CHAPTER TWO

Behavioral Genetics of Aggression and Intermittent Explosive Disorder

Catherine Tuvblad[*,†], Mari Sild[‡,§], Louise Frogner[*], Linda Booij[‡,§]

[*]Örebro University, School of Law, Psychology and Social Work/Criminology, Örebro, Sweden
[†]Department of Psychology, University of Southern California, Los Angeles, CA, United States
[‡]Department of Psychology, Concordia University, Montreal, QC, Canada
[§]Sainte-Justine Hospital Research Centre, Montreal, QC, Canada

Contents

Intermittent Explosive Disorder
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Aggressive Behavior

Aggressive behavior is commonly defined as a behavior that is intended to cause pain or harm to another person who is motivated to avoid that harm (Bushman & Huesmann, 2010). This harm can take many forms and aggressive behavior is divided into various subtypes, based on in what way and situation this behavior is carried out. Subtypes include (but are not limited to) reactive, hostile, or affective aggressive behavior; proactive or instrumental aggressive behavior; indirect or relational aggressive behavior and verbal aggression (Allen & Anderson, 2017). Violence is considered a more extreme form of aggressive behavior that has severe physical harm as its goal. Aggressive behavior and violence are considered to be on the same continuum, where aggressive behavior is at the less severe and violence at the more severe end (Allen & Anderson, 2017). Thus aggressive behavior is not only common, but it is also a very complex phenomenon that can come in various forms.

This chapter will review evidence of genetic and *epi*genetic contributions to aggressive behavior. Specifically, we will review findings from behavioral genetic studies (i.e., twin and adoption studies) and molecular (epi)genetic studies. We will first consider the behavioral genetic research design and its assumptions, followed by findings from metaanalyses, systematic reviews, and recent studies using a behavioral genetic research design. Lastly, we review genome-wide, candidate gene and epigenetic studies on human aggressive behavior. Since empirical studies focusing on Intermittent Explosive Disorder (IED) (or in any other specific diagnostic category) are scarce, our focus is aggressive behavior in general.

Behavioral Genetic Research Design

Behavioral genetic research relies on the different levels of genetic relatedness between family members in order to estimate the relative contribution of heritable and environmental factors to individual differences in a phenotype of interest, in this case aggressive behavior. Behavioral genetic research designs include (1) studies of twins, and (2) studies of adopted individuals and their biological and adoptive family members. However, in the past three decades adoption samples have become less accessible (Moffitt, Caspi, & Rutter, 2005).

In the classical twin design, monozygotic (identical) twins share their common environment and they are assumed to share 100% of their genetic makeup. Dizygotic (fraternal) twins are assumed to share on average 50% of their genes. Both monozygotic and dizygotic twins are assumed to share their common environment. By comparing the resemblance for aggressive behavior between monozygotic and dizygotic twins, the total phenotypic variance of aggression can be divided into additive genetic factors (or heritability, h^2), shared environmental factors (c^2), and nonshared environmental factors (e^2). Shared environmental factors refer to nongenetic influences that contribute to similarity within pairs of twins. Nonshared environmental factors refer to individual experiences that make siblings differ in their levels of aggressive behavior. Heritability is the proportion of total phenotypic variance due to genetic variation. Heritability is time- and population-specific, and it is a population parameter, rather than an individual one (Neale & Cardon, 1992). Genetic influences may also be divided into those that are additive (i.e., allelic effects add up across loci) and those that are nonadditive (i.e., due to dominance or epistasis). However, data from twins reared together do not contain sufficient information to permit evaluation of the contrasting effects of dominant genetic and shared environmental influences. To estimate dominant genetic and shared environmental influences simultaneously would, for example, require an adoptive sibling design.

In sibling adoption studies, the correlation between adoptive siblings is compared with the correlation between biological siblings to estimate the influence of genetic and environmental factors on aggressive behavior (Plomin, DeFries, Knopik, & Neiderhiser, 2013). Resemblance between adoptive siblings for measures of aggression is indicative of shared (or common) family environment, while the extent to which biological sibling resemblance exceeds that of adoptive siblings is taken as evidence of heritable genetic influences for aggressive behavior.

Behavioral Genetic Research Design: Generalizability and Assumptions

Generalizability From Twin Studies to the General Population

Studies examining whether twins differ from singletons on aggressive behavior show that findings from twin research can be generalized to nontwins (Barnes & Boutwell, 2013).

