainly due to nonshared environmental factors. Finally, these findings were found for males only, providing further support that there may be distinctive genotype–phenotype pathways for the development of psychopathy for different sexes. Future studies may concentrate on genetic architecture of these covariances across development from adolescence to adulthood.

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References

- Åberg E, Fandiño-Losada A, Sjöholm LK, Forsell Y, Lavebratt C. The functional Val¹⁵⁸Met polymorphism in catechol-*O*-methyltransferase (COMT) is associated with depression and motivation in men from a Swedish population-based study. *Journal of Affective Disorders*. 2011; 129:158–166.
- Akaike H. Factor analysis and AIC. *Psychometrika*. 1987; 52:317–332.
- Arnett PA. Autonomic responsivity in psychopaths: A critical review and theoretical proposal. *Clinical Psychology Review*. 1997; 17:903–936. [PubMed: 9439873]
- Baker LA, Tuvblad C, Reynolds C, Zheng M, Lozano DI, Raine A. Resting heart rate and the development of antisocial behavior from age 9 to 14: Genetic and environmental influences. *Development and Psychopathology*. 2009; 21:939–960. [PubMed: 19583891]
- Baker LA, Tuvblad C, Wang P, Gomez K, Bezdjian S, Niv S, et al. The Southern California Twin Register at the University of Southern California: III. *Twin Research and Human Genetics*. 2013; 16:336–343. [PubMed: 23394193]
- Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science*. 1995; 269:1115–1118. [PubMed: 7652558]
- Bezdjian S, Raine A, Baker LA, Lynam DR. Psychopathic personality in children: Genetic and environmental contributions. *Psychological Medicine*. 2011; 41:589–600. [PubMed: 20482945]
- Biederman J, Kim JW, Doyle AE, Mick E, Fagerness J, Smoller JW, et al. Sexually dimorphic effects of four genes (COMT, SLC6A2, MAOA, SLC6A4) in genetic associations of ADHD: A preliminary study. *American Journal of Medical Genetics*. 2008; 147B:1511–1518. [PubMed: 18937309]
- Blair R. The amygdala and ventromedial prefrontal cortex in morality and psychopathy. *Trends in Cognitive Sciences*. 2007; 11:387–392. [PubMed: 17707682]
- Blair RJR, Peschardt K, Budhani S, Mitchell D, Pine D. The development of psychopathy. *Journal of Child Psychology and Psychiatry*. 2006; 47:262–276. [PubMed: 16492259]
- Blom, G. *Statistical estimates and transformed beta-variables*. New York: Wiley; 1958.
- Crider A, Kremen WS, Xian H, Jacobson KC, Waterman B, Eisen SA, et al. Stability, consistency, and heritability of electrodermal response lability in middle-aged male twins. *Psychophysiology*. 2004; 41:501–509. [PubMed: 15189473]
- Evans DM, Gillespie N, Martin N. Biometrical genetics. *Biological Psychology*. 2002; 61:33–51. [PubMed: 12385668]

