The relation of ADHD and violent aggression: What can we learn from epidemiological and genetic studies?

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**Abstract**

Disruptive behavior includes psychopathological and behavioral constructs like aggression, impulsivity, violence, antisociality and psychopathy and is often closely related with diagnostic categories like conduct disorder (CD), attention deficit disorder (ADHD) and antisocial personality disorder (ASP). There is now clear evidence that neurobiological and environmental factors contribute to these phenotypes. A mounting body of evidence also suggests interactive effects of genetic and environmental risks. In this selective review we give an overview over epidemiological aspects of the relation between ADHD and antisocial behavior, including violent aggression and psychopathy. Moreover, we summarize recent findings from molecular genetic studies and particularly discuss pleiotropic effects of a functional polymorphism of the serotonin transporter promoter gene (5HTTLPR) and childhood adversity on ADHD and violent behavior. The reported gene–environment interactions are not only informative for understanding the neurobiological underpinnings of disruptive behavior, but also throw some light on the relation between ADHD and violent behavior from a genetic perspective. The impact of genetic research on forensic psychiatry and future directions of neurobiological research are discussed.

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1. Introduction

Social maladaptive, disruptive behavior arises from several conditions including genetic disposition as well as cultural and social factors, which are enforced on the background of the individual’s experiences (Fig. 1). Important progress has been made in identifying genetic risk factors that predispose to antisocial behavior (Raine, 1993; Volavka, 2002). Also much progress has been made in uncovering psychosocial risk factors for antisocial and violent behavior (Farrington, 2000; McCord, 2001). The discussion in the past regarding the role of “nature” and “nurture” has been now followed by research on interaction between genetic and environmental influences on the development of disruptive behavior (Raine, 2002).

Beside research on the influence of genes and environment with disruptive behavior, investigations concerning the association with psychiatric disorders provide an additional source to elucidate the neurobiological and environmental underpinnings of aggression, violence and antisociality. Among other psychiatric disorders like schizophrenia, suicidal depression and cluster B personality disorders, attention deficit/hyperactivity disorder (ADHD) is of particular interest in this context, because it is characterized by psychopathological complex of attentional problems, motor overactivity and impulsivity, which is per se closely linked to behavioral problems. In addition, this disorder starts early in life and, therefore, is suggested to have high impact of an individual’s socialization.

In this report we summarize some work concerning genetic influences on ADHD and violent behavior with a focus on genes involved in the regulation of serotonergic neurotransmission. This work also turns towards the question of gene–environment interactions in the etiology of ADHD and violent aggression and sheds some light on the relation of violence and ADHD from a genetic perspective.

1.1. Genetics of antisocial behavior

Despite the heterogeneity of definitions and classifications used and the difficulties regarding operationalization and assessment of antisocial behavior phenotypes, there is clear evidence from twin, adoption and molecular genetic studies to support the notion that there are genetic influences on antisocial and aggressive behavior (Raine, 1993). It has to be emphasized that the variability of findings regarding the magnitude of environmental and genetic contribution is high. This variability is not only attributable to differences between the investigated populations, but also to the difficulties in the measurement of disruptive disorders or antisocial behavior. The composition of well observable behavioral (e.g. violence, verbal aggression) and psychopathological features (e.g. unemotionality, hostility) differs profoundly between the investigated phenotypes. Moreover, there is often a fluent passage between phenotypes which should be delineated. For instance, an aggressive act might present features of...
proactive and reactive aggression that might provide problems regarding unequivocal classification.

In a meta-analysis of 51 twin and adoption studies Rhee and Waldman (2002) estimated moderate genetic (additive 32%, non-additive 9%) and environmental influences (shared 16%, non-shared 43%) on antisocial behavior. More specifically, moderate heritability has been also found for violent behavior (Cloninger & Gottesman, 1987; Rushton, 1996). Twin- and adoption studies also provide information which go beyond pure quantification of genetic and environmental effects. One example is the evaluation of gender differences. It has been shown that the magnitude of environmental and genetic influences on antisocial behavior is equal for males and females (Rhee & Waldman, 2002; Widom & Ames, 1988), but also a slightly higher genetic load in males was found (Miles & Carey, 1997). Given the higher prevalence of antisocial behavior in males than females and the little or absent difference in the magnitude of genetic effect on antisocial behavior, different genes or environmental factors or both might be important within each sex.