The Equal Environment Assumption (EEA)

The most controversial assumption in behavior genetics is the equal environment assumption. If the equal environment assumption is not met, higher correlations among MZ twins may be due to environmental factors rather than genetic factors and heritability may be overestimated. However, studies examining the equal environment assumption generally report that this assumption tends to hold and that the resulting bias is likely modest (for an extensive review: (Felson, 2014)).

Random Mating

Random mating in the parent generation can lead to increased resemblance for dizygotic but not monozygotic twin pairs, and thereby bias shared environmental estimates upward and additive genetic effects downward. A significant correlation between spouses for a particular trait is usually interpreted as assortative mating (Maes et al., 1998). However, most behavior genetic studies report finding no or very modest influence from the shared environment on aggressive behavior, suggesting that the influence of assortative mating may be minimal.

Gene–Environment Interaction and Correlation

It is also assumed that genetic and environmental influences do not interact and are uncorrelated. Regardless, certain environmental experiences have been found to moderate the genetic influences on aggressive behavior (i.e., GxE), (Dick, 2011). It is also possible that some genetic predispositions may be associated with certain environmental experiences, resulting in a correlation between genes and environments. Gene–environment correlations (r_{ge}) can arise in three different ways (Scarr & McCartney, 1983), (1) Passive r_{ge} occur when genes overlap between parents and their offspring. (2) Evocative/reactive r_{ge} arises when a person's characteristic elicits a particular response from the environment. For example, O'Connor, Deater-Deckard, Fulker, Rutter, and Plomin (1998) found that children at genetic risk (based on the biological mother's characteristics) received more negative parenting from their adoptive parents than children not at genetic risk (O'Connor et al., 1998). (3) Active r_{ge} is defined as the process whereby an individual actively seeks out environmental situations that are more closely matched to the person's genotype. If the assumption of no gene–environment correlation is violated, heritability estimates for aggressive behavior in twin studies could include both additive genetic effects *and*

the effects of gene–environment correlation, which in turn means that the heritability estimate would be inflated.

Generalizability From Adoption Studies to the General Population

Adoptive parents commonly tend to be in good health and from higher socioeconomic backgrounds (Rutter, 2006). Also, adopted children may be at greater risk to display aggressive behavior compared to nonadoptees, since birth parents may have increased rates of externalizing behaviors, including substance use, criminal behavior, and aggression (Lewis, Yeager, Gidlow, & Lewis, 2001). Further, selective placement (i.e., similarities between adoptive and biological parents) for certain traits would result in overestimated correlations between adoptive siblings and thereby overestimated shared environmental effects (Plomin et al., 2013). However, it is unlikely that children with antisocial biological parents are being placed into homes where the adoptive parents are more antisocial. Regardless, results from adoption studies may not be generalizable to the larger population.

Metaanalyses and Systematic Reviews Summarizing Studies Examining the Influence of Genetic and Environmental Factors on Aggressive Behavior

There have been a few metaanalyses and systematic reviews of twin and adoption studies of aggressive behavior and the wider construct of antisocial behavior. Antisocial behavior is broader in scope than aggression as it also includes nonaggressive behaviors, e.g., littering, vandalism, and lying which are considered antisocial behaviors, which are not necessarily aggressive. These studies are summarized in Table 1. Together these studies show that about half or more of the variance in aggressive behavior is explained by heritable influences (Burt, 2009; Ferguson, 2010; Mason & Frick, 1994; Miles & Carey, 1997; Rhee & Waldman, 2002). Two metaanalyses have examined nonadditive genetic effects. Only one found significant nonadditive genetic effects for broader concept of antisocial behavior, but not for aggressive behavior (Burt, 2009; Rhee & Waldman, 2002) It is important to note that genetic influences are consistently found across these reviews, while shared environmental influences are relatively small or nonexistent. Family similarity in aggressive behavior therefore seems to primarily be the result of shared genes, not environment.

