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The Genetic Underpinnings of Callous-Unemotional Traits: A Systematic Research Review

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Introduction

Psychopathic traits describe a set of characteristics that are interpersonal (e.g., egocentrism, social manipulation), emotional (e.g., lack of guilt, shallow affect), and behavioral (e.g., impulsivity, aggression, antisociality; Hare & Neumann, 2005; Salekin, 2017). Although the term ‘psychopath’ is not generally used to describe children, some psychopathic characteristics are clinically observed in childhood, including the emotional deficits known as callous-unemotional (CU) traits. CU traits represent an important construct for understanding psychopathic traits throughout the life-course; however, their genetic and environmental etiology is not well understood. The current systematic review seeks to integrate the current literature on the genetic underpinnings, both molecular and quantitative, of CU traits.

CU traits are widely recognized as a risk factor for future psychopathic traits and antisocial behavior, and an analog of CU traits was recently introduced to the DSM-5 (American Psychiatric Association [APA], 2013). This conduct disorder (CD) specifier, “with limited prosocial emotions,” requires children display two of the following four characteristics: lack of guilt/remorse, lack of empathy, deficient affect, and/or lack of concern about performance (APA, 2013). These *emotional traits* supplement the *behavioral characteristics* described by CD. The lifetime prevalence for CD is approximately 12% for males and 7% for females (Nock, Kazdin, Hiripi, & Kessler, 2006) and approximately 10–32% of these individuals will qualify for the limited prosocial emotions (CU) specifier (Kahn, Frick, Youngstrom, & Kogos Youngstrom, 2012).

The recent inclusion of CU traits in the DSM-5 is not surprising given the usefulness of these traits in delineating youth at the highest risk for severe conduct problems (Frick, 2012; Frick, Ray, Thornton, & Kahn, 2014). Specifically, CU traits appear to be associated with proactive aggression (Centifanti, Fanti, Thompson, Demetriou, & Anastassiou-Hadjicharalambous, 2015; Thornton, Frick, Crapanzano, & Terranova, 2013), violent crime

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(Kruh, Frick, & Clements, 2005; Vitacco & Vincent, 2006), and antisocial personality disorder (ASPD) in adulthood (McMahon, Witkiewitz, & Kotler, 2010). The ability of CU traits to classify youth into those at highest risk for future externalizing behavioral disorders has established CU traits as a construct of specific interest to developmental researchers, particularly those interested in the sequelae associated with adult psychopathy.

CU traits are frequently associated with several core deficits: (i) an impaired ability to recognize the emotional expressions (particularly the distress cues of fear and sadness) of others (Dawel, O’Kearney, McKone, & Palermo, 2012; Marsh & Blair, 2008; Wilson, Juodis, & Porter, 2011); (ii) reduced autonomic arousal to emotional stimuli (e.g., Anastassiou-Hadjicharalambous, & Warden, 2008; Blair, 1999; de Wied, van Bostel, Matthys, & Meeus, 2012; Kimonis et al., 2008); (iii) reduced augmentation of the startle reflex by visual primes (e.g., Fanti, Panayiotou, Lazarou, Michael, & Georgiou, 2016). These deficits have been hypothesized to reflect dysfunction within the amygdala and connected regions and to interfere with social learning and moral development leading to the behavioral manifestations of CU traits (Blair, 1995; Blair 2013). There are also data indicating that CU traits are associated with insensitivity to punishment – either self-report (Fanti, Panayiotou, Lazarou, Michael, & Georgiou, 2016) or task-based (O’Brien & Frick, 1996). However, other data indicate that reinforcement insensitivity is a feature related to conduct problems more generally rather than CU traits specifically (e.g., White et al., 2014).

Despite the fact that the impairments described above are also noted in adults with psychopathy, whether or not the behavioral and emotional manifestations of psychopathy are consistent across age is still a widely debated topic (e.g., Anderson & Kiehl, 2014). Some research suggests that the construct of psychopathy is longitudinally invariant (i.e., symptoms index the same construct) across adolescence and adulthood (Hawes, Mulvey, Schubert, & Pardini, 2014). However, longitudinal invariance is less clear when it comes to the transition from childhood to adolescence, although it has been suggested that callousness is invariant from around age 11 onward (Obradović, Pardini, Long, & Loeber, 2007). For these reasons, a research focus on callousness and unemotionality in childhood is often preferred over the construct of psychopathy.

Rationale & Aims

Given the severity of the adult outcomes associated with high levels of CU traits, discovering the etiological contributions to these traits is of utmost importance to better inform clinical and translational work in the fields of intervention and prevention. Although specific *causal* mechanisms for CU traits have not yet been elucidated, several researchers have presented precise neurohormonal models of CU etiology, specifically as they relate to oxytocin, serotonin, and amygdala dysfunction (e.g., Dadds & Rhodes, 2008; Moul, Killcross, & Dadds, 2012). Furthermore, there has been a substantial amount of research into the etiological sources of variance (genetic vs. environmental) and molecular genetic mechanisms associated with CU traits. In 2012, Viding and McCrory conducted a review of published genetic and neurocognitive studies of CU traits. In the 6 years since this study was published the number of genetic studies of CU traits has nearly doubled - with an especially rapid growth in the number of molecular genetic studies. Given this rapid expansion and

productivity in the field of behavior genetics, a reassessment of the genetic underpinnings of CU traits is warranted with a particular focus on molecular genetic mechanisms.

The aims of the current review were to compile, review, and discuss the extant literature on the genetic underpinnings CU traits including both quantitative genetic and molecular genetic studies. Quantitative genetic studies seek to identify the relative contribution of genes and environment to a trait of interest and generally report the “heritability” of a trait (i.e., the proportion of trait variance in the population that is explained by genetic variation). Quantitative genetic studies seek determine whether or not a trait is influenced by genetics, and researchers generally prescribe to the belief that heritability should be established before the search for molecular genetic mechanisms begins. There are a variety of methods for uncovering molecular genetic mechanisms including candidate gene studies, genome-wide methods, and epigenetic methods. A review of each of these methodologies is included in the methods section of the current review. Considering both quantitative and molecular studies, we conducted a systematic review of the extant CU literature using two relevant databases: PubMed and PsychInfo. The following section describes our systematic review of the literature.

Methods

Due to the often-technical nature of the studies reviewed here, Table 1 defines key terms that have been bolded throughout the manuscript. To be included in the current review manuscripts must have met three criteria: 1) The manuscript must have described original research (i.e., reviews and meta-analyses were not included), 2) The manuscript must have focused on quantitative (e.g., **heritability**) and/or molecular genetic mechanisms (e.g., **candidate gene**, **genome-wide association [GWA]**, **methylation**, etc.) of CU traits, and 3) The manuscript must have described CU traits in a unitary context and not only as it relates to other (or larger) constructs. For example, in a hypothetical study on the larger construct of psychopathy, the study would only be eligible for inclusion in the current review if it also included results on a psychopathy sub-factor that was described as ‘callous,’ ‘affective,’ or ‘callous-unemotional’; however, if only details on the larger psychopathy construct were included then it was not eligible for the current review.

Studies were selected by searching, in August of 2018, the PubMed and PsychINFO databases with the search term algorithm (“*callous*” OR “*callous-unemotional*”) AND (“*twins*” OR “*heritab**” OR “*geneti**” OR “*genom**” OR “*epigen**”). This algorithm ensured the inclusion of quantitative, genetic, genomic, and **epigenetic** studies. Wildcard operators (*) were used to include all possible suffixes on a relevant search term (such as the terms ‘*genomic*’ and ‘*genome*’ captured by the wildcard operator ‘*genom**’). Titles and abstracts were screened to determine if the studies were eligible for inclusion. If questions about eligibility remained then the entire article was reviewed to determine if inclusion criteria were met. This resulted in a total of 35 studies. Additionally, references of relevant review articles were evaluated to ensure no articles were missed. This secondary review resulted in the inclusion of 4 additional studies for a total of 39 studies meeting the eligibility criteria listed above. Figure 1 displays a flow-chart of the article review process.