Another important issue are developmental changes of the genetic and environmental impact on antisocial behavior phenotypes. Although Rhee and Waldman (2002) found a decrease of familial genetic and environmental factors and an increase of non-familial factors from childhood to adulthood, the direction of difference regarding heritability varies across studies (DiLalla & Gottesman, 1989; Miles & Carey, 1997). These discrepancies might be partially due to confounding methods of measurement of behavioral phenotypes, but also to various subtypes of individuals with different life-course patterns of antisociality (e.g. life-course persistent vs. adolescence-limited; Moffitt, 2003).

But not only differentiation of developmental subtypes, but also more detailed psychopathological characterization of antisocial behavior reveals additional information from twin- and adoption studies. Examples for this are the finding that continuous aggressive but not non-aggressive antisocial behavior is largely genetically mediated (Eley, Lichtenstein, & Moffitt, 2003) or that antisocial behavior is more inheritable in children with than without concomitant callous-unemotional personality traits (Viding, Jones, Frick, Moffitt, & Plomin, 2008). It could also be demonstrated that the importance of genetic and environmental influences varies regarding subgroups of individuals with antisocial behavior, if measures of attention deficit disorder, conduct and oppositional disorder and other psychopathological features were used for latent class analysis (Silberg et al., 1996), suggesting heterogeneity of antisocial behavior and emphasizing the need for multivariate approaches for studying phenotypes related with antisociality.

Further, adoption studies provide substantial evidence that environmental and genetic risks interact. For example in a Swedish study 40% of adoptees were criminal when both genetic and postnatal environmental risks were present, but only 12.1% and 6.7% were criminal in presence of either genetic or environmental risks, respectively (Cloninger, Sigvardsson, Bohman, & von Knorring, 1982). These results suggest a non-additive but interactive effect of genetic and environmental risks for antisocial behavior.

Molecular genetic linkage and association studies have now just begun to reveal the architecture of antisocial behavior more in detail. Results from few linkage studies regarding conduct disorder and antisociality performed so far are not consistent (Dick et al., 2004, 2008; Kendler et al., 2006; Stallings et al., 2005). Association studies have mainly focused on risk genes which are involved in the regulation of monoaminergic neurotransmission. They include catecholaminergic and serotonergic genes, but also genes which have been related to aggressive and violent behavior due to animal models, like the nitric oxide synthase (NOS-I) gene (Reif et al., 2009). For example, dopamine receptor D2 (DRD2) and dopamine receptor D4 (DRD4) gene variants and interaction between them are associated with conduct disorder and antisocial behavior (Beaver et al., 2007; Congdon, Lesch, & Canli, 2008).

Also the catechol-o-methyltransferase (COMT) gene has been associated with increased aggressive behavior, at least in several samples of psychiatric patients (Volavka, Bilder, & Nolan, 2004). Most evidence regarding genetic regulation of antisocial behavior has been collected for serotonergic genes and will be outlined below.

Although suggested from epidemiological genetic investigations, the study of gene–environment interactions is still quite new in the field of neuroscience (Caspì & Moffitt, 2006). Several lines of investigations provide increasing evidence that the effect of environmental pathogens on the development of mental disorders or behavioral traits including antisocial behavior is conditional on the individual's genotype. These comprise experiments with animal models, which allow to control both genetic and environmental conditions and studies that compare human genotype groups on their response to environment. Moreover, the use of neuroimaging or neurophysiological techniques allows identifying
functional and anatomical networks, which are involved in the response to environmental stimuli in experimental settings. For example, it could be shown that amygdala volume and prefrontal and amygdala activation in response of emotional stimuli is mediated by the MAO-A genotype (Meyer-Lindenberg et al., 2006). Thus, combination of epidemiological genetics with neuropsychiatric techniques allows progressing insight in the mechanisms of the genetic control of environmental effects in mental disorders or antisocial behavior.