- Fairchild G, Stobbe Y, Van Goozen SH, Calder AJ, Goodyer IM. Facial expression recognition, fear conditioning, and startle modulation in female subjects with conduct disorder. *Biological Psychiatry*. 2010; 68:272–279. [PubMed: 20447616]
- Fairchild G, Van Goozen SH, Stollery SJ, Goodyer IM. Fear conditioning and affective modulation of the startle reflex in male adolescents with early-onset or adolescence-onset conduct disorder and healthy control subjects. *Biological Psychiatry*. 2008; 63:279–285. [PubMed: 17765205]
- Flor H, Birbaumer N, Hermann C, Ziegler S, Patrick CJ. Aversive Pavlovian conditioning in psychopaths: Peripheral and central correlates. *Psychophysiology*. 2002; 39:505–518. [PubMed: 12212643]
- Fowles DC, Dindo L. Temperament and psychopathy: A dual-pathway model. *Current Directions in Psychological Science*. 2009; 18:179–183.
- Fung MT, Raine A, Loeber R, Lynam DR, Steinhauer SR, Venables PH, et al. Reduced electrodermal activity in psychopathy-prone adolescents. *Journal of Abnormal Psychology*. 2005; 114:187–196. [PubMed: 15869350]
- Gao Y, Glenn AL, Schug RA, Yang Y, Raine A. The neurobiology of psychopathy: A neurodevelopmental perspective. *Canadian Journal of Psychiatry*. 2009; 54:813–823.
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
- Hare, RD. Electrodermal and cardiovascular correlates of psychopathy. In: Hare, RD.; Schalling, D., editors. *Psychopathic behavior: Approaches to research*. Chichester: Wiley; 1978. p. 107-143.
- Hare, RD. *Manual for the Revised Psychopathy Checklist*. Toronto: Multi-Health Systems; 1991.
- Hare RD, Frazelle J, Cox DN. Psychopathy and physiological responses to threat of an aversive stimulus. *Psychophysiology*. 1978; 15:165–172. [PubMed: 652911]
- Hare RD, Thorvaldson SA. Psychopathy and response to electrical stimulation. *Journal of Abnormal Psychology*. 1970; 76:370. [PubMed: 5490702]
- Hettema JM, Annas P, Neale MC, Fredrikson M, Kendler KS. The genetic covariation between fear conditioning and self-report fears. *Biological Psychiatry*. 2008; 63:587–593. [PubMed: 17698042]
- Hettema JM, Annas P, Neale MC, Kendler KS, Fredrikson M. A twin study of the genetics of fear conditioning. *Archives of General Psychiatry*. 2003; 60:702. [PubMed: 12860774]
- Iacono WG. Identifying psychophysiological risk for psychopathology: Examples from substance abuse and schizophrenia research. *Psychophysiology*. 1998; 35:621–637. [PubMed: 9844425]
- Iacono WG, Carlson SR, Malone SM. Identifying a multivariate endophenotype for substance use disorders using psychophysiological measures. *International Journal of Psychophysiology*. 2000; 38:81–96. [PubMed: 11027796]
- Isen JD, Iacono WG, Malone SM, McGue M. Examining electrodermal hyporeactivity as a marker of externalizing psychopathology: A twin study. *Psychophysiology*. 2012; 49:1039–1048. [PubMed: 22646690]
- Isen JD, Raine A, Baker L, Dawson M, Bezdjian S, Lozano DI. Sex-specific association between psychopathic traits and electro-dermal reactivity in children. *Journal of Abnormal Psychology*. 2010; 119:216. [PubMed: 20141258]
- Karayiorou M, Sobin C, Blundell ML, Galke BL, Malinova L, Goldberg P, et al. Family-based association studies support a sexually dimorphic effect of COMT and MAOA on genetic susceptibility to obsessive-compulsive disorder. *Biological Psychiatry*. 1999; 45:1178–1189. [PubMed: 10331110]
- LaBar KS, LeDoux JE, Spencer DD, Phelps EA. Impaired fear conditioning following unilateral temporal lobectomy in humans. *Journal of Neuroscience*. 1995; 15:6846–6855. [PubMed: 7472442]
- Lenzenweger MF. Endophenotype, intermediate phenotype, bio-marker: Definitions, concept comparisons, clarifications. *Depression and Anxiety*. 2013; 30:185–189. [PubMed: 23325718]
- López R, Poy R, Patrick CJ, Moltó J. Deficient fear conditioning and self-reported psychopathy: The role of fearless dominance. *Psychophysiology*. 2013; 50:210–218. [PubMed: 23240559]
- Lykken DT. A study of anxiety in the sociopathic personality. *Journal of Abnormal and Social Psychology*. 1957; 55:6.

