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Genetic influences on antisocial behavior: recent advances and future directions

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Understanding the etiology of antisocial behavior (i.e. violence, criminality, rule-breaking), is essential to the development of more effective prevention and intervention strategies. We provide a summary of the genetic correlates of antisocial behavior, drawing upon findings from behavioral, molecular, and statistical genetics. Across methodologies, our review highlights the centrality of environmental moderators of genetic effects, and how behavioral heterogeneity in antisocial behavior is an important consideration for genetic studies. We also review novel analytic techniques and neurogenetic approaches that can be used to examine how genetic variation predicts antisocial behavior. Finally, to illustrate how findings may converge across approaches, we describe pathways from genetic variability in oxytocin signaling to subtypes of antisocial behavior.

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Antisocial behavior (AB), including aggression, violence, and rule-breaking, is highly prevalent (e.g. 6.4% of men in the US) and has serious negative financial, social, and emotional costs for society, perpetrators, victims, and their families [1,2]. Environmental adversity across contexts (e.g. families, peers, neighborhoods) and genetic risk factors jointly predict the emergence and maintenance of AB [3–5]. The current paper provides a brief review of genetic approaches to studying AB, including behavioral (i.e. twin, family studies), molecular (i.e. gene-behavior, gene x environment [GxE] interaction), and statistical (i.e. genome-wide association studies) genetic approaches. This review focuses on findings that have been replicated and/or reported in meta-analyses and/or highlight promising new methodologies. Finally, we demonstrate how the integration of findings across approaches can inform our understanding of the role genes play in the development of specific subtypes of AB, by describing pathways within one neurotransmitter/peptide system (i.e. oxytocin) using multiple approaches.

Heterogeneity in AB

Youth engaging in AB are a heterogeneous group in terms of the onset, duration, and severity of their behaviors. Research has increasingly examined subgroups of youth involved in AB, who share behavioral features and etiology. One prominent subtyping approach focuses on the age of onset (i.e. early versus late-onset), with early-onset (i.e. before age 10) antisocial youth showing a more chronic and escalating trajectory of AB and high familial risk (e.g. harsh parenting) [6••]. Youth with the early-onset subtype are hypothesized to have greater genetic risk factors for AB compared to youth with the adolescent-onset subtype who have a less severe trajectory of AB [6••]. A second subtyping approach distinguishes youth based on the specific forms of AB that the youth engages in (i.e. aggression versus rule-breaking). Of note, this grouping largely overlaps with the age of onset distinction, as early-starting youth are most likely to commit aggressive acts [7].

A third approach focuses on the co-occurrence of psychopathic traits in adults and callous-unemotional (CU) traits (i.e. reduced empathy, interpersonal affect, and guilt) in youth [8]. AB in the presence of CU traits has a unique neuroetiology, including a potentially different genetic pathway to AB [9••], and is linked to higher levels of AB. Thus, given potential differences in etiology, examining subtypes of AB is key to understanding and integrating findings across behavioral, molecular, and statistical genetic approaches.

Behavioral genetic approaches

Twin, sibling, family, and adoption study designs rely on the principles of genetic inheritance to decompose the variance in AB due to environmental and genetic factors. Thus, behavioral genetic studies provide an estimate of the relative contribution of genetic processes involved in AB, but cannot identify specific genetic markers for AB. For example, a twin design assumes that monozygotic (MZ) and dizygotic (DZ) twins reared together share environments; differences in phenotypic similarity can thus be attributable to differences in shared genetic material (i.e. MZ twins share 100% and DZ twins share

50% of their DNA) or nonshared environment. Using twin designs, meta-analyses indicate that heritable effects explain nearly 50% of the variance in AB, while shared and nonshared environmental effects account for roughly 14% and 37%, respectively [10].