2. ADHD and antisocial behavior

Attention deficit–hyperactivity disorder (ADHD) is a highly heritable, disruptive condition with childhood onset and about 50% persistence in adulthood (Biederman & Faraone, 2005). ADHD is associated with risks regarding daily functioning (Barkley, 2002). The number of jobs in a given time period is increased as well as separation and divorce rates. Many adults with ADHD have difficulties with bad parenting. The risk of accidents at home, school, and vocational affairs and during leisure is much higher than in controls. Even in cases of severe injury due to an accident ADHD is significantly overrepresented (Kaya et al., 2008). The risk of violations of the road traffic rules in adults with ADHD is much higher. According to a review by Jerome, Habinski, and Segal (2006) speeding, driving under alcohol, driving without licence and a much higher prevalence of accidents are the most frequent problems in ADHD populations when comparing with individuals without ADHD.

According to recent epidemiologic research the transnational prevalence of ADHD in adults was 3.7% (Fayyad et al., 2007). In the USA a prevalence of 4.4% (Kessler et al., 2006) and in Germany a prevalence of 3.1% was found, respectively. In contrast, in offender populations the prevalence of adult ADHD varies between 4% and 72% (Vermeiren, 2003). The majority of studies found prevalence rates between 14% and 19%. In a German study with 129 male adolescent and young adult incarcerated subjects the prevalence of ADHD according to DSM-IV was 45% (Retz, Retz-junginger, Hengesch et al., 2004; Rösler et al., 2004). Also among female detainees the rate of ADHD is higher compared to normal population (10%; Rösler, Retz, Yaqoobi, Burg, & Retz-junginger, 2009). The high variety of findings concerning prevalence rates of ADHD in offender populations might be due to differences between the samples investigated, different criminal law systems, differences regarding the mean age of study populations and diagnostic procedures. Nevertheless, there is much evidence that ADHD is increased in forensic populations.

Conduct disorder (CD) – and early-onset (before age 10 years) CD in particular – is highly prevalent in ADHD children (Angold, Costello, & Erkanli, 1999; Loeb, Green, Keenan, & Lahey, 1995). There is a controversial discussion regarding the problem whether ADHD, comorbid CD or both conditions predict antisociality and criminal behaviour in adults with ADHD. From a genetic perspective it has been argued that ADHD with comorbid CD might be a more severe variant of ADHD and not distinct disorders (Dick, Viken, Kaprio, Puukkinen, & Rose, 2005; Nadder, Rutter, Silberg, Maes, & Eaves, 2002; Thapar, Harrington, & McGuffin, 2001). Babinski, Hartsough, and Lambert (1999) found that conduct disorder and hyperactivity/impulsivity but not inattention contributed to the risk of criminal involvement in a group of male offenders with recidivist crimes. On the other hand, the majority of studies suggested that CD and not ADHD predicts adult antisociality (Lahey, Loeb, Burke, & Applegate, 2005; Satterfield et al., 2007). Since the diagnostic criteria for CD do not refer to psychopathological symptoms, but exclusively to disruptive behavior including criminal acts, it seems a truism to predict antisociality and criminality in adulthood by “criminal” conduct in childhood and adolescence and does not elucidate the specific role of comorbid ADHD for the development of delinquent behavior. Other studies, however, consistently emerged ADHD as a moderator of conduct problems in children. It seems that the decision over antisocial outcome of ADHD children is given early. Numerous studies have shown that children with both CD and ADHD, as compared with children with conduct problems alone, tend to have an earlier onset and a more stable course of antisocial behavior (Loeb et al., 1995; Moffitt, 1990). As a result of such findings, the presence or absence of ADHD has become one key component of children’s CD that is early “delinquent” behavior (Moffitt, 2003).