The studies reviewed below generally fall into one of two categories: 1) Quantitative genetic studies or 2) molecular genetic studies. Of the 39 reviewed studies, 24 included quantitative components and 16 included molecular components (one study included both quantitative and molecular results). A brief review of the methodology most frequently used in these studies is included below.

Quantitative Genetic Studies

Quantitative genetic studies seek to determine the relative contribution of several genetic and environmental sources of variance to a phenotype of interest: **Additive genetic (A)**, **dominant genetic (D)**, **common/shared/family environmental (C)**, and **unique/non-shared environmental (E)**. *A* reflects the additive effect of all **polymorphic alleles**. *D* reflects the non-additive effects of all polymorphic alleles, including phenomena like gene-gene interaction (i.e., “epistasis”). *C* refers to environmental factors that make family members more alike compared to random pairs of individuals, and *E* refers to environmental factors that are unique to each individual, plus measurement error. **Biometrical structural equation modeling** (SEM; a.k.a. “twin modeling”) is the method most often used to decompose the observed variation in a trait into these sources of variance.

The classical twin model uses two correlations, one between pairs of monozygotic (MZ) twins and the other between pairs of dizygotic (DZ) twins, to decompose the variance of a trait into A, C, & E, or A, D, & E factors. MZ twins theoretically share 100% of their polymorphic alleles, 100% of their shared/family environment, and 0% of their non-shared environment, so the MZ correlation can be represented as $r_{MZ} = A + C$. DZ twins share, on average, 50% of their polymorphic alleles, 100% of their shared/family environment, and 0% of their non-shared environment, so the DZ correlation can be represented as $r_{DZ} = 1/2A + C$. Using these two equations as its basis, biometrical SEM compares several models for which different etiological influences are considered (for example, ACE, AE, CE, & E models) and $-2 \log$ -likelihood ($-2LL$) fit statistic values are compared to determine the best-fitting most parsimonious model (Neale & Cardon, 1992). These procedures form the foundation of the classical twin model and are the basis for the quantitative genetic (twin) studies reviewed below. However, some quantitative studies include more complicated methodology, including examination of genetic sex effects, **genetic correlations** between more than 1 trait, and/or heritability estimated directly with molecular data via **genome-wide complex trait analysis** (GCTA).

Genetic sex effects can take the form of either **quantitative sex effects** or **qualitative sex effects**. The presence of quantitative effects indicates that the *proportion*, or *amount*, of genetic influences is different in males and females. On the other hand, qualitative effects indicate that different *sets of genes* are influencing CU traits in males and females. **Genetic correlations** (r_G) are statistics that reflect the degree to which the groups of genes influencing two separate phenotypes are correlated (i.e., include the same genes). Finally, GCTA is a method used to compute heritability without the use of twins. In this method, the small degree of genetic relatedness among individuals that would normally be considered unrelated is estimated via common SNVs measured with GWA methodology (Yang, Lee, Goddard, & Visscher, 2011).

Molecular Genetic Studies

Molecular genetic studies are generally performed after determining that a phenotype is heritable and these studies seek to determine the specific genetic mechanisms underlying the trait of interest. These studies are undertaken using a wide variety of methods, but modern studies mostly fall into three broad categories of interest to the current review: 1) candidate gene (CG) studies, 2) genome-wide association (GWA) studies, and 3) epigenetic and **gene expression** studies.

Candidate gene (CG) studies.—A CG study uses 1 or more pre-selected genetic single nucleotide variant(s) (SNV; a.k.a. “variant”) for which the sample is genotyped. This genotypic data is then used to examine the association between the number of alleles (0, 1 or 2) of a genetic variant and the trait of interest. Most researchers choose variants for CG studies based on some underlying hypothesis about the biological etiology of the phenotype. For example, a variant located in a gene that plays a role in the re-uptake of serotonin may be a biologically plausible mechanism to study in regards to a phenotype that is hypothesized to be causally related to a dysfunctional serotonin system. Once variants are determined and genotyped in a sample, linear or logistic regression is used to examine potential associations (van der Sluis & Posthuma, 2008), where the genetic predictor variables may be binary (e.g., 0 alleles vs. 1 or 2 alleles) or ordinal (e.g., 0 alleles vs. 1 allele vs. 2 alleles) in nature.

A concept that is frequently discussed in CG studies is **gene x environment (GxE) interaction**. Gene-environment interaction can be conceptualized as different genotypes responding differently to the same environmental process. Alternatively, it can also be conceptualized as differential effects of genotype based on environmental processes.

Genome-wide association (GWA) studies.—In contrast to CG studies, GWA studies simultaneously examine a large number of variants across a participant’s genome. Associations are tested between a phenotype and hundreds of thousands of common genetic variants without any *a priori* hypotheses. The statistical methods used are much the same as that of CG studies (Sullivan & Purcell, 2008). However, a single GWA study variant must meet a stringent multiple testing burden *p*-value, generally set at 5×10^{-8} (Clark et al., 2011; Pe’er, Yelensky, Altshuler, & Daly, 2008). This stringent significance threshold and lack of *a priori* hypotheses means that significant GWA results are generally perceived as more credible than CG results. However, replication of findings in multiple independent samples is still needed before any conclusions can be drawn from GWA (or CG) results.

Epigenetic studies.—Epigenetics refers to DNA or chromatin modifications that can influence gene expression but do not influence gene structure. The amount of protein a gene produces can vary due to epigenetic factors that regulate the gene’s expression (sometimes referred to as turning a gene “on” or “off,” although the process is actually much more complex). It is important to remember that while DNA sequence is inherited, epigenetic modifications to the genome are most frequently mediated by environmental processes and not inherited directly from one’s parents. Currently, the most commonly studied epigenetic mechanism is DNA methylation, whereby a methyl group is added to a specific DNA site

making the gene less accessible to the cellular machinery responsible for gene transcription (the process of copying DNA into RNA). The blockage of the transcriptional machinery can decrease the expression of a particular gene (Allis & Jenuwein, 2016). A study that assesses epigenetic mechanisms can take the form of either a CG or GWA study by assessing modifications at one (or a few) DNA site(s), or across the entire genome, respectively.

Results

Quantitative Genetic Studies

Table 2 lists the 24 reviewed quantitative genetic studies of CU traits and includes relevant sample descriptives and a brief presentation of the main results. These 24 studies use a variety of instruments and methods, and the reported heritability of CU traits ranges from 25–80%. Several of these studies use selected samples (e.g., selected for a behavioral disorder, in the top 10% of the CU trait distribution, etc.), and these studies tend to report the highest heritabilities (63–80%; Fontaine, Rijdsdijk, McCrory & Viding, 2010; Humayun, Kahn, Frick, & Viding, 2014; Larsson, Viding, & Plomin, 2008; Saunders et al., 2018; Viding, Blair, Moffitt, & Plomin, 2005). It is important to note that the concept of heritability is specific to the population under study and only assesses the genetic influences on trait variability in members of that specific population. Therefore, the studies using selected samples indicate that *among those with very high levels of CU traits*, genetic factors influence a high proportion of the variability *within these individuals*. However, these studies do not provide any information on the proportion of genetic influences on trait variation in the general population. Importantly, these studies do not provide information about the differences between individuals with high and low CU traits, which is generally how the term heritability is conceptualized. Although these studies provide information about variation among individuals with pathological levels of CU traits, care should be taken to describe these results as separate from general population studies as to not upwardly bias heritability estimates (e.g., Neale, Eaves, Kendler, & Hewitt, 1989).

Of the remaining quantitative genetic studies using non-selected samples to estimate heritability, the greatest variation in heritability estimates is observed in the youngest samples (ages 2–5), which is not surprising given the infrequent investigation of CU in very young samples, and the questions about whether or not CU/psychopathic traits are tapping into the same construct in young children. The youngest of these samples (Flom & Saudino, 2017a; Flom & Saudino, 2017b) used data from the parent-report Child Behavior Checklist (CBCL; Achenback & Rescorla, 2001) in $N = 628$ twins aged 2–3 years and estimated the heritability of CU traits at age 2 and 3 at 72% and 65%, respectively. Conversely, in a slightly older sample (age 5; Tuvblad, Fanti, Andershed, Colins, & Larsson, 2017), the teacher-report Child Problematic Traits Inventory (CPTI; Colins et al., 2014) in $N = 1,189$ twins generated the lowest reported estimate of heritability: 25%. The variation in heritability estimates for young children could be due to the different measures and reporters used, and these issues may be compounded by longitudinal non-invariance. That is, there is a distinct possibility that researchers using very young samples may be tapping into a psychological construct that differs from the traditional conceptualization of CU traits seen in adolescents and adults (e.g., Hawes et al., 2014; Obradović et al., 2007).