However, these estimates belie the complexity of AB, as genetic and environmental effects vary drastically by AB subtype and developmental stage. For example, aggression (e.g. physical fights) is more heritable (65%) and under less environmental influence (5%) than rule-breaking (e.g. property theft) (additive genetic: 48%; shared environment: 18%) [11]. Similarly, relatively higher heritability estimates have been reported for AB with CU traits (81%), than AB without CU traits (30%) [12]. Moreover, meta-analyses have found larger genetic effects for AB that emerges earlier in development [10,11], with evidence from longitudinal designs indicating that genetic risk for AB in early childhood partially accounts for heritable contributions to AB in later developmental stages [13] (Table 1). Thus, genetic effects on AB are qualified by subtype and time of onset.

Adoption studies can also separate genetic etiology from environmental factors by studying families in which the child is genetically unrelated to the rearing parent(s). In one example, severe AB of biological parents predicted greater child CU traits (i.e. the heritable effect), whereas greater positive parenting by the adoptive parent predicted lower child CU traits (i.e. the independent environmental effect) [14•]. This type of behavior genetic approach is critical as it addresses the potential for gene-environment correlation (e.g. parenting may be related to child aggression via genetic pathways, rather than the parenting itself) found in much observational (and GxE interaction) research [15].

Molecular genetic approaches

Most molecular genetic studies of AB have employed a candidate gene approach by examining associations between genetic variants (e.g. single nucleotide polymorphisms [SNPs]) and AB. Researchers have typically focused on genetic polymorphisms that are involved in dopaminergic and serotonergic neurotransmission, due to their roles in emotion, reward, and learning-processes that are often impaired in AB [16].

Altered levels of dopamine, an excitatory neurotransmitter that is involved in the neural reward system, may contribute to the heightened reward sensitivity characteristic of many forms of AB [16]. While there have been no meta-analyses to date, several studies have found

Table 1

Novel approaches to studying genetic risk for antisocial behavior

Type of approach	Description of approach	Empirical example(s)
Longitudinal biometric modeling	Leverages longitudinal data and Cholesky decomposition models within a twin sample to estimate genetic and environmental influences on AB at multiple developmental stages.	In two large twin cohorts totaling more than 10,000 twin pairs, one study examined the longitudinal stability of aggressive behaviors from ages 7 to 12. Genetic influences on AB at younger ages largely explained the genetic variance in AB at later ages. The results also suggest, however, that there may be different genetic risk factors for AB that emerges at different developmental stages [13].
Biologically-informed polygenic risk scores	Additively combines genetic variants within biologically-relevant systems to create one polygenic risk score (PGS). This approach draws upon previous cross-species research to identify which genetic variants increase risk for the outcome under study. The resultant PGS can also be weighted using k-fold cross-validation methods with the individual genetic variants in the same or another sample.	A sample of 8834 participants from the Add Health study, [50] combined six genetic variants from dopaminergic, serotonergic, and catecholamine catabolizing genes (e.g. *DAT1*, *MAOA*) into a weighted PGS. Higher polygenic risk was associated with persistently high AB from age 13 to 32, and, among males only, school connectedness moderated the association between polygenic risk and longitudinal AB profiles.
Gene-set analyses	Examines the joint effects of multiple SNPs within a biologically-relevant set of genes. All genotyped SNPs within the identified gene regions are included in the analyses.	In a sample of ~2000 children from the Generation R Study, a dopamine gene-set composed of 12 genes and 151 genetic variants, was significantly associated with greater externalizing behaviors, but only among children exposed to low levels of harsh parenting [51].
Genome-wide polygenic risk scores	Genome-wide polygenic scores (PGS) capture the cumulative influence and predictive ability of multiple SNPs across the genome for a given phenotype. PGSs are constructed as weighted sums of the effect alleles, where weights are drawn from previous GWAS meta-analyses in independent samples.	One study constructed PGSs in two adolescent and young adult samples using weights from a GWAS of a latent externalizing behavior in adults; polygenic risk predicted externalizing behavior and impulsivity in both samples, but peer influences moderated the genetic effect among adolescents [33]. Another recent study [32] found that a lower PGS for educational attainment was associated with greater risk for criminal offending and life-course persistent AB in two birth cohorts.