3. ADHD, antisocial personality disorder (ASP) and psychopathy

Follow-up studies with ADHD children revealed high rates of Antisocial Personality Disorder (ASP) in later life (Barkley, Fischer, Smallish, & Fletcher, 2004; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998; Satterfield & Schell, 1997; Weiss, Hechtman, Milroy, & Perlman, 1985). They exceed by far an expected rate of accidental co-occurrence of both disorders of 0.06%, given an estimated prevalence of adult ADHD of about 3% and a prevalence for ASP from population based epidemiological studies of about 2%. Interestingly, a high proportion of ADHD children without CD at time of inclusion in the New York follow up studies (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993) were diagnosed with ASP in later life, suggesting that early onset CD is not a necessary condition for later ASP. Moreover, Satterfield et al. (2007) published the results of a 30-year prospective follow-up study of hyperactive boys with conduct disorder and found that there was a steady decline in offence rates with increasing age. Thus, conduct problems which occur together with ADHD during childhood and adolescence may persist in adulthood as ASP and seem to be followed by decline of both, ADHD and antisociality. It should be considered that ASP in context with ADHD might represent a special subtype of ASP, but more studies are needed to confirm this hypothesis.

The concept of psychopathy (Hare, 1996) refers to a core population of ASP individuals and goes beyond bare description of antisocial behavior. Psychopathy according to Hare comprises traits dealing with interpersonal and affective deficits (e.g. shallow affect, superficial charm, manipulativeness, lack of empathy) and symptoms relating to antisocial behavior (e.g. criminal versatility, juvenile delinquency). This construct goes back to the beginning of the 19th century when Prichard (1835) described the psychopathology of “moral insanity.” Psychopathy is associated with poor treatment response and the forensic prognosis is unfavourable in almost all cases. The total score of the Psychopathy Checklist (PCL; Hare et al., 1990) is a valid risk factor indicating criminal offences and in particular violent behavior. Psychopaths are a small population but they account for an excess quantity of felony crimes and for criminal recidivism. An association between ADHD and the psychopathy concept could be assumed since there is certain overlap between the DSM-IV items referring to the syndromic complex of hyperactive–impulsive features in ADHD and the PCL factor focussing on poor behaviour control and impulsivity. However, if the hypothesis is true that ASP in combination with ADHD represents a subtype with more favourable prognosis, it should be able to differentiate these individuals from psychopaths in terms of psychopathology and outcome.

In order to elucidate the relation between ADHD and psychopathy, we conducted a study with 230 incarcerated male subjects. All had committed felony crimes and were incarcerated for more than 2 years. ADHD syndrome and psychopathy scores were established by means of the ADHD self report scale (Rösler et al., 2006) and the PCL-SV, respectively. We found a rank correlation of 0.2 between PCL-SV and ADHD-SR mean scores, which was statistically significant (p < 0.01), but clinically not meaningful. In order to investigate possible associations between features of psychopathy and diagnostic ADHD criteria we performed a factor-analysis. We expected to find factors of common psychopathology in the case of an association between ADHD and psychopathy. A seven factors model accounted for 68% of the variance. No factor comprised items from both concepts, but there
were 3 pure ADHD and 4 pure psychopathy factors (Retz & Rösler, 2007). It is apparent from this finding that there is no association between diagnostic items of ADHD with those of psychopathy in the sample under investigation, suggesting different pathways of antisocial behavior in psychopaths and ADHD subjects. In accordance with this finding Fowler and colleagues recently reported elevated total psychopathy and emotional-dysfunction scores according to norms in ADHD adolescents, but none scored in the clinical range of psychopathy (Fowler et al., 2009). More specifically, Eisenbarth et al. could show an increase of behavioral features of psychopathy in adult ADHD patients, but a reduction of emotional features like coldheartedness and stress immunity compared to controls (Eisenbarth et al., 2008).