Table 1 Summary of Metaanalysis and Systematic Reviews: Aggressive Behavior

Author, Year	Measure	Estimates			
(Mason & Frick, 1994) 12 twin studies (3795 twin pairs); 3 adoption studies (338 adoptees)	Antisocial behavior	a^2 48%			
(Miles & Carey, 1997) 20 twin studies (1757 twins); 4 adoption studies 3157 adoptees)	Aggressive behavior	a^2 50%			
(Rhee & Waldman, 2002) 41 twin studies; 10 adoption studies	Antisocial behavior	a^2 32%	d^2 9%	c^2 16%	e^2 43%
(Rhee & Waldman, 2002) 41 twin studies; 10 adoption studies	Aggressive behavior	a^2 44%	c^2 6%	e^2 50%	
(Burt, 2009) 15 twin studies; 4 adoption studies	Aggressive behavior	a^2 65%	c^2 5%	e^2 30%	
(Ferguson, 2010) 38 twin studies	Antisocial behavior	a^2 56%	c^2 11%	e^2 31%	
(Tuvblad & Baker, 2011) 33 twin studies; 4 adoption studies	Aggressive behavior	a^2 50%	c^2 0%	e^2 50%	

Note. a^2, genetic effects; c^2, shared environmental effects; d^2, dominant effects; e^2, nonshared environmental effects.

Some of the metaanalyses examined whether moderators influenced the magnitude of genetic and environmental influences on aggressive behavior. Mason and Frick (1994) did not find that different definitions of antisocial behavior, i.e., criminality, aggression, and antisocial personality varied across effect sizes (Mason & Frick, 1994). Rhee and Waldman (2002) found that effect sizes varied across different definitions of antisocial behavior, i.e., criminal behavior, delinquency, psychopathy, conduct disorder, and antisocial personality disorder, as well as aggressive behavior (Rhee & Waldman, 2002). Assessment method, zygosity determination method, and age were also significant moderators of the magnitude of genetic and environmental influences on antisocial behavior, but there were no significant differences in the magnitude of genetic and environmental influences for males and females. Burt (2009) found that effect sizes varied across age, with heritable influences being more important at older ages. Estimates were similar for

males and females. Type of informant (i.e., self, parent, teacher) was also a significant moderator (Burt, 2009). Ferguson (2010) reported that effect sizes varied across different definitions of antisocial behavior, with broader measure of aggression obtaining higher effect sizes than measures limited to DSM-IV criteria for antisocial personality disorder (Ferguson, 2010). Finally, Tuvblad and Baker (2011) found that form of aggressive behavior (reactive, proactive, direct /physical, indirect/relational), method of assessment (laboratory observation, self-report, ratings by parents and teachers), and age of the participants were significant moderators of the magnitude of genetic and environmental influences on aggressive behavior (Tuvblad, Narusyte, Grann, Sarnecki, & Lichtenstein, 2011). Neither study design (twin vs. sibling adoption design) nor sex (male vs. female) seemed to impact the magnitude of the genetic and environmental influences on aggressive behavior.

Recent Studies Using a Behavioral Genetic Research Design

There have been several papers published examining the influence of genetic contributions to aggressive behavior since the last metaanalysis was published in 2011. Some notable findings include a recent study showing that the variance in relational aggression is largely explained by additive genetic effects (0.15–0.77) (Slawinski, Klump, & Burt, 2018). Another large study included longitudinal data from a large sample of twins participating in the Netherlands Twin Register ($N = 42{,}827$, age range 3–16) (Lubke, McArtor, Boomsma, & Bartels, 2018). The study showed that the *overt* and more physical aspects of childhood *aggression* (OA) are highly heritable between ages 3 and 16. Additive genetic effects explained between 50% and 68% of the variance. The study also showed that OA is largely affected by the same genes throughout childhood. Environmental effects shared by children from the same family typically account for 20% of the variance of OA early in childhood, but they are negligible in adolescence. Nonshared environmental effects on OA are comparatively smaller in childhood (20% variance explained) than in adolescence (40%). Another recent study compared the development of aggressive behavior between Dutch and English population samples and showed that the stability and heritability of aggressive behavior was high for both samples, with longitudinal genetic correlations being the main reason for stability of aggressive behavior (Porsch et al., 2016). Harden et al. (2015) reported that genetic influences specific to rule-breaking increased as a function of pubertal development controlling for age

(a gene × puberty interaction), but did not vary as a function of age controlling for pubertal status. There were no developmental differences in the genetic etiology of aggression. Family level environmental influences common to aggression and rule-breaking decreased with age, further contributing to the differentiation between these subtypes of antisocial behavior from childhood to adolescence (Harden et al., 2015).