The picture of CU trait heritability among general population samples of individuals in late childhood, adolescence, and early adulthood (aged 7–19) is much less variable, ranging from 36–67% (Bezdjian, Raine, Baker, & Lynam, 2011; Blonigan, Hicks, Kreuger, Patrick, & Iacono, 2006; Ficks, Dong, & Waldman, 2014; Henry et al., 2018a; Henry et al., 2018b; Henry, Pingault, Boivin, Rijdsdijk, & Viding, 2016; Kendler, Patrick, Larsson, Gardner, & Lichtenstein, 2013; Larsson, Andershed, & Lichtenstien, 2006; Moore et al., 2017; O’Nions et al., 2015; Taylor, Loney, Bobadilla, Iacono, & McGue, 2003; Mann, Briley, Tucker-Drob, & Harden, 2015; Tuvblad, Bezdjian, Raine, & Baker, 2014; Viding et al., 2013; Viding, Frick, & Plomin, 2007). Furthermore, two studies of this age range suggest that genetic factors account for a substantial proportion of *stable variation* in CU traits across time; 58% from age 17 to 24 (Blonigan et al., 2006) and up to 89% across ages 7–12 (Henry et al., 2018a). However, no study has yet investigated whether or not the heritability of CU traits changes dynamically throughout development. Such changes in heritability have been observed in other externalizing psychopathology of adolescence such as substance abuse (for a review see Dick, Adkins, & Kuo, 2016) and may be a relevant phenomenon to consider for CU traits.

Although almost all studies demonstrate that CU traits are significantly influenced by genetics; only three of the 24 quantitative studies report a significant influence of shared/family environment. First, Tuvblad and colleagues (2017) report 17% of the variance in CU is accounted for by shared/family environment among a sample of $N = 1,189$ 5-year-old twins. The other two studies report a significant influence of shared/family environment in girls only. One of these studies used latent trajectory analysis to analyze a stable-high CU group in $N = 9,462$ children aged 7–12, and found the variance in this group to be influenced primarily by genetics in males ($A = 78\%$) but primarily influenced by shared/family environment in females ($C = 75\%$; Fontaine, Rijdsdijk, McCrory, & Viding, 2010). The final study investigated the relationship between CU and CD in a sample of over 6,000 7-year-olds and found that shared/family environment accounted for 20% of the CU variance in girls, but was an insignificant factor for boys’ CU. Interestingly, although the influence of C is a common finding in antisocial behavior (for a review see Rhee & Waldman, 2002) it is a relatively rare finding in studies of CU traits. Therefore, the significant influence of shared/family environment found in these three studies may stem from study-specific data collection and/or analyses procedures or they may simply be spurious findings.

The examination of potential sex-differences in CU trait heritability has been neglected by the majority of studies. However, a few studies have begun to investigate genetic sex effects on CU traits. Some studies have reported the presence of quantitative sex effects (Bezdjian et al., 2011; Fontaine et al., 2010; Viding et al., 2007). These studies report a greater influence of genetic factors on CU traits in males as compared to females. However, others have failed to replicate these findings (Larsson et al., 2006; Ficks et al., 2014; Tuvblad et al., 2017), suggesting no *consistent* indication of quantitative sex effects. Only two studies have formally tested for qualitative sex effects (different sets of genes influencing CU in males vs. females), and neither found evidence for such differences (Larsson, Andershed, & Lichtenstein, 2006; Ficks, Dong, & Waldman, 2014).

In regard to the different measures used to assess CU traits, the majority of quantitative genetic studies reviewed above rely on measures of CU traits derived from instruments originally designed to assess psychopathic traits and/or personality more broadly (e.g., APSD [Frick & Hare, 2001], Child Psychopathy Scale [CPS; Lynam, 1997], CPTI, Minnesota Temperament Inventory [MTI; Loney, Taylor, Butler, & Iacono, 2002], Multidimensional Personality Questionnaire [MPQ; Tellegen & Waller, 2008], SDQ [Goodman, 1997], Youth Psychopathic Traits Inventory [YPI; Andershed, Kerr, Stattin, & Levander, 2002]). Such studies usually perform a series of factor analyses and/or extract a score for a handful of items corresponding to the authors' conceptualization of CU traits. However, several problems with these methods have been noted. Specifically, these extracted measures often include only a small number of items (sometimes as few as 4) with limited response options resulting in negatively skewed responses. These measurement issues often result in significant psychometric issues such as poor internal consistency (For a review of these issues, see Frick & Ray, 2014). The use of a scale designed specifically to assess CU traits is one potential way to avoid several of these shortcomings and also increase the comparability of results across studies.

The Inventory of Callous-Unemotional Traits (ICU; Frick, 2004; Kimonis et al., 2008) is one measure that was designed to assess CU traits as a unitary construct. However, the ICU is not without its flaws. Psychometric properties of the ICU, specifically the unemotional subscale, have been inconsistent (e.g., Hawes et al., 2014; Henry et al., 2016; Moore et al., 2017) and problems with the directionality of wording have been noted (e.g., Hawes et al., 2014; Ray, Frick, Thornton, Steinberg, & Cauffman, 2015). However, the ICU is still one of the most frequent measurements used to provide a more complete assessment of CU traits in children and adolescents (Fanti, Frick, & Georgiou, 2009). Three studies have thus far examined the heritability of CU traits using the ICU (Henry et al., 2016; Mann et al., 2015; Moore et al., 2017). In a sample of over 10,000 16-year old twins, Henry and colleagues (2016) reported a bifactor model for the parent-report ICU consisting of a general, callous-uncaring, and unemotional factor, and estimated the heritability of these factors at 58%, 70%, and 79%, respectively. Moore and colleagues (2017) used data from $N = 678$ 9–14 year old twins assessed at two time points approximately 3 weeks apart to estimate heritability while controlling for measurement error (which is usually included in estimates of non-shared environment). This study estimated parent-report ICU heritability at 39% before measurement error was accounted for, with this estimate increasing to 46% when error was accounted for in the model. Using $N = 535$ twins and triplets aged 13–21 years, Mann and colleagues (2015) found a similar heritability using self-report ICU: approximately 40%.

A molecular methodological alternative to twin studies, Genome-wide Complex Trait Analysis (GCTA), was recently used to estimate the heritability of CU traits in $N = 2,930$ children aged 7–12 years (Viding et al., 2013). This GCTA analysis estimated the heritability of CU traits, as measured by the APSD and SDQ, at 7%; far less than the 40–60% reported in twin studies. However, large discrepancies between twin- and GCTA-based heritability estimates are not uncommon. For example, GCTA-based heritability for parent-report psychopathy and teacher-report ASPD were recently estimated at 14% and 8%, respectively, while the corresponding twin-based heritabilities in the same samples were 47% and 62%,

respectively (Cheesman et al., 2017). Furthermore, even for anthropomorphic and cognitive traits, GCTA-based heritability estimates are about half of the twin-based estimates (Plomin et al., 2013). These differences in GCTA- vs. twin-based heritability likely stem from the fact that GCTA methodology does not capture the full range of genetic architectures (e.g., common vs. rare variants, additive vs. multiplicative effects, etc.; Gibson, 2012; Chatterjee et al., 2013; Wray et al., 2013). Researchers have noted that GCTA-based heritability estimates reflect the ceiling for genetic effects discovered in genome-wide methodology (e.g., Cheesman et al., 2017). Therefore, researchers should consider uncovering the underlying genetic architecture one of the most important future directions for genetic studies of CU traits.