4. ADHD and aggression

Aggressive behavior is a common phenomenon accompanying childhood ADHD (Barkley, 1998; Hinshaw, 1992). Considering heterogeneity of aggression and violence which is often associated with delinquent behavior, a sensible construct has been created in hypothesizing a dichotomy between a reactive–impulsive–hostile–affective subtype and a proactive-controlled-instrumental-preatory subtype of aggressive and violent behavior (Vitiello & Stoff, 1997). In children with conduct problems, it has been shown that ADHD is a moderator of reactive but not proactive aggression (Wachbusch & Willoughby, 2007). In addition, Bennett, Pitale, Vora, and Rheingold (2004) showed that reactive antisocial behavior was more closely related to ADHD than proactive antisocial behavior in 8 to 15 year old children and that the relation between ADHD symptoms and proactive antisocial behavior increased from middle childhood to adolescence. Association of ADHD with reactive aggression seems plausible with regard to the characteristic psychopathology of ADHD. Reactive aggression is not planned but always spontaneous, a reaction to a provocation or a conflict. Reactive aggression is driven by affective outbursts. It is short-lived and has no finalistic target except the reduction of tension and agitation. Usually reactive violence is not rational but impulsive. There is no systematic or instrumental character of aggressive actions. In so far, there are some similarities to the hyperactive–impulsive psychopathology of ADHD.

Following the hypothesis that reactive, but not proactive aggression is associated with ADHD in adult offenders, we performed a pilot study with 66 males from a forensic population with and without ADHD, which has been previously described (Reif et al., 2007; Retz et al., 2008). We found a strong association between the presence of ADHD and reactive violent aggression ($\chi^2 = 210.0$, $p = .000$, OR: 2.7; 95% CI: 1.5–107.9, Retz & Rösler, 2007). In contrast, proactive violent aggression was found predominately in absence of ADHD (Fig. 2). These results corroborate the findings in ADHD children and have to be further elaborated.

Concerning the epidemiological findings mentioned above, the pathways from childhood ADHD to functional disabilities and antisocial behavior in adulthood are summarized in Fig. 3.

5. ADHD, serotonergic genes and environment

Genetic epidemiological studies indicate heritability of ADHD up to 90% (Thapar, Holmes, Poulton, & Harrington, 1999). Up to now, only a few genome-wide linkage studies have been performed, indicating that several chromosomal regions are implicated in ADHD. Moreover, a large number of association studies have been realized, inspired by high evidence of monoaminergic dysfunction in ADHD (Pliszka, McCracken, & Maas, 1996). Replicated and in pooled analyses confirmed findings suggest significant association of ADHD with the dopamine D4 and D5 receptor genes and the dopamine DATI transporter gene (Faraone et al., 2005). In addition, there is a mounting body of evidence suggesting an association of ADHD with genes involved in the regulation of serotonergic transmission. Independent replicated associations have been reported regarding ADHD and the serotonin transporter gene (SHT transporter linked polymorphic region, 5HTTLPR). Association of the long (L) 5-HTTLPR allele and the long/long (LL)-genotype, respectively, has been demonstrated by different groups using population-based and family-based case control studies (Beitchman et al., 2003; Manor et al., 2001; Seeger, Schloss, & Schmidt, 2001; Zoroglu et al., 2002) and quantitative trait loci approaches (Retz, Thome, Blocher, Baader, & Rösler, 2002; Curran, Purcell, Craig, Asherson, & Sham, 2005). Kent et al. (2002) reported a small but significant association when they analysed pooled data from three studies, but only a statistical trend in their own study, but there are also studies which did not corroborate these findings (Langley et al., 2003).

Although genetic epidemiological and molecular genetic studies clearly indicate a crucial impact of genes in the etiology of ADHD, heritable factors only partially explain the pathogenesis of this disorder. The work of Rutter and colleagues emphasized the role of psychosocial environmental factors including family conflict, social class, family size, maternal psychopathology, and paternal criminality for the risk for child psychopathology (Rutter, 1999). These findings were confirmed in recent studies particularly with regard to ADHD, which could also show, that males are more vulnerable to environmental adversity than female subjects (Biederman et al., 1995, Biederman, Faraone, & Monuteaux, 2002). Additionally, recent studies suggest that association of 5-HTTLPR with behavioural phenotypes and certain disease states may depend on environmental influences and individual life-history experiences (Barr et al., 2003; Caspi et al., 2003; Fox et al., 2005; Sjöberg et al., 2005). They also indicate that genetic regulation of serotonergic neurotransmission may be sensitive to environmental influences (Bennett et al., 2002; Manuck, Flory, Ferrell, & Muldoon, 2004).