Neurobiology of Aggression—Where to Look for the Relevant Genes?

As aggressive behavior is not a uniform behavioral construct and likely comprises several neurobiological mechanisms, pinpointing specific genetic components of aggression is challenging (Waltes, Chiocchetti, & Freitag, 2016). Aggression varies in its extent over the lifespan and progresses nonlinearly (Petersen, Bates, Dodge, Lansford, & Pettit, 2015). Additionally, pathological aggression is highly comorbid with psychiatric disorders such as major depression, posttraumatic stress disorder, borderline personality disorder, schizophrenia, autism spectrum disorder, attention deficit hyperactivity disorder (ADHD) and is often accompanied by phenotypic traits such as negative emotionality, greater affective instability, and impulsive decision-making (Fettich, McCloskey, Look, & Coccaro, 2015). This suggests possible shared or overlapping underlying mechanisms for aggression and other psychiatric conditions/phenotypes as well as interactions between aggression and developmental processes.

Various studies in populations characterized by high aggression have reported alterations in neurotransmitter systems (involving serotonin (5-HT), dopamine, glutamate, GABA, and noradrenaline) and neuroendocrine processes (e.g., cortisol, testosterone) (Rosell & Siever, 2015), leading to the design of specific candidate gene studies. Additionally, genome-wide and epigenetic studies have advanced the field by identifying other possible candidate genes and potential relevant physiological processes. Following, we will discuss some of the relevant literature. Additional detailed discussions can be found in several excellent reviews (e.g., Fettich et al., 2015; Petersen et al., 2015; Rosell & Siever, 2015; Waltes et al., 2016).

Candidate Gene Studies

The candidate gene approach focuses on investigating genetic variations based on a priori hypotheses about the roles of the selected genes or pathways in a phenotype or disease. Commonly, polymorphisms are tested

for the association by comparing their occurrence in groups of cases with the disease/phenotype and controls. Candidate genes in aggression research have been mainly selected based on their relation to monoaminergic neurotransmitter systems. The first systematic metaanalysis of 185 candidate gene studies (31 genes) in relation to aggression did not derive any significant associations (Vassos, Collier, & Fazel, 2014).

Regulation of Monoamine Level: MAOA and MAOB

Monoamine oxidases *MAOA* and *MAOB* are X-linked genes encoding enzymes that regulate the levels of monoamines by catabolizing 5-HT, norepinephrine, and dopamine in the brain. 5-HT is mostly degraded by MAOA (Shih, Chen, & Ridd, 1999). Since the association of a missense mutation in *MAOA* with familial impulsive aggression (Brunner syndrome) (Brunner, Nelen, Breakefield, Ropers, & van Oost, 1993), *MAOA* has become a target of many candidate gene studies. A common nucleotide tandem repeat (VNTR) polymorphism upstream of the *MAOA* coding sequence (also known as MAOA-uVNTR) was found to affect transcription, with certain alleles being transcribed 2–10 times more efficiently. "High-activity" but more often "low-activity" alleles have been reported to be associated with aggression in different studies (Kolla & Vinette, 2017; Smeijers, Bulten, Franke, Buitelaar, & Verkes, 2017; Waltes et al., 2016). MAOA-uVNTR genotype has been reported to interact with environment (Waltes et al., 2016), affecting the outcome of adulthood aggressive behavior in individuals who suffered various extents of childhood adversity (Gorodetsky et al., 2014). Furthermore, the MAOA-uVNTR x childhood adversity interaction may be moderated by sex (Holz et al., 2018). The less studied *MAOB* gene does not appear to be significantly involved in aggressive behavior, but lack of MAOB may exacerbate the severity of MAOA dysfunction (Bortolato, Floris, & Shih, 2018).