Although most quantitative genetic studies focus on CU traits as a unitary context, a subset of these studies also report genetic correlations between CU traits and related phenotypes. Unsurprisingly, CU traits are highly correlated with CD at the genetic level. Genetic correlations for these two phenotypes have been estimated at $r_G = .77$ in a mixed-sex sample (Saunders et al., 2018), and estimated separately for females and males at $r_G = .65$ and $r_G = .57$, respectively (Viding et al., 2007). The genetic correlation between CU and antisocial behavior has been estimated at $r_G = .78$ in adolescent males (Taylor et al., 2003). However, the genetic correlation appears much lower, $r_G = .16$, when estimated in a mixed-sex sample (Blonigan et al., 2005) indicating potential sex-differences in the genetic covariance between CU and antisocial behavior. Finally, Kendler and colleagues (2013) investigated the genetic correlation between a range of externalizing phenotypes, and found that 32% of the genetic variance in CU traits was shared with a general externalizing factor that also influenced traits such as delinquency, grandiosity, impulsivity, and criminality. Together, these studies suggest that there is substantial genetic overlap between CU traits and other behavioral, impulsive, and antisocial traits. However, a substantial portion of CU's genetic variance is unique to CU, suggesting a partially distinct etiology.

Molecular Genetic Studies

Table 3 lists the 16 reviewed molecular genetic studies of CU traits and includes relevant sample descriptives/methods and a brief presentation of the main results. Of these 17 studies, 11 were traditional CG studies, 2 were traditional GWA studies, and 3 were CG methylation studies.

Candidate gene (CG) studies.—CG studies have potentially implicated several genes in the etiology of CU traits, including *BDNF*, *COMT*, *HTR1B*, *HTR2A*, *MAOA*, *OXTR*, & *SLC6A4*. Most significant candidate gene findings thus far are associated with genes belonging to the serotonin and oxytocin systems.

Several variants in genes involved in coding proteins for the serotonin **receptors** have been investigated as potential candidates for CU traits. The biological plausibility for these variants is clear, especially given that manipulation of the serotonergic system (for example, via tryptophan depletion) can induce features central to psychopathy (e.g., reduced fear recognition and reduced response to punishment; Blair et al., 2008; Finger et al., 2007; Marsh et al., 2006). Furthermore, recent research has demonstrated a negative association

between peripheral blood levels of serotonin and CU traits (Moul, Dobson-Stone, Brennan, Hawes, & Dadds, 2013). Genes that code for serotonin receptors have been associated with CU traits in a sample of $N = 157$ males with CD (age 3–16), including G/T **heterozygous** status at rs11568817 in the *HTR1B* gene and C/C homozygous status at rs6314 in the *HTR2A* gene (Moul et al., 2013).

In studies examining associations between CU traits and the 5-HTTLPR promoter polymorphism in the *SLC6A4* gene that codes for the serotonin **transporter**, results have been mixed. In a study of 147 adolescents with ADHD, Fowler and colleagues (2009) found significant associations with several genetic variants and callousness as measured by the psychopathy checklist (PCL-YV; Forth, Kosson, & Hare, 2003), including **homozygous** status for the 5-HTTLPR short allele. Contrary to the direction of this reported association, another study found a *positive* association between the number of 5-HTTLPR long alleles and CU traits in a sample of $N = 230$ children aged 5–10 years (Brammer, Jezoir, & Lee, 2016). Adding even more uncertainty to the picture of 5-HTTLPR genotype, Sadeh and colleagues (2010) found no overall association between 5-HTTLPR and CU traits in two separate samples ($N = 118$ & 178) using two different methods of measuring CU. However, they did report a gene-environment interaction such that individuals with the long/long 5-HTTLPR genotype had higher CU traits in the presence of low socioeconomic status. These inconsistent 5-HTTLPR genotypic associations may indicate that some significant results are false-positives. However, the presence of an interaction effect may also suggest that the serotonin transporter exerts differential effects under various environmental circumstances (i.e., gene x environment interaction).

Some of the more recent genetic associations with CU traits involve variants in the oxytocin system (involved in coding protein for oxytocin **precursors** and oxytocin receptors). Oxytocin represents another biologically plausible mechanism for CU traits, specifically given its role in modulating amygdala activity (e.g., Gorka et al., 2015) and the association between psychopathic traits and peripheral blood levels of oxytocin (Dadds et al., 2014b). In a sample of $N = 162$ aggressive youth aged 6–16 years, the A/A genotype at rs237885 in the *OXTR* gene was positively associated with CU traits (Beitchman et al., 2012). Furthermore, another nearby *OXTR* variant, rs1042778, was positively associated with CU traits as measured by the APSD and SDQ in two independent samples ($N = 121$ & 59) of youth aged 4–16 with conduct problems (Dadds et al., 2014a). Given their close proximity to one another in the genome (within 1000 base pairs), these two variants are likely indexing the same genetic signal. However, these results are tempered by the fact that the associations between CU traits and oxytocin variants have not been universally replicated. One recent study used a sample of $N = 236$ aggressive youth (aged 6–16) to examine a set of 8 SNVs within two oxytocin genes (*OXTR* and *OXT*) and was unable to find any significant associations with CU traits (Malik, Zai, Abu, Nowrouzi, & Beitchman, 2012).

Several other genetic variants have also been investigated in CG studies of CU traits although less frequently. A significant gene x environment interaction for CU traits was reported in a sample of $N = 171$ children in which harsh/intrusive parenting predicted early (age 3) CU traits, but only among children possessing a specific *BDNF* genotype (G/A or A/A at rs6265; Willoughby, Mills-Koonce, Propper, & Waschbusch, 2013) that codes protein

for brain-derived neurotrophic factor (BDNF), which is involved in synaptic transmission and plasticity (Weizmann Institute of Science [WIS], 2008). Two additional significant associations were reported by Fowler and colleagues (2009) in their study of 147 adolescents with ADHD. First, there was a significant association between CU and the high-risk allele (2–3 repeats) of the 30bp **variable number tandem repeat** in the *MAOA* gene that codes protein for monoamine oxidase A, which is involved in the metabolism of amine neurotransmitters such as dopamine, norepinephrine, and serotonin, among others (WIS, 2008). Second, Fowler and colleagues (2009) reported a significant association between CU and val/val homozygous status at the val158met SNV in the *COMT* gene responsible for the clearance of catecholamine neurotransmitters from the synaptic cleft by catechol-O-methyltransferase (WIS, 2008; the authors did not include the **rs number** for the *COMT* SNV, but one assumes they are referring to the oft-researched rs4680). Unfortunately, some of Fowler and colleagues' (2009) results have failed to replicate. For example, in another CG study of $N = 144$ individuals (age 6–11), researchers examined associations between CU traits and several variants in the *COMT* gene, including rs4680, and no significant associations were found (Hirata, Zai, Nowrouzi, Beitchman, & Kenndey, 2013).

Genome-wide association (GWA) studies.—Given the large sample sizes required for GWA studies to be sufficiently powered, the two preliminary GWA studies that have been conducted (Viding et al., 2010; Viding et al., 2013) are both likely quite underpowered to detect relevant effects. In the first GWA study of CU traits Viding and colleagues (2010) used data from a total of $N = 1,186$ individuals aged 7 years, while Viding and colleagues (2013) more than doubled their original sample size to $N = 2,930$ children aged 7–12 years. Neither study identified any significant genome-wide associations with CU traits as measured by the APSD and SDQ. However, the authors ranked SNVs based on their associated p -values and suggested that future genetic studies consider these top SNVs as potential research targets. Following this advice, a separate research group investigated the top 13 SNVs from Viding (2010) in $N = 213$ individuals aged 3–16 years. Although one variant was associated with CD, none were significantly associated with CU traits (Dadds, Moul, Cauchi, Hawes, & Brennan, 2013). Therefore, no significant findings have thus far emerged from genome-wide methods investigating the etiology of CU traits.

Epigenetic studies.—The epigenetic mechanisms involved in CU traits, like other psychiatric phenotypes, are only just beginning to be studied. The serotonin and oxytocin systems are receiving the most attention, which is not surprising given the results of the CG studies reviewed above and the neural mechanisms associated with serotonin and oxytocin. More specifically, oxytocin appears to modulate amygdala activity (e.g., Gorka et al., 2015), serotonin depletion appears to induce some of the core symptomatology of psychopathy (e.g., Marsh et al., 2006), and emerging evidence suggests that peripheral blood levels of serotonin and oxytocin may serve as **biomarkers** for CU traits (Moul et al., 2013; Dadds et al., 2014b).

