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Dopamine D3 receptor gene polymorphism and violent behavior: relation to impulsiveness and ADHD-related psychopathology

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Summary. Several lines of evidence indicate that dopaminergic neurotransmission is involved in the regulation of impulsive aggression and violence and that genetically determined variability in dopaminergic gene expression modifies complex traits including that of impulsivity and aggression. In this study we report an association of the dopamine D3 receptor (DRD3) polymorphism with impulsiveness according to Eysenck's EIQ and scores on the German short version of the Wender Utah Rating Scale (WURS-k), which we used for the assessment of a history of ADHD-related symptoms. This association was detected in a group of violent offenders, but not in non-violent individuals. Highest scores of EIQ impulsiveness and of the WURS-k were found in heterozygous violent individuals, while homozygotes showed significant lower rating scores, suggesting an heterosis effect. The results of our study suggest that variations of the DRD3 gene are likely involved in the regulation of impulsivity and some psychopathological aspects of ADHD related to violent behavior.

Keywords: Attention deficit, hyperactivity disorder, violence, impulsiveness, dopamine, polymorphism.

Introduction

Twin studies suggest a high heritability of the personality traits of impulsivity, aggressiveness and their behavioral consequences, such as violent or self-injurious behavior (Coccaro et al., 1997; Roy et al., 1997; Sherman et al., 1997). Behavioral genetic studies demonstrate a heritability for many behaviors in the range of 50% of the observed variance (Plomin, 1990). Seroczynski et al. (1999) reported joint genetic and environmental influences on impulsivity and aggression measures in mono- and dizygotic male twin pairs and a

heritability of 0.47. Systematic studies on inheritance of impulsivity indicate that these complex traits are likely polygenetic (Goldman et al., 1995).

The presence of a heritable factor for impulsivity raises the possibility that biologic correlates might be identified. Concerning central neurotransmission, there is extensive literature supporting a link between serotonergic functioning and impulsive, aggressive and violent behavior (Berman and Coccaro, 1998; Lesch and Merschdorf, 2000), but also providing some evidence for the involvement of dopaminergic transmission. In animal models, for example, pharmacological manipulation of the dopaminergic system (Pucilowski et al., 1986) and knockout of the catechol-O-methyltransferase, which is involved in the metabolic degradation of dopamine, result in aggressive behavior (Gogos et al., 1998). An association of aggressive and violent behavior with polymorphisms of the catechol-O-methyltransferase gene has also been reported for humans suffering from schizophrenic psychoses (Strous et al., 1997; Lachman et al., 1998; Kotler et al., 1999). However, this has not yet been investigated in non-psychotic subjects.

Results of CSF studies of dopamine in humans generally parallel those of serotonin, i.e. an inverse correlation of dopamine activity with aggressive behavior (Limson et al., 1991; Linnoila et al., 1983; Virkkunen et al., 1989). Serotonergic neurotransmission probably controls dopamine turnover in humans, which may account for these parallels (Ågren et al., 1986). In addition, Harrison and coworkers (1997) demonstrated that increased impulsivity after central serotonin depletion may be mediated by altered serotonin-dopamine interactions, with the serotonergic deficit lacking an inhibitory influence over dopamine neurotransmission.

A crucial role of mesolimbic dopamine for response thresholds and thus the balance between impulsivity and inhibition has been emphasized by King (1986). This hypothesis has been supported by the finding of an increase of dopamine-mediated spontaneous eye-blinks in high-impulsive compared to low-impulsive individuals (Barratt, 1971).

Cloninger (1993) has theorized that impulsivity primarily involves serotonergically mediated behavioral disinhibition and dopaminergically mediated "novelty seeking". It has been shown that growth hormone release induced by the dopamine agonist apomorphine is correlated with the "novelty seeking" score in alcoholic patients (Wiesbeck et al., 1995). Moreover, high "novelty seeking" scores were found to be associated with polymorphisms of the dopamine D4 receptor gene (Benjamin et al., 1996; Ebstein et al., 1996; Okuyama et al., 2000) the dopamine D3 receptor gene (Staner et al., 1998; Thome et al., 1999) and the catechol-O-methyltransferase gene (Benjamin et al., 2000).