- Lykken D, Iacono W, Haroian K, McGue M, Bouchard T. Habituation of the skin conductance response to strong stimuli: A twin study. *Psychophysiology*. 1988; 25:4–15. [PubMed: 3353484]
- Lynam DR. Pursuing the psychopath: Capturing the fledgling psychopath in a nomological net. *Journal of Abnormal Psychology*. 1997; 106:425–438. [PubMed: 9241944]
- Malkani S, Wallace KJ, Donley MP, Rosen JB. An *egr-1* (zif268) antisense oligodeoxynucleotide infused into the amygdala disrupts fear conditioning. *Learning & Memory*. 2004; 11:617–624. [PubMed: 15466317]
- Montag C, Buckholtz JW, Hartmann P, Merz M, Burk C, Hennig J, et al. COMT genetic variation affects fear processing: Psychophysiological evidence. *Behavioral Neuroscience*. 2008; 122:901–909. [PubMed: 18729643]
- Muthén, LK.; Muthén, BO. *Mplus user's guide*. 5. Los Angeles: Author; 2007.
- Öhman A, Mineka S. Fears, phobias, and preparedness: Toward an evolved module of fear and fear learning. *Psychological Review*. 2001; 108:483. [PubMed: 11488376]
- Patrick, CJ.; Bernat, EM. Neurobiology of psychopathy. In: Berntson, GG.; Cacioppo, JT., editors. *Handbook of neuroscience for the behavioral sciences*. 2. Hoboken, NJ: Wiley; 2009.
- Patrick CJ, Fowles DC, Krueger RF. Triarchic conceptualization of psychopathy: Developmental origins of disinhibition, boldness, and meanness. *Development and Psychopathology*. 2009; 21:913–938.10.1017/S0954579409000492 [PubMed: 19583890]
- Patrick CJ, Hicks BM, Nichol PE, Krueger RF. A bifactor approach to modeling the structure of the Psychopathy Checklist—Revised. *Journal of Personality Disorders*. 2007; 21:118–141. [PubMed: 17492917]
- Plomin, R.; DeFries, JC.; McClearn, GE.; McGuffin, P. *Behavioral Genetics*. 5. New York: Worth; 2008.
- Posthuma D, Beem AL, De Geus EJ, Van Baal GCM, von Hjelmberg JB, Iachine I, et al. Theory and practice in quantitative genetics. *Twin Research*. 2003; 6:361–376. [PubMed: 14624720]
- Raftery AE. Bayesian model selection in social research. *Sociological Methodology*. 1995; 25:111–164.
- Rijsdijk FV, Viding E, De Brito S, Forgiarini M, Mechelli A, Jones AP, et al. Heritable variations in gray matter concentration as a potential endophenotype for psychopathic traits. *Archives of General Psychiatry*. 2010; 67:406. [PubMed: 20368516]
- Rosen JB. The neurobiology of conditioned and unconditioned fear: A neurobehavioral system analysis of the amygdala. *Behavioral and Cognitive Neuroscience Reviews*. 2004; 3:23–41. [PubMed: 15191640]
- Rothmund Y, Ziegler S, Hermann C, Gruesser SM, Foell J, Patrick CJ, et al. Fear conditioning in psychopaths: Event-related potentials and peripheral measures. *Biological Psychology*. 2012; 90:50–59. [PubMed: 22387928]
- SAS. *SAS/STAT 9.2 user's guide*. Cary, NC: Author; 2008.
- Schalling, D. Psychopathy-related personality variables and the psychophysiology of socialization. In: Hare, RD.; Schalling, D., editors. *Psychopathic behavior: Approaches to research*. Chichester: Wiley; 1978. p. 85-106.
- Steiger JH. Tests for comparing elements of a correlation matrix. *Psychological Bulletin*. 1980; 87:245.
- Sylvers P, Brubaker N, Alden SA, Brennan PA, Lilienfeld SO. Differential endophenotypic markers of narcissistic and antisocial personality features: A psychophysiological investigation. *Journal of Research in Personality*. 2008; 42:1260–1270.
- Tranel D, Damasio H, Denburg NL, Bechara A. Does gender play a role in functional asymmetry of ventromedial prefrontal cortex? *Brain*. 2005; 128:2872–2881. [PubMed: 16195242]
- Tuvblad C, Gao Y, Isen J, Botwick T, Raine A, Baker LA. The heritability of the skin conductance orienting response: A longitudinal twin study. *Biological Psychology*. 2012; 89:47–53. [PubMed: 21945549]
- Tuvblad C, Wang P, Bezdjian S, Raine A, Baker L. Psychopathic personality development from ages 9 to 18: Genes and environment. 2014 Manuscript submitted for publication.

- van den Oord EJ, Simonoff E, Eaves LJ, Pickles A, Silberg J, Maes H. An evaluation of different approaches for behavior genetic analyses with psychiatric symptom scores. *Behavior Genetics*. 2000; 30:1–18. [PubMed: 10934795]
- Viding, E.; Larsson, H. Genetics of child and adolescent psychopathy. In: Randall, DRL.; Salekin, T., editors. *Handbook of child and adolescent psychopathy*. New York: Guilford Press; 2010. p. 113-134.
- Waldman, ID.; Rhee, S. Genetic and environmental influences on psychopathy and antisocial behavior. In: Patrick, CJ., editor. *Handbook of psychopathy*. New York: Guilford Press; 2006. p. 205-228.
- Walker DL, Davis M. Double dissociation between the involvement of the bed nucleus of the stria terminalis and the central nucleus of the amygdala in startle increases produced by conditioned versus unconditioned fear. *Journal of Neuroscience*. 1997; 17:9375–9383. [PubMed: 9364083]
- Wang P, Baker LA, Gao Y, Raine A, Lozano DI. Psychopathic traits and physiological responses to aversive stimuli in children aged 9–11 years. *Journal of Abnormal Child Psychology*. 2012; 40:759–769. [PubMed: 22228313]
- Williams LM, Gatt JM, Kuan SA, Dobson-Stone C, Palmer DM, Paul RH, et al. A polymorphism of the MAOA gene is associated with emotional brain markers and personality traits on an antisocial index. *Neuropsychopharmacology*. 2009; 34:1797–1809. [PubMed: 19194374]