HTR1B, a serotonin receptor gene that has been investigated as a CG for CU traits, has also been investigated for potential associations between methylation level and CU traits. Using a sample of $N = 117$ youth (aged 3–16) researchers found that CU traits measured by the

APSD and SDQ are positively associated with *HTR1B* methylation (at 19 examined CpG sites), but only among individuals who are heterozygous (G/T) at a specific SNV (rs11568817) in the *HTR1B* gene (Moul, Dobson-Stone, Brennan, Hawes, & Dadds, 2015). This unique finding indicates a genotype x methylation interaction in the *HTR1B* gene, a phenomenon that is currently not well characterized. However, the authors of this study hypothesize that increased HTR1B methylation “may serve to counteract the increased transcription of HTR1B that is created by the presence of the minor allele at rs11568817” (Moul et al., 2015, p.11).

Two additional studies have reported associations between CU traits and methylation of the *OXTR* gene in late childhood and early adolescence. First, in a sample of $N = 84$ 13-year-olds with CD, level of *OXTR* methylation at birth (at 12 examined CpG sites) was positively associated with CU traits, but only among those without internalizing problems (Cecil et al., 2014). The authors of this study hypothesize that there are distinct etiological pathways to CU traits in individuals with and without associated internalizing psychopathology (Cecil et al., 2014). Second, in two partially overlapping samples ($N = 156$ & 37) of children and adolescents with CD, *OXTR* methylation level (at 11 examined CpG sites) was positively associated with CU traits as well as lower plasma levels of oxytocin. However, these associations were present only in older children (9–16 years old compared to 4–8 years old; Dadds et al., 2014b) which highlights the developmentally dynamic nature of epigenetic modifications.

Discussion

A review of the extant literature revealed 39 quantitative and/or molecular genetic studies on CU traits. 24 of these studies included quantitative components, and the range of heritability reported was 25–80%. However, upon further inspection it appears that the heritability of CU traits in the *general population* of individuals in middle childhood, adolescence, and adulthood (where the construct of CU appears longitudinally invariant [e.g. Obradović et al., 2007]) lies between 36–67%, which is similar to most other temperament and personality traits of childhood and adolescence (for a review, see Polderman et al., 2015). Sixteen studies reviewed here included molecular components. Several SNVs, particularly those involved in the serotonin and oxytocin systems, have been implicated in CU traits. However, replicating significant CG findings has not been particularly successful. Furthermore, no GWA study has thus far identified any associated SNV at a genome-wide level of significance.

One factor that influences the large range of heritability estimates for CU traits is the frequent use of selected samples. This is not surprising given the relative rarity of CU traits in children as well as the historical tendency to consider psychopathology in terms of categorical constructs (APA, 2013). However, many researchers advocate for taking a dimensional approach to psychopathology research (e.g., Widiger and Gore, 2014). Specifically in genetic analyses where heritability is estimated based entirely on variation between individuals within a specific sample, sample selection at a distribution's tail will produce biased estimates (e.g., Neale et al., 1989). For this reason, it is important to study the heritability of ‘extreme’ phenotypes (such as CU and psychopathy) in appropriate

samples, such as those measured either as continuous or as case-control assuming an underlying normal distribution. These approaches allow for the study of variation among the general population, including psychopathic and non-psychopathic individuals as opposed to studying the variation among only extremely psychopathic individuals. At the risk of overgeneralizing, studying the heritability among a case-control or community sample is akin to comparing a psychopath to a normal individual, whereas studying heritability among a highly selected sample is akin to comparing one psychopath to another psychopath – two very different research questions.

Although most quantitative studies indicate that CU traits are substantially heritable, the search for associated molecular genetic variants has not been particularly successful. Although CG studies tend to implicate genes that play important roles in the serotonin and oxytocin systems, these results are infrequently replicated and the percentage of variance accounted for is small. The difficulty in replicating CG results is not unique to CU traits. The limitations of CG studies have been widely noted for some time, especially for complex psychiatric phenotypes whose etiology is likely **multifactorial** and **polygenic** (for a review see Duncan & Keller, 2011).

The massively polygenic nature of most psychiatric phenotypes, influenced by hundreds to thousands of SNVs of very small effect, serves to highlight the core problems of CG studies; they are underpowered, infrequently replicated, and create unfortunate noise in the literature (Duncan & Keller, 2011). The era of CG studies has been referred to as the “dark era” of psychiatric genetics (Moore, Sawyers, Adkins, & Docherty, 2017), and the National Institute of Mental Health (NIMH) has recently advanced this view in their updated research policies by emphasizing “the need for robust evidence of [genetic] association, generally resulting from adequately powered genome wide association studies, as opposed to candidate gene approaches.” (National Institute of Mental Health, 2017).

Although most researchers believe that CG studies represent obsolete methodology, there is at least some evidence of potential biological plausibility for the serotonin and oxytocin systems given the emerging evidence that peripheral blood levels of these neurotransmitters may serve as biomarkers for CU traits (Moul et al., 2013; Dadds et al., 2014b). However, despite the potential biological plausibility, the research to date is insufficient to suggest a genetic association between these genes and CU traits. Much work is needed in this area, and it is our view that researchers should focus on the genome-wide methodology that will allow for statistically sound inferences to be drawn.

GWA studies are one potential way to use genome-wide molecular data to elucidate novel genetic etiology. However, only two studies have examined CU traits using this methodology, and neither resulted in successful identification of associated variants. These null results are not entirely surprising given the relatively small sample sizes of these studies ($N < 3,000$) compared to other successful GWA studies. This is especially true considering the first genome-wide significant variants in Schizophrenia GWA studies were only identified after data on more than 21,000 individuals had been analyzed (The Schizophrenia Psychiatric Genome-Wide Association Study Consortium [Schizophrenia PGC], 2011). However, the success of schizophrenia GWA, as evidenced by gene identification,

replication, and phenotype prediction (e.g., Docherty et al., 2017; Hamshere et al., 2013; Schizophrenia PGC, 2011; Vassos et al., 2017), may not be obtainable for traits where amassing such large samples is unlikely.

Despite the very large samples required for GWA studies, some newer genetic techniques allow for the examination of genetic associations with more modestly sized samples (for a review see Moore et al., 2017). One of these methods, the **polygenic risk score (PRS)**, uses summary statistics from previous well-powered GWA studies to assign individuals a quantitative risk-score that can be used to predict the same, or a different, phenotype (Wray et al., 2014; Moore et al., 2017). However, this approach does not allow the discovery of new risk variants.

Another genetic methodology that has recently become more cost-effective is **next-generation genome sequencing**, which sequences the whole **genome** or **exome** of individuals with the primary aim of identifying rare causal mutations responsible for disease (ten Bosch & Grody, 2008). This is a particularly interesting avenue for future research on CU traits, especially in light of the discrepancy between heritability reported in twin studies (25–80%) vs. GCTA (7%; Viding et al., 2013). Since GCTA only indexes *common* genetic variants, one potential explanation for the discrepancy in heritability estimates across study methodologies is the presence of *rare* genetic variants of large effect, which would potentially be probed in sequencing studies. However, sequencing can require even larger sample sizes than GWA since even more variants are tested.

Given the current scarcity of significant replicated genetic findings, it is important to remember that a large proportion of the variance in CU traits (20–75%, depending on the study) is accounted for by environmental factors. Environmental contributions to CU etiology are arguably easier to identify and are certainly more easily modifiable with clinical intervention. For example, parenting behaviors are one potential environmental mechanism influencing CU traits. In a recent study by Hyde and colleagues (2016), positive reinforcement provided by an adoptive mother was found to be protective of CU traits even in the presence of significant biological risk (i.e., a biological mother with antisocial traits). Furthermore, a similar study used an **MZ-differences design** to control for genetic effects and determined that negative parental discipline, while a unique environmental risk factor for CD, was not a salient factor in the development of CU (Viding, Fontaine, Oliver, & Plomin, 2009). Taken together, this research suggests that specific parenting practices such as increased positive reinforcement, but not negative reinforcement, represent targetable environmental experiences that may potentially counteract one's genetic risk for CU. Therefore, specific parenting practices represent important targets for future clinical and prevention research.