Serotonin Transporter 5-HTT (SLC6A4)

The 5-HTT (also known as SERT; 5-HT transporter; SLC6A4) regulates extracellular levels of 5-HT by transporting it from the synaptic cleft to the presynaptic neuron. The most extensively studied polymorphism of the *SLC6A4* gene is 5HTTLPR (5-HT transporter-linked polymorphic region) that is located in the promoter area and constitutes "long" and "short" 5HTTLPR variants due to a 44-bp insertion. The "long" (L) variant leads to higher expression of 5-HTT than the "short" (S). The S allele has more often than the L allele been associated with increased

aggressive behavior and impulsivity in children (Haberstick, Smolen, & Hewitt, 2006) and adults (Retz, Retz-Junginger, Supprian, Thome, & Rösler, 2004). 5-HTT includes other gene variations that have been studied in the context of aggression, including a polymorphism within the 5HTTLPR "long" version that can alter the 5-HTT expression level to more similar of that of the S allele (Praschak-Rieder et al., 2007). This accentuates the importance of considering the polymorphism–polymorphism interactions. A metaanalysis of 31 studies concluded that the "low-activity" allele of the MAOA-uVNTR and the "short" allele of the 5HTTLPR (both variants thought to increase the availability of synaptic 5-HT and considered risk alleles) were both significantly associated with aggressive or antisocial behavior (Ficks & Waldman, 2014).

5-HT Receptors and Tryptophan Hydroxylases

Type 1 5-HT receptors are involved in the negative control of 5-HT signaling, whereas type 2 5-HT receptors are positive mediators of 5-HT transmission (Waltes et al., 2016). Various tested *HTR2C* or *HTR1A* gene variants were not found to contribute to aggression-related behaviors in a sample of suicide attempters and controls, despite there may be a sex-by-genotype interaction effect on trait anger. However, the functional *HTR1A* polymorphism C(−1019)G has been associated with impulsivity (Benko et al., 2010; Waltes et al., 2016).

HTR1B polymorphisms have been associated with childhood aggression, impulsive–aggressive behaviors in adults, and conduct disorder (Hakulinen et al., 2013; Zouk et al., 2007). The "risk polymorphisms" in *HTR1B* are generally thought to be related to lower gene expression levels, either through functional modifications or via linkage disequilibrium with other variants. There is also evidence for sex-by-genotype interactions for *HTR1B* in the context of aggression (Waltes et al., 2016). Polymorphism rs6313C > T in *HTR2A* may be associated with increased aggression in Alzheimer's disease whereas *HTR2A* rs6311 C > T has been found associated with impulsive behavior in healthy controls and aggression-related traits in suicide attempters. Furthermore, a potentially functional *HTR2A* SNP rs7322347 T allele was associated with hostility, anger, and physical aggression in healthy individuals (Waltes et al., 2016). Several other *HTR2A* polymorphisms have been suggested to be associated with impulsive behavior in psychiatric patients (Bruce et al., 2005; Tsuang et al., 2013). A stop codon variant of the *HTR2B* gene (*20) was identified exclusively in Finnish population and found to cosegregate with psychiatric diseases marked by

impulsivity (Bevilacqua et al., 2010). However, an association with aggression was not found in a study of Finnish violent offenders (Tiihonen et al., 2015).

Tryptophan hydroxylases (TPH) are the rate-limiting enzymes for 5-HT synthesis, with TPH1 primarily operating in the peripheral and TPH2 exclusively in the central nervous system. Despite their importance in 5-HT synthesis, only a few association studies have been performed in relation to aggression. *TPH1* A218C was studied twice and yielded opposing results, possibly because one of the studies was in a healthy sample and other investigated patients with Alzheimer's disease. A *TPH2* "risk haplotype" was found associated with borderline personality disorder diagnosis, aggression, and affective instability scores (Waltes et al., 2016).

Components of the Dopaminergic System

COMT (catechol-*O*-methyltransferase) is an enzyme inactivating catecholamine neurotransmitters including dopamine. The most studied polymorphism in *COMT* Val158Met (rs4680G > A) Met variant reduces the enzymatic activity almost fourfold. The studies of Val158Met in relation to aggression have yielded inconsistent results (Qayyum et al., 2015). A recent metaanalysis did not find a significant association of this polymorphism with aggression in general (Vassos et al., 2014). However, the low or high activity *Val158Met* polymorphisms may be associated with aggression in schizophrenia or conduct problems in ADHD patients, respectively (Qayyum et al., 2015). A VNTR in the dopamine transporter *DAT1* has been associated with aggression in a cohort of heroin users. Polymorphisms in different dopamine receptor genes have been reported associated with aggression in children (*DRD2*), patients with Alzheimer's disease (*DRD1*), and patients with schizophrenia (*DRD4*). A 7 repeat (7-R) risk allele of a VNTR in *DRD4* may interact with 5HTTLPR "short" variant to increase the level of externalizing behavior in adolescents (Fresan et al., 2007; Waltes et al., 2016). DRD4 may also be involved in a GxE interaction whereby prenatal stress correlates with higher levels of aggression and attenuated cortisol secretion in young adults with the *DRD4* 7-*R* risk allele (Buchmann et al., 2014).