Figure 1. Correlated factors solution with 95% confidence intervals for bivariate genetic analysis between manipulative/deceitful traits and skin conductance responses (SCR), including males only. The number 1 in the triangle indicates a constant, and its loading to each observed variable denotes the intercept/mean value of that variable. (a) Manipulative/deceitful and anticipatory NS-SCRs and (b) manipulative/deceitful and aversive NS-SCRs. A, Additive genetic variance; C, shared environmental variance; E, nonshared environmental variance; anticipatory nonspecific SCR (NS-SCR), NS-SCR at signaled prenoise phase; aversive NS-SCR, NS-SCR at postnoise phase, combining signaled and unsignaled conditions.

Intrafamily correlations of SCR measures by zygosity and their sex-specific correlations with two Child Psychopathy Scale factors

Table 1

	MZM (<i>n</i> = 78)	DZM (<i>n</i> = 49)	MZF (<i>n</i> = 93)	DZF (<i>n</i> = 69)	DZO (<i>n</i> = 87)
Anticipatory NS-SCR	.39*	.26	.45*	.34*	.21
Aversive NS-SCR	.52*	.18	.45*	.25*	.26*

	Impulsive/Disinhibited		Manipulative/Deceitful	
	Boys (<i>n</i> = 341)	Girls (<i>n</i> = 411)	Boys (<i>n</i> = 341)	Girls (<i>n</i> = 411)
Anticipatory NS-SCR ^a	-.07	-.02	-.14*	-.02
Aversive NS-SCR	-.05	-.05	-.17*	-.01

Note: Pearson correlations based on rank-normalization transformed data are presented. SCR, Skin conductance response; MZM, monozygotic males; MZF, monozygotic females; DZM, dizygotic males; DZF, dizygotic females; DZO, dizygotic opposite sex; anticipatory NS-SCR, non-specific SCR at signaled prenoise phase; aversive NS-SCR, NS-SCR at postnoise phase, combining signaled and unsignaled conditions.

^aThis was also reported in Wang et al. (2012).

* $p < .05$.

Table 2

Model comparisons in univariate genetic analyses

	Overall Fit				Chi-Square Difference Test				Parameter Estimates (95% CI)					
	-2LL	Free P.	χ^2	df	AIC	BIC	χ^2	df	p	A	C	E	Means	
Anticipatory NS-SCRs														
0. Saturated model	4436.41	25												
1. ACE males females	4454.02	8	17.61	17	4470.00	4502.75								
Mean males females														
2. ACE males = females	4454.70	5	18.29	20	4464.70	4485.15	0.68	3	.88	0.27	0.14	0.59	M: 0.19	
Mean males females										(0.02-0.77)	(0-0.61)	(0.47-0.73)	F: 20.16	
3. ACE males = females	4474.57	4	38.16	21	4482.57	4498.94	19.87	1	< .01					
Mean males = females														
Aversive NS-SCRs														
0. Saturated model	4445.00	25												
1. ACE males females	4463.79	8	18.79	17	4479.79	4512.52	18.79	17	.34					
Mean males females														
2. ACE males = females	4463.80	5	18.80	20	4473.80	4494.26	0.01	3	1					
Mean males females														
3. ACE males = females	4467.19	4	22.19	21	4475.19	4491.56	3.39	1	.07	0.44	0.02	0.54	0.01	
Mean males = females										(0.15-0.89)	(0-0.11)	(0.43-0.66)		

Note: Best-fitting models are in bold. Anticipatory NS-SCR, nonspecific skin conductance response at signaled prenoise phase; aversive NS-SCR, NS-SCR at postnoise phase, combining signaled and unsignaled conditions.