associations between dopaminergic genes, including dopamine receptors (e.g. *DRD2*, *DRD4*) and the dopamine transporter gene (e.g. *DAT1*), and AB in adults and adolescents [17]. Additionally, greater circulating serotonin, a neurotransmitter involved in mood regulation, is associated with poor impulse control and irritability, which are characteristic of AB [18]. AB has been linked to the short-allele of the serotonin transporter polymorphism (5-HTTLPR) in a meta-analysis [19], and to variation within serotonin receptor genes (e.g. *5HTR2A*, *5HTR1B*, *5HTR2C*), as well as the monoamine-oxidase-A (*MAOA*) gene, which catabolizes monoamines including serotonin [17].

However, a large body of research suggests that the effects of genetic variation on AB are conditional on environmental experience (or vice versa) [15]. In a GxE interaction, genetic variation predicts AB only in the context of specific environmental factors (e.g. harsh parenting). Many studies have tested interactions between genetic variants within genes underlying dopamine and serotonin function as well as catecholamine catabolism (e.g. *DRD4*, 5-HTTLPR, *MAOA*) and environmental risk factors (e.g. neighborhood disadvantage, parenting behaviors) [20,21]. Moreover, meta-analyses have supported *MAOA* and 5-HTTLPR GxE interactions as predictors of AB [22,23] (Table 2).

There are still several limitations to GxE interaction studies. First, as numerous environmental factors are associated with later AB [3–5], more work is needed that accounts for multiple environments (GxExE) and multiple genes (GxGxE) [24]. Second, underpowered studies often fail to detect significant effects and/or produce non-replicable findings [25]. Novel molecular genetic approaches, including biologically-informed polygenic risk scores and gene-set analyses, may address these limitations by moving beyond single genetic variants to characterize genetic risk within functionally relevant systems (Table 1). Third, demographic factors including race, sex, and SES, may moderate GxE associations [24,26•]. Fourth, accounting for heterogeneity within

Table 2

Summary of genome-wide association studies of antisocial behavior and related phenotypes

Author information	Population (*N*, age)	Phenotype	Major finding(s)
Tielbeek *et al.* (2017)	Discovery: *N* = 16,400, Replication: *N* = 9381; Mean age range across cohorts = 6.7–56.1 years	Broad-spectrum AB that varied across cohorts	No genome-wide significant associations in the total sample, but there were suggestive sex-discordant associations (for females, Chr 1: rs2764450, Chr 11: rs11215217, and for males, Chr X, rs41456347) [52].
Dick *et al.* (2011)	Discovery: *N* = 3,963, no replication sample; Age range = 18–77 years	Retrospectively-reported DSM-IV CD symptoms, and CD case/control status	Four SNPs reached genome-wide significance: Chr 4: rs16891867, rs1861046, Chr 11: rs7950811, and Chr 13: rs11838918. The SNPs on Chr 2 were in the gene *C1QTNF7*, which encodes a tumor necrosis factor-related protein [53].
Pappa *et al.* (2015)	Discovery: *N* = 18,988, no replication sample; Mean age = 8.44 years; Age range across cohorts = 3–15 years	Predominantly parent-reported child aggressive behavior	One genome-wide significant association on Chr 2, rs11126630, located between genes *LRRTM4* and *SNAR-H*, which regulate excitatory synapse development and transcription processes, respectively [31].
Salvatore *et al.* (2015)	Discovery: *N* = 1,379, Replication: *N* = 1796; Mean age = 43.8 years; Age range = 18–79 years	Symptoms of DSM-IV ASPD	No genome-wide significant associations. The top suggestive SNP on Chr 7, rs4728702, was in the *ABCB1* gene, which encodes a transporter protein; this suggestive association did not replicate in the replication sample [54].
Viding *et al.* (2010)	Discovery/stage 1 sample: *N* = 600 (n = 300 high- and n = 300 low-AB/CU), Replication/stage 2 sample: N = 586 (n = 293 high- and n = 293 low-AB/CU); Age = 7 years	Teacher-rated conduct problems and CU traits	No genome-wide significant associations. In the stage 2 analysis, 14.2% of the top 3000 hits from stage 1 were significantly associated with being classified as high AB/CU. Several top SNPs were located near neurodevelopmental genes (e.g. *ROBO2*) [30].
Rautianen *et al.* (2016)	Discovery: *N* = 5,850, Replication: *N* = 3766; ASPD cases mean age ≈ 34 years; controls ≈ 56 years	Clinical diagnosis of ASPD	No genome-wide significant associations. Suggestive associations were replicated on Chr 6, within the gene region of the major histocompatibility complex, previously linked to other psychiatric disorders and expressed in cerebellum tissue [29•].