The dopamine D3 receptor (DRD3) together with the D4 receptor (DRD4) have been classified as D2-like receptors based on their sequence homologies and similar pharmacological and biochemical properties (Sokoloff et al., 1990). They share a typical structure of G-protein coupled receptors that inhibit adenylyl cyclase to a different extent (Cox et al., 1995). The neuroanatomical distribution of the DRD3 markedly differs from DRD2 and DRD4.

Lannfelt and colleagues (1992) reported a point mutation in the D3 receptor gene (A>G), which consists of the substitution of a glycine (allele A2) for serine (allele A1) residue in the extracellular receptor N-terminal domain and results in the creation of a *Bal*I restriction endonuclease site. It has been speculated that theiresulting amino-acid substitution may modify the incorporation of the receptor into the membrane (Mant et al., 1994). The different receptors of each allele have been found to exhibit a differential affinity for dopamine in vitro (Lundstrom and Turpin, 1996).

Associations of the DRD3 polymorphism are under discussion in several psychiatric disorders, including schizophrenic psychoses (Crocq et al., 1992), affective disorders (Dikeos et al., 1999), drug abuse (Comings et al., 1999), alcoholism (Thome et al., 1999) and attention deficit/hyperactivity disorder (ADHD) (Muglia et al., 2002), which are all characterized by impulsive, and sometimes antisocial and violent behavior. Obviously, the DRD3 gene has pleiotropic effects affecting a wide range of normal and abnormal behavior with relative independence from clinical classifications of psychiatric disorders. Indeed, an association between "novelty seeking" and the dopamine D3 receptor gene has been reported in bipolar patients as well in patients suffering from alcoholism (Staner et al., 1998; Thome et al., 1999). In this study, we investigated a possible association between DRD3 genotype and the results of psychometric tests focusing on impulsiveness, violent behavior and childhood ADHD-related symptomatology in a forensic psychiatric population in order to further elucidate the role of DRD3 in the modulation of psychopathological traits.

Material and methods

Subjects

146 adult male (mean are 34.3 y; SD 10.6 y; range 18–78 y) volunteers, which were sent for an expert examination of the Forensic-Psychiatric Institute of the University of the Saarland, entered the study after giving informed consent. The probands were assigned to a violent (n = 72) and a non-violent group (n = 74). Violence was defined as overt and intentional physically aggressive behavior against another person according to Volavka (1999) and an expert consent (Filley et al., 2001). Mean age was 34.7 years (SD 10.5 years) in the violent and 33.9 years (SD 10.7 years) in the nonviolent group. All participants underwent diagnostic neurological and psychiatric evaluations and a standardised psychometrical test battery. For this investigation we used the following psychometrical instruments: (1) The Eysenck Impulsiveness Questionnaire (EIQ) (Eysenck et al., 1990). This is a 54 item questionnaire for the assessment of impulsiveness, venturesomeness and empathy. The score for impulsiveness ranges from 0 to 17. (2) The German short form of the Wender Utah Rating Scale (WURS-k) was used for the assessment of history of ADHD-related psychopathology (Retz-Junginger et al., 2002). The WURS-k is a retrospective dimensional measure of ADHD symptomatology, which is characterized by attention problems, motor hyperactivity and high impulsivity. The instrument is based on the widely used Utah criteria for the diagnosis of ADHD and the original version of the Wender Utah Rating Scale (Ward et al., 1993; Wender et al., 1995). Psychiatric diagnoses were determined according to ICD10 criteria. Diagnoses in the violent and non-violent group are given in Fig. 1.