Recently, we have reported the association of the 5HTTLPR LL-genotype with childhood ADHD symptoms and persistent ADHD in a forensic population (Retz et al., 2008). The results confirmed prior findings of an association of the ADHD phenotype with the long allele of the 5-HTTLPR (Retz et al., 2002) and a significant impact of adverse childhood environment on childhood ADHD symptomatology, which has been suggested in several studies before (Biederman et al., 1995, 2002). It was also shown that interaction between the 5-HTTLPR and environmental conditions has a significant influence on ADHD symptomatology (Fig. 4a). In this study, carriers of the LL-genotype had a higher risk for presenting more ADHD symptoms, when childhood psychosocial adversity was low. There was only little increase of ADHD psychopathology in these individuals under unfavourable environmental conditions. By contrast, carriers of at least one S-allele were much more responsive to adverse environment regarding the development of
ADHD symptomatology. The results suggested that the 5-HTTLPR mediated risk for ADHD is moderated by environmental adversity and that the impact of environment depends on an individual’s genetic background. This finding is in agreement with experiments with 5-HTT knock-out mice, which exhibit an increased stress-responsive phenotype (Murphy et al., 2001). They also corroborate the findings of Caspi et al. (2003), who were able to demonstrate that the relation of stressful life-events on affective disturbances is moderated by the 5-HTTLPR genotype with highest vulnerability in carriers of the SS-genotype. Similar findings were reported by Wilhelm et al. (2006). Under the light of these studies the LL-genotype does not simply increase the risk for ADHD psychopathology, at least under favourable environmental conditions, but seems to have protective effects against adverse environmental influences on serotonergic brain function.

6. Violence, serotonergic genes and environment

So far, genetic studies in humans concerning aggressive behavior have mainly focused genes involved in the regulation of serotonergic neurotransmission. Indeed, since socio-psychological research underscores the relation between cognition, emotion, and aggression, it appears reasonable that neural circuits that affect emotional states, like the central serotonergic system, also affect the predisposition towards aggressive behaviors. Serotonergic susceptibility genes for human aggression include the monoamine-oxygenase A (MAOA) gene, the serotonin transporter promoter gene (5HTTLPR), the tryptophane hydroxylase 2 (TPH2) gene and the serotonin receptor 1a and 1b (5HTR1a and 5HTLPR1b) genes (Papova, 2006).

In the last years molecular genetic studies provided also evidence suggesting interactive effects of biological and social factors on disruptive behavior. Gene–environment interactions in the development of aggressive behavior were demonstrated for childhood maltreatment and the MAOA gene (Caspi et al., 2002; Foley et al., 2004; Huang et al., 2004). Data from the Dunedin longitudinal study (Caspi et al., 2002) suggested that childhood maltreatment is a risk factor for conduct disorder, antisocial personality disorder and violent behavior. High MAO-A activity, i.e. long MAOA alleles, protected against the development of violent behavior in the presence of childhood maltreatment, whereas short MAOA alleles predisposed towards violent behavior, at least in case of exposure to childhood maltreatment. Likewise, low-activity MAOA alleles could be found more often in conduct disorder exclusively in the presence of adverse childhood environment (Foley et al., 2004). Nilsson et al. (2006) reported that the short MAOA allele interacted with adverse psychosocial risk factors during adolescence to result in criminal behavior in general, but also specifically with violence in a Swedish population. Conflicting with some of these findings, short MAOA alleles in turn appeared to be associated with a history of childhood abuse and with higher impulsivity measures, but not with Brown-Goodwin Aggression Scale scores (Huang et al., 2004). Other studies failed to replicate the findings of the Dunedin study and an association of the MAOA genotype with conduct problems (Haberstick et al., 2005; Young et al., 2006), or found genetic and environmental influences, but no interactive effects (Reif et al., 2007). According to a meta-analysis of 5 studies, the association between maltreatment and antisocial behavior was found significantly stronger in male carriers of the short MAOA allele (Kim-Cohen et al., 2006) suggesting that the MAOA gene influences vulnerability to environmental stress in childhood.