AB = antisocial behavior; CD = conduct disorder; CU = callous-unemotional; ASPD = antisocial personality disorder.

Table 3

Summary of previously-reviewed candidate gene x environment interactions examined in relation to antisocial behavior and related phenotypes (see citations 20, 21 for a full review)

Gene	Environments	Results from meta-analyses and/or reviews
Dopamine genes		
DRD4 Dopamine receptor D4	Neighborhood crime Maternal insensitivity Parental rearing practices Early maternal care Maternal hostility Maternal sensivitiy Harsh parenting Parental criticism Parental separation/divorce Socioeconomic status Neighborhood disadvantage Prenatal stress Negative and positive parenting	Nine studies found significant interactions for DRD4 × family adversity in predicting externalizing behaviors; two studies found larger effects in the short-allele carriers; seven studies found larger effects in the long allele carriers; three studies had null findings [21].
DAT1 Dopamine active transporter 1 gene	Adverse childhood environment Parental criticism Family closeness Prenatal smoking Negative and positive parenting Maternal expressed positive emotion Peer rejection Maternal warmth Low birth weight Neighborhood disadvantage Neighborhood crime	Two studies found significant interactions for DAT1 × family adversity in predicting externalizing behaviors; one study found this effect in carriers of the 9-repeat allele; one study found this effect in carriers of the 10-repeat allele; two studies had null findings [21].
DRD2 Dopamine receptor D2	Parental incarceration Parental separation/divorce Neighborhood disadvantage Family closeness Neighborhood crime	Three studies found significant interactions for DRD2 × family adversity in predicting AB, with all effects larger in carriers of the A1 allele; one study had null findings [21].
DRD5 Dopamine receptor D5	Low birth weight Prenatal smoking	One study found significant interaction for DRD5 × prenatal risks (lower birth weight and maternal prenatal smoking) in predicting AB with larger effects in the carriers of the 5-repeat allele [20].
Serotonin genes		
5-HTTLPR Serotonin-transporter-linked polymorphic region in in SLC6A4, the gene that codes for the serotonin transporter	Disadvantaged environments Socioeconomic status Maternal unresponsiveness Maternal stress and depression Adverse childhood environment Parental criticism Chronic life stress Maternal expressed positive emotion Maternal warmth Harsh parenting	Meta-analysis found an overall significant interaction found between 5-HTTLPR and environmental adversity, but was unable to demonstrate whether the significant interaction effect was driven by the short or long allele [23].
Catecholamine catabolism genes		
MAOA Monoamine oxidase A	Childhood adversity Childhood maltreatment Childhood physical and sexual abuse Neighborhood characteristics Deviant peer behavior Deprivation Parental involvement Parental discipline Parental care Prenatal smoking Leaving school Parental incarceration Inter-parental violence Adolescent victimization Early stressful life events	Meta-analysis found low activity MAOA × childhood maltreatment specifically predicted increased AB and this association was stronger in males; some evidence that high activity MAOA × childhood maltreatment predicts increased AB preferentially in females [22,55].