Future Directions

Based on the reviewed literature, it is clear that the search for molecular genetic mechanisms underlying CU traits has only just begun. Most researchers have thus far chosen to focus on candidate genes studies, and these results have been infrequently replicated. Therefore, we recommend researchers focus on genome-wide approaches to understanding CU traits, including GWA and PRS studies. This type of research will require increasingly large

sample sizes, and collaboration between research groups will be advantageous. Researchers with genome-wide data on CU traits should consider following the lead of other groups and forming a CU consortium, in the style of the psychiatric genomics consortium (PGC; www.med.unc.edu/pgc) or genetics of personality consortium (GPC; www.tweelingenregister.org/GPC/). Such collaborations will increase the speed and quality of the discoveries regarding the underlying genetic mechanisms of CU traits.

Conclusions

Although CU trait variance appears to be substantially influenced by genetic factors, the search for replicable genetic mechanisms has been, thus far, largely unsuccessful. Given the current lack of molecular genetic associations, paired with the heterogeneous and pathological nature of CU traits, it is likely that very large sample sizes and advanced genetic methodology will need to be employed in the search for its underlying genetic etiology. Future research should seek to elucidate relevant genetic etiology while also striving to identify environmental factors that are targetable mechanisms for prevention and intervention.

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Figure 1.
Flow-chart of article review process

Table 1.**Glossary of Key (Bolded) Terms**

Term	Definition
Additive Genetic Effects (A)	The additive effect of all polymorphic SNVs across the genome.
BDNF	A protein-coding gene for brain derived neurotrophic factor, which plays a role in synaptic transmission and plasticity.*
Biomarker	An objective biological measure that is associated with a phenomenon, disease, or trait.
Biometrical Structural Equation Modeling	A statistical method used to quantify the influence of genes and environment on a trait or behavior, usually via twin and family studies.
Candidate Gene (CG) Study	A type of study where one or more genetic variant(s) is chosen a priori and the association with a phenotype of interest is examined.
Common/Shared/Family Environmental Effects (C)	The overall effect of the environmental factors that are shared between twins.
COMT	A protein-coding gene for catechol-O-methyltransferase, which plays a role in the clearance of catecholamine neurotransmitters (dopamine, norepinephrine, epinephrine) from the synaptic cleft.*
CpG Site	Refers to a location in the genome where a cytosine (C) nucleotide is followed by a guanine (G) nucleotide in the 5' to 3' direction. These CpG sites can be methylated to form 5-methylcytosine, which reflects the process underlying epigenetic methylation.
Dominant Genetic Effects (D)	The non-additive, or multiplicative, effect of all polymorphic SNVs across the genome.
Epigenetic	Refers to processes that effect gene expression, but do not involve changes in the nucleotide sequence of DNA. Includes both chromatin and DNA modifications.
Exome	The portion of the genome that is formed by exons, which are sections of genes that code for a final mRNA product. Comprises approximately 1% of the genome.
Gene x Environment Interaction	An interaction between a genotype and an environment, such that different genotypes respond differently to the same environmental process.
Gene Expression	The process by which DNA is synthesized (transcribed, spliced, translated, etc.) to produce a gene product/protein.
Genetic Correlation	A measure of similarity between sets of genes influencing separate phenotypes. This statistic indicated the degree to which the same genes influence two or more traits.
Genome	All the genetic information contained by an organism.
Genome-Wide Association (GWA) Study	An examination of a large number of SNVs across the genome to determine which are associated with a phenotype.
Genome-Wide Complex Trait Analysis (GCTA)	A method of estimating heritability using non-family samples, by directly estimating the small degree of genetic relatedness for each pair of individuals in the dataset (via measured genetic variants).
Heritability	The proportion of a trait's phenotypic variance that is due to genetic variance in the population.
Heterozygous	Indicates the possession of two different alleles (for example, G/T or A/C) for a specific SNV.
Homozygous	Indicates the possession of two identical alleles (for example, C/C or T/T) for a specific SNV.
HTR1B	A protein-coding gene for 5-hydroxytryptamine (serotonin) receptor 1B, which acts as a G-protein coupled receptor for serotonin.*
HTR2A	A protein-coding gene for 5-hydroxytryptamine (serotonin) receptor 2A, which acts as a G-protein coupled receptor for serotonin.*
MAOA	A protein-coding gene for monoamine oxidase A, which is involved in the metabolism of amine neurotransmitters (dopamine, norepinephrine, epinephrine, histamine, serotonin).*
Methylation	The process by which a methyl group is added to a CpG site, rendering a region of DNA less accessible to the cellular machinery responsible for transcription.
MZ-Differences Design	A methodology that uses differences between members of an MZ-pair on traits of interest to investigate unique/non-shared environmental effects. This design leverages the fact that MZ twins theoretically share all of their genes

Term	Definition
	and shared/family environment, and therefore differences are thought to be due entirely to unique/non-shared environment.
Next-Generation Genome Sequencing	A fast method of genomic sequencing that simultaneously sequences millions of small DNA fragments and then uses bioinformatic techniques to piece the respective fragments of genetic code together.
OXT	A protein-coding gene for oxytocin/neurophysin I prepropeptide, which acts as a precursor protein for oxytocin and neurophysin I.*
OXTR	A protein-coding gene for the oxytocin receptor, which acts as a G-protein coupled receptor for the neurotransmitter oxytocin.*
Phenotype	An observable characteristic or set of observable characteristics (in the case of a disease or disorder).
Polygenic	A term referring to a phenotype that is causally influenced by more than one SNV.
Polygenic Risk Score	A metric, usually derived from GWA summary statistics, that is used to quantify an individual's level of genetic risk for a specific phenotype.
Precursor	An inactive protein that can be turned into an active protein via modification (such as the addition or removal of a molecule).
Polymorphic Allele	When a mutation in a gene produces more than one variation of that gene in the population, each form is a polymorphic allele.
Qualitative Sex Effects	A term used to describe the phenomenon where the variance of a trait is influenced by different sets of genes in males and females.
Quantitative Sex Effects	A term used to describe the situation in which a trait is influenced by the same set of genes in males and females, although to a different degree (stronger heritability in one sex vs. the other).
Receptor	A neurotransmitter receptor is a protein within neuronal cellular membranes that binds with neurotransmitter to trigger electrochemical signal transmission from one neuron to another.
Rs Number	The reference SNV cluster ID, or rs number, is an identifier used by researchers and databases to refer to a specific genomic SNV.
Single Nucleotide Variant (SNV)	A variation of a single base pair at a specific genomic location.
SLC6A4	A protein-coding gene for a serotonin transporter, which clears serotonin from the synaptic cleft and transports it back to the pre-synaptic terminal.*
Transporter	A protein that clears neurotransmitter from the synaptic cleft and transports it back to the pre-synaptic terminal.
Unique/Non-Shared Environmental Effects (<i>E</i>)	The overall effect of environmental factors that are unshared between twins, plus error.
Variable Number Tandem Repeat (VNTR)	A section of the genome that is repeated a variable number of times within the population.

* Information retrieved from *GeneCards* human gene database (Weizmann Institute of Science, 2018).

Table 2.