Oxytocin and Arginine Vasopressin Systems

Oxytocin and arginine vasopressin (also known as AVP, antidiuretic hormone) are highly conserved neuropeptides that mediate the regulation of complex social behaviors. A SNP rs35369693 in arginine vasopressin receptor

1B (*AVPR1B*) has been associated with childhood aggression (Waltes et al., 2016). Possible interaction between *AVPR1A* and *RS3* genes may occur in impulsive aggression in patients with borderline personality disorder (Vogel et al., 2012). In the largest study exploring children's aggressive behavior to date ($N = 18,988$), *AVPR1A* was the only gene which variations were found significantly associated with childhood aggression in the gene-based analysis (Pappa et al., 2016). Polymorphisms rs6770632G > T and rs1042778C > A in the oxytocin receptor gene (*OXTR*) have been suggested to play a role in pervasive childhood aggression (Malik et al., 2014).

Other Candidate Genes of Interest

Various other polymorphisms have been investigated in relation to aggression, including variations in genes related to stress response, cholesterol metabolism, nitric oxide, and BDNF signaling. There is evidence suggesting involvement of genes relevant for hormonal regulation, e.g., the androgen receptor, in aggression (Rosell & Siever, 2015; Waltes et al., 2016).

Genome-Wide Association Studies (GWASs)

Genome-wide association studies (GWASs) enable a hypothesis-free approach whereby a large number of polymorphic markers (such as Single Nucleotide Polymorphisms (SNPs)) from all over the genome are tested for association with a disease or phenotype. Genome scan results of cases with the disease/phenotype are compared with these of the controls.

GWASs of Aggression

Despite some promising leads, GWASs in aggression have not reported any conclusively significant association. In addition, a recent metaanalysis comprising genome-wide data from five large population-based cohorts in association with antisocial behavior ($N = 16,400$) did not reveal any significant markers (Tielbeek et al., 2017). A GWAS of aggressive behavior in children (the EAGLE consortium) included 18,988 participants and measured aggressive behavior in childhood and early adolescence. Metaanalysis of the total cohort identified a near genome-wide significant region on chromosome 2p12, near the gene *LRRTM4* that is involved in excitatory synapse development (Pappa et al., 2016). A GWAS in 8747 European adults investigated associations with an aggression-related trait—proneness to anger. This study reported a nominally significant finding on the chromosome 6q21 in the

gene coding for the nonreceptor protein-tyrosine kinase Fyn. Fyn participates in signaling pathways important for memory, learning, and neuronal survival and may therefore be involved in cognitive regulation in aggression (Mick et al., 2014). A GWAS in two cohorts of violent offenders imprisoned in Finland revealed a suggestive polymorphism rs11649622 on chromosome 16q23.3 inside the intron of a gene coding for a neural adhesion protein cadherin 13 (*CDH13*) (Tiihonen et al., 2015) that has previously been associated with various psychiatric diseases including ADHD. Another GWAS investigating genetic etiology of adult antisocial behavior did not detect genome-wide significance, but the most associated gene *DYRK1A* encodes for an enzyme considered important for synaptic plasticity and brain development (Tielbeek et al., 2012). Finally, a study in children with ADHD found an ADHD-related polygenic risk score including 46,156 alleles to correlate positively with the number of aggressive conduct disorder symptoms (Hamshere et al., 2013), despite no significant variation has been detected in GWASs investigating aggression in ADHD (Aebi et al., 2016; Brevik et al., 2016). In summary, several markers in loci related to genes that are important for neuronal function have been found to reach near significance in GWASs investigating aggression. Notably, GWASs on aggression did not find significant associations for the genes that are mostly being studied in candidate gene studies.