So far, only a few studies have concerned a possible relation between the 5-HT transporter promoter gene polymorphism and violence. The 5HTTLPR genotype has been shown to be associated with Neuroticism (Lesch et al., 1996), especially in patients with cluster C personality disorders (Jacob et al., 2004) and particular aspects of negative emotionality like hostility and agreeableness (Lesch & Merschdorf, 2000). Zalsman et al. (2005) and coworkers have
reported a significant difference in violence measures in suicidal patients carrying the L/L and L/s genotypes. In a study regarding homicidal behavior in schizophrenics, no association was observed with the 5-HT transporter promoter gene polymorphism (Kotler et al., 1999). In heroin addicts, the s/s genotype was associated with violent offence, but not Buss-Durkee Hostility Inventory scores (Gerra et al., 2004). Additional data also pointed towards an association of the s/s genotype with violent crime (Liao, Hong, Shih, & Tsai, 2004), and a study from our group demonstrated that the s allele was found significantly more often in violent crime offenders especially when ADHD psychopathology was present, explaining 5% of the genetic variance of violent behavior (Retz, Retz-Junginger, Supprian, Thome, & Rösler, 2004). Further, Beitchman et al. (2006) reported association between 5HTTLPR genotype and childhood aggression.

Investigating the influence of both, childhood psychosocial adversity and 5HTTLPR genotype, on the appearance of violent aggression in adult offenders, Reif et al. (2007) recently showed that homozygotes for the 5HTTLPR L-allele were generally less likely to develop later-life violent behavior, while carriers of at least one S-allele were influenced by environmental factors (Fig. 4b). The results of this study suggest that this polymorphism might have a role in balancing aggressive behaviors in differing societies. Corresponding to this finding, in rhesus monkeys adverse early environment interacted with the monkey analogue of the 5HTTLPR in exactly the same manner as in the present study (Barr et al., 2003), further arguing for the notion that this polymorphism modulates the response towards adverse environments.

7. Violence, ADHD, 5HTTLPR and environment

The reported results of studies concerning association of the 5HTTLPR genotype and childhood psychosocial adversity with ADHD and violent behavior reported here not only support the notion of gene–environment interactions in the etiology of these phenotypes, but also throw some light on the relation of ADHD and violent behavior on the background of genetic and psychosocial risk factors shared by both phenotypes. It has been shown that the risk for ADHD was generally high in carriers of the 5HTTLPR LL-genotype and independent from psychosocial influences, whereas the prevalence of habitual violent behavior in these individuals was low. In contrast, carriers of the 5HTTLPR SS/SL-genotype had a low risk for both ADHD and violent behavior in absence of psychosocial adversity, but the risk for ADHD and violent behavior increased markedly, if psychosocial adversity was high (Table 1). It has to be concluded, that violent behavior is not inevitably associated with ADHD, but co-occurrence depends on particular genetic and environmental constellations. This finding is in good agreement with epidemiological studies, which have reported an association of ADHD with disruptive behavior including impulsive aggression and antisociality, but not with instrumental violence and psychopathy according to the concept of Hare.

In general, the results of the studies reported here support the notion, that common genetic polymorphisms like 5HTTLPR might have pleiotropic effects on several phenotypes, which are substantially influenced by environmental conditions. Presuming interactions of genetic and environmental factors on several levels – gene–gene, gene–environment, environment–phenotype etc. – it becomes obvious that genes do not linearly influence human behavior. For example, Cadoret et al. (2003) failed to detect a main effect between 5HTTLPR and aggressivity, CD or ADHD, but association of the 5HTTLPR S-allele with externalizing behavior was found when confounding variables like sex and parental antisociality were taken into account. Therefore, it is necessary to assess pleiotropic genetic polymorphisms like 5HTTLPR for differential influence on males and females and in different co-occurring phenotypes regarding different environmental – psychosocial and biological – conditions.