Table 3 (*Continued*)

Gene	Environments	Results from meta-analyses and/or reviews
COMT Catechol-O-methyltransferase	Maternal stress Socioeconomic status Childhood maltreatment Childhood physical and sexual abuse Parental separation/divorce Prenatal smoking	Four studies found significant interactions for COMT × family adversity in predicting AB; two studies found the effect was stronger in the Val carriers; two studies found the effect was stronger in the Met carriers [21].

AB, such as the co-occurrence of psychopathic or CU traits, is vital to disentangling potentially differential developmental trajectories. For example, the long allele of 5-HTTLPR, which has been linked to reduced amygdala reactivity, may be a risk factor for psychopathic or CU traits. The short allele, related to increased amygdala reactivity, may instead be a risk factor for impulsive aggression and AB more broadly [27]. Finally, few studies have accounted for development, which is critical to understanding the genetic foundations of AB, as the impact of environmental factors also vary on the timing of the experience [24,28].

Statistical genetics approaches

Another approach to studying genetic risk factors for AB is through hypothesis-free genome-wide association studies (GWAS). A GWAS examines whether individual differences in a phenotype are associated with allelic differences in hundreds of thousands, to millions of SNPs across the genome. Table 3 displays a selection of existing GWAS of AB. Notable genome-wide and/or suggestive associations have been found in genes related to immune functioning [29•] and neurodevelopment [30,31], though these genetic variants have not been replicated across GWAS.

Small sample sizes and the heterogeneity in AB phenotypes may underlie the non-significant findings in GWAS of AB. Complex human behaviors like AB result from the cumulative impact of many genetic variants, each of small effect. Thus, huge sample sizes are needed to detect genetic effects — sample sizes that have not yet been reached in GWAS of AB. Moreover, phenotypes have ranged from teacher-report of conduct problems to clinical symptoms antisocial personality disorder — with little attention to subtypes of AB (though see [30]), which may obscure the genetic etiology of different forms of AB.

Though the utility of GWAS for gene discovery related to AB is currently limited, existing GWAS of other, related phenotypes, can provide cumulative measures of genetic risk for AB using genome-wide polygenic scores (PGS). This approach addresses molecular genetic limitations associated with examining single genetic variants. By constructing weighted sum scores of the effect alleles from relevant GWAS in independent samples, recent research has found that low PGS for educational attainment and high PGS for substance use and antisocial behavior predicts life-course persistent/early-starting AB [32] and greater AB in adolescents that may be contingent on environmental adversity [33] (Table 1).