Epigenetics of Aggression

Epigenetic modifications, such as DNA methylation or histone acetylation, can change the activity of the genes in the absence of DNA sequence changes. Epigenetic modifications may occur in response to environmental influences, e.g., early life adversity, and are potentially reversible (Nestler, Peña, Kundakovic, Mitchell, & Akbarian, 2016). DNA methylation is the most studied epigenetic modification in the context of human aggression, with epigenetic changes mainly measured in peripheral blood cell DNA. 5-HT system components may be affected by epigenetic regulation. For example, women who had been sexually abused during childhood were found to exhibit hypermethylation of the *5-HTT* promoter that in turn associated with increased symptoms of antisocial behavior in comparison to controls. Furthermore, 5-HTTLPR polymorphism seemed to affect the outcome, whereby *5-HTT* promoter methylation in individuals homozygous for the "long" variant of 5-HTTLPR was not significantly associated with antisocial behavior symptoms (Beach, Bordy, Todorov, Gunter, & Philibert, 2011).

Higher *5-HTT* promoter methylation levels were also found in adult males with higher levels of childhood aggression which correlated with lower in vivo 5-HT synthesis in orbitofrontal cortex (Wang et al., 2012). In line with that, *MAOA* promoter region was found hypermethylated in incarcerated individuals with antisocial personality disorder. Functional studies indicated that such increased promoter methylation contributes to decreased expression of MAOA (Checknita et al., 2015). As alterations in cytokine levels have been found correlated with physical aggression, epigenetic profiles of the loci of numerous cytokines were analyzed in a longitudinal sample of adult males with chronic physical aggression trajectory in comparison to males with normal aggression trajectory. Differentially methylated regions between groups were found in the loci of *IL-6, IL-1α, IL-8, IL-4, IL-10* and their transcriptional regulators *NFkB1*, *NFAT5*, and *STAT6* (Provencal et al., 2013).

Epigenome-wide promoter-targeting studies have uncovered similar DNA methylation signatures (over 400 distinct differentially methylated promoter regions) for adult males and females who have exhibited childhood chronic physical aggression, in comparison to individuals with normal aggression levels (Guillemin et al., 2014; Provencal et al., 2014), also pinpointing some genes that have previously been associated with aggressive phenotypes using other approaches, such as *AVPR1A*, *HTR1D*, and *SLC6A3* (Provencal et al., 2014). In the first *epi*genome-wide association study (EWAS) in relation to aggressive behavior, no epigenome-wide significance was detected. Areas close to the trichorhinophalangeal syndrome I (*TRPS1*) gene and activity-dependent neuroprotective protein 2 (*ADNP2*) gene were among the most promising loci. Gene ontology enrichment analyses suggested the involvement of pathways implicated in development, metabolism, and central nervous system/neural function-related processes (van Dongen et al., 2015). Another recent EWAS in a small group of individuals with IED and controls also revealed numerous suggestive loci, despite none with epigenome-wide significance. Functional enrichment analysis pointed toward the importance of the immune system, endocrine system, and components of the neuronal differentiation pathways in IED (Montalvo-Ortiz, Zhang, Chen, Liu, & Coccaro, 2018). In a study examining prospective associations between epigenome-wide methylation patterns at birth and trajectories of early onset conduct problems, differential methylation was detected at seven loci across the genome, with additional subthreshold associations close to the typical candidate genes in aggression—*MAOA*, *BDNF*, and *FKBP5* (Cecil et al., 2018).

Conclusion

Aggression has been consistently shown to have a large genetic component based on findings from behavioral genetic studies. However, candidate gene and GWA studies on aggression have not identified a significant genetic marker. This does not mean that there are no genes relevant for aggression, but possibly indicates a complex interplay between various genetic components and environmental factors/triggers in aggression. Additionally, distinct forms of aggressive behavior (e.g., reactive, proactive, direct/physical, indirect/relational) may differ in their underlying neurobiological mechanisms. The extent to which environment affects epigenetic processes may depend on genotype, as well as other factors such as age, sex, and developmental history. The nonlinear occurrence of aggression over the lifetime (Petersen et al., 2015) hints the involvement of developmental processes in the manifestation of aggression. Also, pathological aggression is highly comorbid with numerous psychiatric disorders and the concept of aggression is very heterogeneous, which further increases the complexity in the search for genetic and epigenetic markers. Notably, while most clinical studies focus on antisocial personality disorder, (epi) genetic research in psychiatric disorders that have aggression as a core symptom (such as IED) is scarce. Multidisciplinary collaborative research of genetic and epigenetic factors at various ages throughout the lifespan in well-characterized clinical and nonclinical study samples is needed to further shed light on the specific genetic and epigenetic contributions to (different types of) aggression including IED.

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