Quantitative Genetic Studies, Chronologically within Sample

Sample	Authors & Date	N	Sex	Age (years)	Instrument(s)	Selected sample	Results
Boston University Twin Project	Flom & Saudino, 2017a	<i>N</i> = 628 (314 twin pairs)	53% male	2–3	Child Behavior Checklist 11/2–5 (PR)	N	CU @ 2 years old <i>A</i> = 72%, <i>E</i> = 28%. CU @ 3 years old <i>A</i> = 65%, <i>E</i> = 35%. 42% of genetic variance at age 2 persisted to age 3.
	Flom & Saudino, 2017b	<i>N</i> = 628 (314 twin pairs)	53% male	2–3	Child Behavior Checklist 11/2–5 (PR)	N	At age 2, CU <i>A</i> = 71% (27% specific to CU, 44% shared with ADHD and ODD), <i>E</i> = 29% (25% specific to CU, 4% shared with ADHD and ODD).
Child and Adolescents Twin Study in Sweden (CATSS)	Saunders et al., 2018	<i>N</i> = 426	58% male	15	Youth Psychopathic Traits Inventory (SR)	Y	CU <i>A</i> = 63%, <i>E</i> = 37%. <i>r_G</i> = .77 for CU and CD, .36 for CU and hyperactivity, and –.23 for CU and emotional problems.
Georgia Twin Registry	Ficks, Dong, & Waldman, 2014	<i>N</i> = 1770 (885 twin pairs)	49% males	4–17	Antisocial Process Screening Device (PR)	N	CU factor <i>A</i> = 49%, <i>E</i> = 51%. No quantitative or qualitative sex effects.
Minnesota Twin and Family Study	Taylor, Loney, Bobadilla, Iacono, & McGue, 2003	<i>N</i> = 796 (398 twin pairs)	100% male	16–18	Minnesota Temperament Inventory (SR)	N	CU factor <i>A</i> = 40%, <i>E</i> = 60%. <i>r_G</i> = .78 for CU traits and antisocial behavior.
	Blonigen, Hicks, Krueger, Patrick, & Iacono, 2005	<i>N</i> = 1,252 (626 twin pairs)	46% male	17	Multidimensional Personality Questionnaire (SR)	N	CU factor <i>A</i> = 45%, <i>E</i> = 55%. <i>r_G</i> = .16 for CU traits and antisocial behavior.
	Blonigen, Hicks, Krueger, Patrick, & Iacono, 2006	<i>N</i> = 1,252 (626 twin pairs)	46% male	17, 24	Multidimensional Personality Questionnaire (SR)	N	CU factor <i>A</i> = 42%, <i>E</i> = 58%. Genetic factors accounted for 58% of the stability in CU traits from age 17 to 24.
Preschool Twin Study in Sweden (PETSS)	Tuvblad, Fanti, Andershed, Collins, & Larsson, 2017	<i>N</i> = 1,189	50% male	5	Child Problematic Traits Inventory (TR)	N	CU factor <i>A</i> = 25%, <i>C</i> = 17%, <i>E</i> = 58%. No quantitative sex effects.
Quebec Newborn Twin Study (QNTS)	Henry et al. 2018a	<i>N</i> = 1,324 (662 twin pairs)	Unknown	7–12	Inventory of Callous-Unemotional Traits (TR) & Antisocial Process Screening Device (TR)	N	CU @ age 7 <i>A</i> = 46%, <i>E</i> = 54%. CU @ age 9 <i>A</i> = 59%, <i>E</i> = 41%. CU @ age 10 <i>A</i> = 39%, <i>E</i> = 61%. CU @ age 12 <i>A</i> = 50%, <i>E</i> = 50%. In both longitudinal models (growth and Cholesky) genetic factors accounted for the majority of the stability across age.
	Henry et al., 2018b	<i>N</i> = 1,324 (662 twin pairs)	Unknown	7–12	Inventory of Callous-Unemotional Traits (TR) & Antisocial Process Screening Device (TR)	N	CU <i>A</i> = 65%, <i>E</i> = 35%. Heritability of CU decreased as warm-rewarding parenting increased (gene-environment interaction).
Southern California Twin Project	Bezdjian, Raine, Baker, & Lynam, 2011	<i>N</i> = 1,219 (605 sets of twins and triplets)	49% male	9–10	Child Psychopathy Scale (SR; PR)	N	Callous/disinhibited factor <i>A</i> = 64% in boys, <i>A</i> = 49% in girls, remaining variance accounted for by <i>E</i> .
	Tuvblad, Bezdjian, Raine, & Baker, 2014	<i>N</i> = 1,208 (604 twin pairs)	49% male	14–15	Child Psychopathy Scale (SR; PR) & Antisocial	N	Callous/disinhibited factor of CPS (SR) <i>A</i> ≈ 42%, <i>E</i> ≈ 58%. Callous/disinhibited factor of CPS (PR) <i>A</i> ≈ 46%, <i>E</i> ≈

Sample	Authors & Date	N	Sex	Age (years)	Instrument(s)	Selected sample	Results
The Swedish Twin Study of Child and Adolescent Development	Larsson, Andershed, & Lichtenstein, 2006	$N = 2,180$ (1,090 twin pairs)	48% male	16	Process Screening Device (SR;PR) Youth Psychopathic Traits Inventory (SR)	N	$\approx 54\%$. CU factor of APSD (SR) $A \approx 47\%$, $E \approx 53\%$. CU factor of APSD (SR) $A \approx 63\%$, $E \approx 37\%$. Callous/unemotional factor $A = 43\%$, $E = 57\%$. No qualitative or quantitative sex effects.
The Texas Twin Project	Kendler, Patrick, Larsson, Gardner, & Lichtenstein, 2013	$N = 884$ (442 twin pairs)	100% male	16–17	Youth Psychopathic Traits Inventory (SR)	N	Callous/unemotional factor $A = 36\%$, $E = 61\%$, & $C = 3\%$. 68% of CU's genetic variance was specific to CU, while the other 32% was attributable to a genetic factor common to several externalizing traits (delinquency, grandiosity, impulsivity, criminality, etc.) ICU $A = 40\%$, $E = 60\%$.
Twins Early Development Study (TEDS) ⁺	Mann, Briley, Tucker-Drob, & Harden, 2015 Viding, Blair, Moffitt, & Plomin, 2005	$N = 535$ (264 sets of twins and triplets) Total $N = 7,374$. Analytic $N_s = 808-1,071$	50% male (as of 2012) 47% male	13–21 7	Inventory of Callous-Unemotional Traits (SR) Antisocial Process Screening Device (TR) and Strengths and Difficulties Questionnaire (TR)	Y	Extreme CU traits $A = 67\%$, $E = 33\%$. Extreme antisocial behavior with extreme CU traits $A = 81\%$, $E = 19\%$. Extreme antisocial behavior without extreme CU traits $A = 30\%$, $E = 70\%$.
	Viding, Frick & Plomin, 2007	Total $N = 6,464$, (3,232 twin pairs)	47% male	7	Antisocial Process Screening Device (TR) and Strengths and Difficulties Questionnaire (TR)	N*	Quantitative sex differences for overall model including both CU and CD. For males CU $A = 67\%$, $C = 4\%$, $E = 29\%$, CU/CD $r_G = .57$. For females, CU $A = 48\%$, $C = 20\%$, $E = 32\%$, CU/CD $r_G = .65$.
	Larsson, Viding, & Plomin, 2008	$N = 4,430$ (Analytic N differed for each analysis)	47% male	7	Antisocial Process Screening Device (TR) and Strengths and Difficulties Questionnaire (TR)	Y	Extreme CU traits without extreme antisocial behavior $A = 68\%$, $E = 32\%$. Extreme CU traits with extreme antisocial behavior $A = 80\%$, $E = 20\%$.
	Fontaine, Rijdsdijk, McCrory, & Viding, 2010	$N = 9,462$	47% male	7, 9, 12	Antisocial Process Screening Device (TR) and Strengths and Difficulties Questionnaire (TR)	Y	Quantitative sex-differences for stable-high CU group. In boys $A = 78\%$, $C = 01\%$, $E = 21\%$. In girls $C = 75\%$, $E = 25\%$.
	Viding et al., 2013**	$N = 5,772$ (2,886 twin pairs)	47% male (Total sample)	7, 9, 12	Antisocial Process Screening Device (TR) & Strengths and Difficulties Questionnaire (TR)	N	Via twin modeling, CU $A = 64\%$, $E = 36\%$. Via GCTA, CU $A = 7\%$, environmental variance (C & E) $= 93\%$.
	Humayun, Kahn, Frick, & Viding, 2014	Total $N = 7,374$. Analytic $N_s = 210-992$	47% male	7	Antisocial Process Screening Device (TR) and Strengths and Difficulties Questionnaire (TR)	Y	Extreme CU traits without extreme anxiety $A = 75\%$, $E = 25\%$. Extreme CU traits with extreme anxiety $A = 66\%$, $E = 34\%$.
	O'Nions et al., 2015	Total $N = 14,556$ (7,278 twin pairs)	47% male	7	Antisocial Process Screening Device (TR) and Strengths and Difficulties Questionnaire (TR)	N	CU $A = 66\%$, $E = 34\%$. 74% of the genetic variance in CU was specific to CU, with the remaining 26% attributable to a genetic factor influencing CU, social interaction and social communication difficulties.
	Henry, Pingault, Boivin, Rijdsdijk, & Viding, 2016	$N = 10,184$ (5,092 twin pairs)	47% male	16	Inventory of Callous-Unemotional Traits (PR)	N	General factor $A = 58\%$. Callous-uncaring factor $A = 70\%$. Unemotional factor $A = 79\%$. Remaining variance due to E .