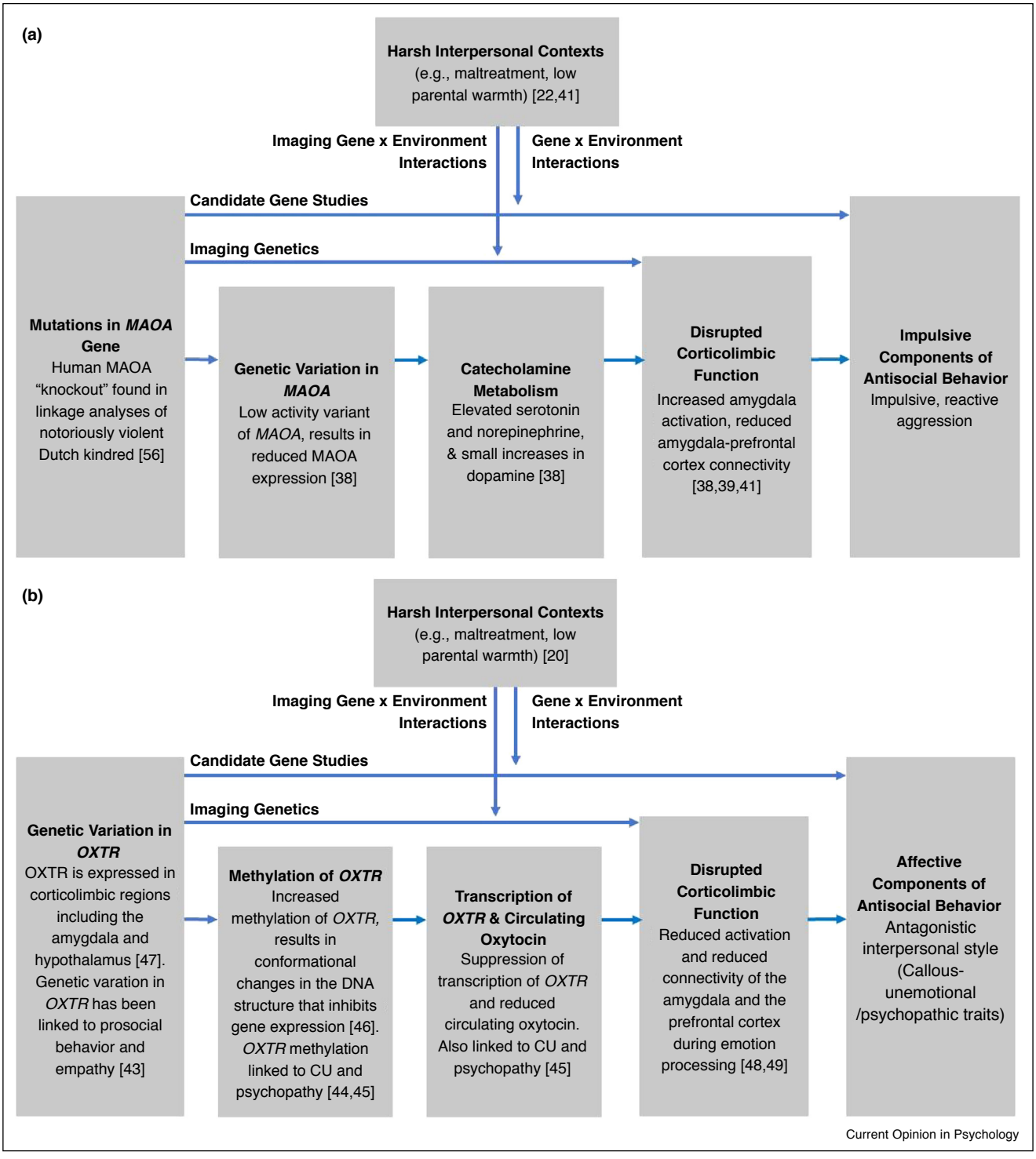
Neurogenetic approaches

Neurogenetics integrates methods across multiple levels of analysis (e.g. genetics, neuroimaging, behavior) to test pathways through which genetic variation in neurotransmitter systems impacts neural processes that contribute to AB [34,35]. Thus, neurogenetics focuses on the mechanisms of *how* genes potentiate risk for AB. Cross-disciplinary research from animal and human studies (e.g. MRI, EEG, pharmacological) can help to identify the neural regions, neurotransmitters, and genetic risk factors related to AB. Neural regions of interest are identified by their associations with discrete behavioral phenotypes central to AB including abnormal responses to fear and threat (e.g. amygdala), disinhibition (e.g. prefrontal regions), and increased reward sensitivity (e.g. striatum) [9••,36]. As genetic variation in serotonin and dopamine signaling have been linked to neural function within the amygdala, prefrontal cortex (PFC), and striatum, neurogenetics can provide plausible mechanistic pathways by which specific genes affecting these neurotransmitter systems lead to increased risk for AB.

For example, impulsive AB (without CU traits) has been associated with greater amygdala reactivity, hypo-activation in prefrontal regions (e.g. orbitofrontal cortex/ventromedial prefrontal cortex), and weaker amygdala-PFC connectivity [9••,36]. These patterns of activation are thought to reflect hypersensitivity of the amygdala to emotional cues (particularly to fear), and blunted regulation of amygdala function by prefrontal regions. The low-activity *MAOA* variant (which inefficiently catabolizes serotonin, potentially resulting in greater circulating serotonin; though see [37], which suggests this effect may be restricted to certain neurodevelopmental stages) has been associated with these neural patterns characteristic of impulsive AB — greater amygdala activation and reduced connectivity with prefrontal regions during affective processing [38,39] (see Figure 1a).