8. Implications for forensic psychiatry – general conclusions

Studies on interactive effects of genes, environment and phenotypes are an important issue of research in forensic psychiatry with respect to the ongoing discussion about the freedom of will and the biological determination of human behavior. The findings in this field show that disruptive and criminal behaviors are not sufficiently predictable by genetic or environmental factors alone. Considering the enormous variety of potential interactions between biological and environmental factors, it has to be concluded that genetic factors do not narrow human behavior, but increase its degree of freedom. Advantageous environmental conditions might give some protection against genetic risks, and conversely, particular genetic constellations might have some protective effects against environmental adversity. Thus, the genetic background likely stabilizes the individual’s socialization by giving a frame, in which environmental factors shape the

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**Table 1**

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Fig. 4. (a) Influence of the 5-HTTLPR genotype (LL vs. SS/SL) on the prevalence of ADHD is modulated by psychosocial adversity during childhood (high vs. low CAEI) (Retz et al., 2008). (b) Influence of the 5-HTTLPR genotype (LL vs. SS/SL) on the prevalence of violent behavior is modulated by childhood psychosocial adversity (high vs. low) (Reif et al., 2007). CAEI: Childhood Adverse Environment Index.
personality and behavioral styles rather than predict behavior. It should be emphasized that genes do not directly code for aggression, violence or delinquent behavior. They do not directly determine concrete behavior. Rather, allelic variation is responsible for individual differences in neural functioning, resulting in a disposition for violent aggression or delinquent behavior. They do not specify behavior directly but rather encode molecular products that build and govern the functioning of the brain through which behavior is expressed. The genes’ effects are not deterministic but probabilistic and leave a wide margin for self-rulled decisions. Therefore, knowledge of genetic effects on human behavior in general and of specific genetic variants in particular is only a weak argument in the discussion about biologic determination of human behavior to assume irresponsibility for any individual’s misconduct.

In this context it is also important to note that complex behavioral phenotypes like antisociality and violent aggression cannot be attributed to a single gene. They are likely to involve a number of genes and the interplay between them. Moreover, genetic heterogeneity of these complex phenotypes has to be considered, suggesting that different genetic constellations might contribute to similar phenotypes, at least in interaction with environmental factors. Therefore, it is not unexpected that single genetic or environmental factors have only small effects on the variance of behavioral phenotypes in genetic association studies. Even statistically significant associations of genetic variations with behavioral phenotypes explained only a short proportion of behavioral phenotype, and they are not specific for any particular behavior. Therefore, genetic tests for responsibility or prognosis are still utopian. Second, the more general question has to be discussed whether identification of risk genes for violent aggression necessarily leads to the conclusion that offenders carrying such risk genes have to be considered as impaired in their accountability and criminal responsibility (Bernet, Vienencj-Jones, Farahany, & Montgomery, 2007; Blair, 2008). The fact that we have now started to identify specific risk genes and to show specific neuronal network activation with functional imaging techniques (Dresing et al., 2008) does not apply really new aspects to the fundamental question of the human’s responsibility, which is a principle cornerstone of our legal system. The definition of responsibility and the decision about what to do with criminal people – to leave them unpunished, to detain them or to treat them – are normative acts which do not automatically result from our knowledge about the etiology of criminal behavior. Answers to the question, which conclusions we should draw from the fact that genes and environment have impact on human behavior and whether offenders should be treated or detained in forensic psychiatric hospitals or prisons cannot be given by neuroscientists or mental health professionals alone, but only by a discourse together with representatives of legal professions, criminologists, sociologists, philosophers and politicians. However, it is necessary to communicate and explain the results of neuroscientific research and their correct interpretation to all those who participate in this discussion.

References