Sample	Authors & Date	N	Sex	Age (years)	Instrument(s)	Selected sample	Results
Virginia Commonwealth University Juvenile Anxiety Study (VCU-JAS)	Moore et al., 2017	N = 678 (339 twin pairs)	48% male	9–14	Inventory of Callous-Unemotional Traits (PR)	N	CU A = 39%. Accounting for measurement error, liability to CU A = 46%. Remaining variance due to E.

Notes: A = additive genetic effects. C = shared/family environmental effects. E = non-shared environmental effects. rG = genetic correlation. SR = self-report. PR = parent-report. TR = teacher-report. Y/N = yes/no to whether or not these samples were selected for high levels of CU.

[†] In the TEDS sample, “extreme” phenotypes mean the proband twin was in the top 10% of the TEDS distribution.

* A Selected sample was used for some analyses, however those results are not included here.

** Viding et al. (2013) study reported both quantitative (twin, GCTA) analysis as well as molecular (GWAS) analysis and is therefore included in tables 1 & 2

Table 3.

Molecular Genetic Studies, Chronologically

Authors & Date	N	Sex	Age (years)	Instrument(s)	Methods	Genes	Results
Fowler et al., 2009	N = 147	93% male	12–19	Psychopathy Checklist (SR)	CG	COMT, MAOA, SLC6A4	In youth with ADHD, callousness associated with val/val at COMT val158met (no rs provided by authors, although one assumes rs4680), short/short 5-HTTLPR alleles, & homozygous high-risk (2 & 3 repeat) versions of MAOA 30bp VNTR.
Sadeh et al., 2010	Study 1: N = 118 Study 2: N = 178	Study 1: 42% male Study 2: 45% male	Study 1: mean = 14.3 Study 2: mean = 10.8	Study 1: Antisocial Process Screening Device (SR) Study 2: Inventory of Callous-Unemotional Traits (SR)	CG; GxE	SLC6A4	For both studies, 5-HTTLPR long allele positively associated with CU in children, but only in those with low SES.
Viding et al., 2010	N = 600 (discovery); N = 586 (replication)	48% male	7	Antisocial Process Screening Device (TR) & Strengths and Difficulties Questionnaire (TR)	GWAS	Genome-wide	No genome-wide significant results.
Beitchman et al., 2012	N = 162	65% male	6–16	Psychopathy Screening Device (PR)	CG	OXT, OXTR	Among aggressive youth, A/A rs237885 (in OXTR gene) positively associated with CU.
Malik, Zai, Abu, Nowrouzi, & Beitchman, 2012	N = 236	69% male	6–16	Psychopathic Screening Device (PR)	CG	OXT, OXTR	Examining OXT and OXTR variants among aggressive youth, no significant associations with respect to CU behaviors.
Willoughby, Mills-Koonce, Propper, & Waschbusch, 2013	N = 171	63% male	0–3	Achenbach System of Empirically Based Assessment (PR)	CG; GxE	BDNF	Early harsh-intrusive parenting was associated with CU at age 3, but only among those with G/A or A/A at rs6265 in the BDNF gene.
Cecil et al., 2014	N = 84	50% male	Birth, 7, 9, 13	6-item questionnaire (PR), highly correlated with CU scale of the Antisocial Process Screening Device	Epigenetic; CG	OXTR	Among youth with early-onset persistent CD, OXTR methylation level (12 probes examined) at birth was positively associated with CU at age 13, but only for those without internalizing problems.
Dadds, Moul, Cauchi, Hawes, & Brennan, 2013	N = 210	77% male	3–16	Antisocial Process Screening Device (PR, TR, SR) & Strengths and Difficulties Questionnaire (PR, TR, SR)	CG; GWAS Replication	13 SNVs from Viding (2010) within 20kb of a gene	Examining 13 suggestive SNVs from Viding (2010) GWAS, no replicated SNVs in terms of CU (although some significant findings for CD).
Hirata, Zai, Nowrouzi, Beitchman, & Kennedy, 2013	N = 144	72% male	6–16	Psychopathy Screening Device (PR)	CG	COMT	Examining variants in the COMT gene, no significant results.
Moul, Dobson-Stone, Brennan, Hawes, & Dadds, 2013	N = 35–157 (depending on analysis)	100% male	3–16	Antisocial Process Screening Device (PR) & Strengths and Difficulties Questionnaire (PR)	CG	HTR1A, HTR1B, HTR2A, HTR3B,	Among boys with conduct problems, high CU associated with G/T at rs11568817 (in HTR1B gene), and C/C at rs6314 (in HTR2A gene);

Authors & Date	N	Sex	Age (years)	Instrument(s)	Methods	Genes	Results
Viding et al., 2013 [*]	N = 2,930	47% male (total sample)	7, 9, 12	Antisocial Process Screening Device (TR) & Strengths and Difficulties Questionnaire (TR)	GWAS	TPH1, TPH2, SLC6A4 Genome-wide	High CU also associated with lower serum serotonin. No genome-wide significant results.
Dadds et al., 2014a	N = 121 (discovery) N = 59 (replication)	71% male (discovery) 78% male (replication)	4–16	Antisocial Process Screening Device (PR, TR, SR) & Strengths and Difficulties Questionnaire (PR, TR, SR)	CG	OXTR	Among youth with conduct problems, T/T rs10427778 (in OXTR gene) was associated with CU traits (Bonferroni-corrected); this finding was replicated in a separate sample.
Dadds et al., 2014b	N = 37–156 (depending on analysis)	100% male	4–16	Diagnostic Interview Schedule—CU CD Specifier (PR; PR & SR when > 8)	Epigenetic; CG	OXTR	Among 9–16 year olds with CD, OXTR methylation level (11 probes examined) was positively associated with CU. In a partially-overlapping sample plasma oxytocin was negatively associated with CU traits. Neither of these associations held true in the 4–8 year old group.
Moul, Dobson-Stone, Brennan, Hawes, & Dadds, 2015	N = 117	100% male	3–16	Antisocial Process Screening Device (PR) & Strengths and Difficulties Questionnaire (PR)	Epigenetic; CG; GxE	HTR1B	CU was positively associated with heterozygous (G/T) status for rs11568817 in the HTR1B gene. CU was positively associated with HTR1B methylation level (19 sites examined) only among individuals heterozygous (G/T) for rs11568817.
Brammer, Jezoir, & Lee, 2016	N = 230	69% male	5–10	Antisocial Process Screening Device (PR)	CG	SLC6A4	Number of 5-HTTLPR long alleles positively associated with CU traits.
Hirata et al., 2016	N = 123	78% male	6–16	Antisocial Process Screening Device (PR)	CG	PRL, PRLR	Two PRL gene SNVs and 3 PRLR gene SNVs were examined. No significant associations with CU traits.

Notes: SR = self-report. PR = parent-report. TR = teacher-report. GWAS = genome-wide association study. GCTA = genome-wide complex trait analysis. CG = candidate gene study. GxE = gene-environment interaction study. var = proportion of variance accounted for. CD = conduct disorder.

^{*} Viding et al. (2013) study reported both quantitative (twin, GCTA) analysis as well as molecular (GWAS) analysis and is therefore included in both tables.