Neuroimaging studies have also revealed robust associations between AB and hyper-activation of the ventral striatum (VS), which is implicated in reward-related

Figure 1



Pathways from genetic variation in the oxytocin receptor gene and monoamine oxidase A gene to differential components of antisocial behavior. **(a)** Integration of findings across genetic methodologies demonstrates how alterations in monoamine oxidase A gene (*MAOA*) functioning may predict later impulsive aggression. Genetic variation in *MAOA* was originally linked to antisocial behavior (i.e. violence, aggression) using linkage analysis (an early family-based behavior genetic approach) in a large Dutch kindred characterized by high levels of violence across generations [56]. Researchers identified a mutation in *MAOA* that essentially functioned as a knockout, resulting in reduced expression of *MAOA* [56]. *MAOA* knockout models in mice indicate that the absence of MAOA results in increased reactive aggression and deficits in fear learning [38]. While the mutation observed in the Dutch kindred is rare, the low-activity variant of *MAOA* has also been associated with reduced MAOA expression *in vivo* [38] (though see [37]). As MAOA degrades catecholamines such as serotonin, reduced *MAOA* expression is associated with elevated levels of

behaviors and learning [9••]. Using a biologically-informed polygenic risk score approach, one study reported that a mulitlocus genetic risk score for dopamine signaling (e.g. SNPs within *DRD4*) was associated with greater reward-related VS reactivity [40]. Future studies should integrate this polygenic risk score approach (Table 1) to test whether genetic variation in dopaminergic signaling predicts AB via alterations in reward-related circuitry.

Though genetic variation within serotoninergic and dopaminergic signaling has been linked to amygdala and striatum function, few studies have attempted to link these associations to AB as well as integrate measures of environmental adversity to test 'Imaging Gene x Environment' (IGxE) interactions [28]. IGxE models posit that brain structure and function mediate the paths from GxE interactions to psychopathology. In one recent example, men with the low-activity *MAOA* variant who were also exposed to childhood maltreatment showed greater amygdala reactivity, weakened amygdala-prefrontal cortex coupling, and greater reactive aggression and AB [41••] (see also [42••]). Taken together, these findings support the brain as a potential mechanism through which genetic variation is related to AB and emphasize the importance of incorporating measures of risk across multiple levels of analysis (see Figure 1).

Integration across genetic methodologies

Integration across genetic methodologies is key to delineating the pathways through which genetic variation can impact specific forms of AB. As an example, the peptide oxytocin, which functions as a hormone and a neurotransmitter, influences the expression of prosocial and affiliative behaviors that are often impaired in AB [43•]. Preliminary evidence across genetic approaches suggests a pathway from variation within the oxytocin receptor gene *OXTR* (i.e. via genetic variation or epigenetic methylation of this receptor) to affective components of AB, such as psychopathic or CU traits, via disrupted corticolimbic function (Figure 1b). Genetic variation within *OXTR* has been linked to prosocial behavior and empathy [43•]. Greater *OXTR* methylation (which results in less gene expression) has also been associated with lower plasma oxytocin [45] and greater CU traits in adolescents with concurrent AB [44,45]. In relation to the brain, animal models indicate that *OXTR* is expressed in the amygdala [46] and, in humans, oxytocin availability has been associated with amygdala reactivity during socio-affective paradigms [47]. Using a neurogenetics approach, one study found that genetic variation in *OXTR* was related to AB via greater amygdala reactivity to threat [48•]. Another study found that greater methylation of *OXTR* and increased CU traits in adolescence interacted to predict reduced activation of frontoparietal regions and disrupted connectivity with the amygdala during emotion processing [49••]. Thus, findings from across studies suggest that genetic or epigenetic variation in *OXTR* may increase risk for AB via impacting brain systems relevant to prosocial behavior. However, these pathways appear to be modulated by environmental factors. For instance, one study found that prenatal parental risk factors were associated with *OXTR* methylation at birth, which was then predictive of higher levels of CU traits in adolescents [44]. These studies therefore show a potential pathway through which genetic variation in *OXTR* may predict affective components of AB (e.g. psychopathy, CU traits) related to social cognition (e.g. empathy) via reductions in corticolimbic activation (Figure 1b). Interestingly, a separate though related line of integrative research suggests that *MAOA* variation may predict neural and behavioral phenotypes associated with impulsive, not callous, AB via *increased* corticolimbic activation

(Figure 1 Legend Continued) serotonin, which could then shape activation and connectivity within corticolimbic regions involved in social evaluation and emotion regulation, though these effects may happen neurodevelopmentally, early in life [37]. Indeed, previous imaging genetics studies have linked the low activity *MAOA* variant to increased amygdala activation and reduced amygdala-prefrontal cortex connectivity during emotion processing [38,39]. However, environmental factors, specifically early life stress, have been shown to moderate the associations between *MAOA* variation and antisocial behavior in both animals and humans [22,39]. Taken together, these findings across genetics approaches highlight a pathway from genetic variation in *MAOA* to impulsive aggression via alterations in neural function that are dependent on environmental adversity. **(B)** Integration of findings across genetic methodologies demonstrates how alterations in oxytocin receptor gene (*OXTR*) functioning may predict later CU/psychopathic traits. First, genetic variation within the *OXTR*, which is expressed in corticolimbic regions including the amygdala [46] has been associated with behavioral phenotypes, such as empathy, that are relevant to antisocial behavior (AB) [43•]. It is hypothesized that *OXTR* variation impacts social behavior via lower circulating plasma oxytocin [43•,47]. Studies have linked increased epigenetic methylation of *OXTR*, which suppresses gene transcription [46] and is associated with less circulating oxytocin, to higher levels of later CU/psychopathic traits [44,45]. Lower circulating oxytocin in corticolimbic regions may disrupt the functioning and connectivity of these regions, which could, in turn, impact related cognitive processes and behaviors. Imaging genetics studies have begun to examine associations between genetic variation as well as methylation of *OXTR* and disrupted corticolimbic function (e.g. amygdala reactivity), which has been previously identified as a neural correlate of AB [48•,49••]. Moreover, environmental factors likely interact with genetic variation to predict later CU/psychopathic traits via corticolimbic function, given associations between the development of CU/psychopathic traits and harsh interpersonal contexts such as maltreatment and low parental warmth [44], although no studies have yet examined this imaging gene x environment interaction model. Based on these findings, *OXTR* functioning (determined by genetic variation and epigenetic methylation) may impact emotional processing and social cognition at the level of the brain (i.e. diminished activation in regions of the corticolimbic system), which may be further exacerbated by harsh interpersonal contexts, and result in an antagonistic interpersonal style (CU/psychopathic traits).

stemming from decreased modulation by prefrontal regions (Figure 1a).

Conclusions

Genetic variation clearly plays an important role in the development of AB, as demonstrated by substantial heritability estimates from twin studies and replicated associations within specific candidate genes (i.e. *MAOA*). However, genetic effects are also qualified by environmental influences (which may themselves exert larger effects than single genes) and may vary by the type of AB measured and the age of measurement. The current body of work is limited by single candidate gene and GxE interaction studies that often utilize small sample sizes and imprecise measures of AB. Further, GWAS has not been able to identify any single gene(s) linked to AB, emphasizing the need to look for biological substrates through which genes may indirectly impact AB. Novel, integrative approaches, including neurogenetics and IGxE studies, represent exciting potential avenues to better understanding the mechanistic processes through which genetic variation predicts AB.

Conflict of interest statement

The authors report no conflicts of interest.

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