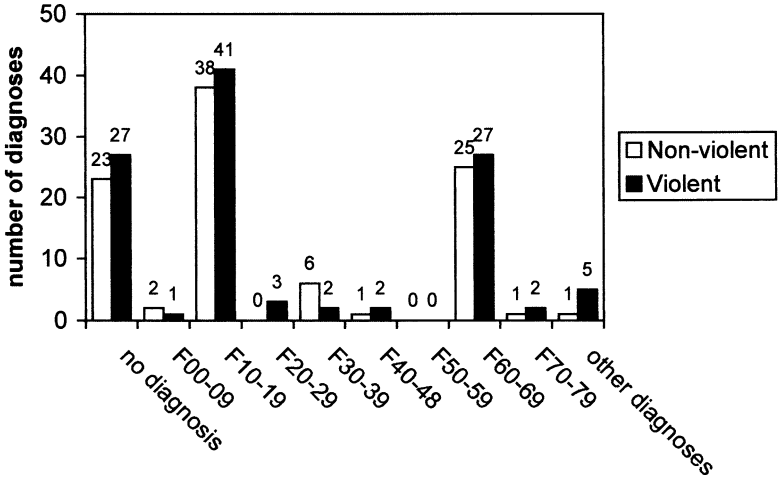


Fig. 1. Number of diagnoses according to the diagnostic categories of the ICD10 of the patients (n = 146). 27 patients of the violent and 21 patients of the non-violent group had more than one diagnosis. *F00–09* Organic, including symptomatic, mental disorders. *F10–19* Mental and behavioral disorders due to psychoactive substance use. *F20–29* Schizophrenia, schizotypal and delusional disorders. *F30–39* Mood (affective) disorders. *F40–48* Neurotic, stress-related and somatoform disorders. *F50–59* Behavioral syndromes associated with physiological disturbances and physical factors. *F60–69* Disorders of adult personality and behavior. *F70–79* Mental retardation

Genotyping

Genomic DNA was extracted from whole blood samples of each individual. Polymerase chain reaction (PCR) amplification of DNA was conducted with primers flanking a 462 bp segment of the first exon containing the *Bal*I/*Mlu*NI polymorphism (forward primer: 5′-GCT CTA TCTCCA ACT CTC ACA-3′, reverse primer: 5′-AAG TCT ACT CAC CTC CAG GTA-3′). DNA was amplified in 25 µl total volume containing 2.5 µl 10 × PCR buffer (100 mM Tris-HCL), 15 mM MgCl2, 500 mM KCl, (pH 8.3), 0.5 µl dNTP (10 mM), 10 µml of each primer (20 pmol/µl) and 1 U Taq DNA polymerase. The PCR conditions consisted of an initial denaturation step for 6 min at 95°C, 30 cycles of one min denaturation at 94°C, 0.5 min annealing at 55°C, and 0.75 min extension at 72°C and a single final extension step of 10 min at 72°C. PCR products were digested overnight with the restriction endonuclease *Mlu*NI (*Bal*I isoschizomer). All chemicals and enzymes were purchased from Roche (Mannheim, Germany). Fragments were separated by electrophoresis on an ethidium bromide stained agarose gel (2%), and analyzed under uv-light. The single genotypes showed characteristic bands at the following molecular weights: A1/A1 304, 111 and 47 bp; A1/A2 304, 206, 111, 98 and 47 bp; A2/A2 206, 111, 98 and 47 bp.

Statistical evaluation

All statistical tests were performed with SPSS for Windows™. The significance of differences in genotype distribution between groups was tested by the Pearson χ^2 statistic. Nonparametric correlations between psychopathological measures (WURS-k and EIQ) and DRD3 genotypes were calculated using Kruskal-Wallis and Mann-Whitney tests. Differences regarding frequencies of diagnoses and age between non-violent and violent patients have been calculated by Mann-Whitney and t-tests. η^2 was calculated using one-way analysis of variance (ANOVA) to estimate the magnitude of variance explained by the DRD3 genotype.

Table 1. DRD3 genotype and allele frequencies of the entire study population, non-violent and violent individuals. χ^2 test did not reveal significant differences between non-violent and violent patients

Genotype	Non-violent (N = 74)	Violent (N = 72)	Total (N = 146)
A1/A1	30 (40.5%)	35 (48.6%)	65 (44.5%)
A1/A2	40 (54.1%)	29 (40.3%)	69 (47.3%)
A2/A2	4 (5.4%)	8 (11.1%)	12 (8.2%)
f(A1)	0.676	0.688	0.682
f(A2)	0.324	0.312	0.318

Results

The genotype and allele frequencies of the entire study population and the subgroups of non-violent and violent individuals are given in Table 1. The two groups did not differ significantly regarding DRD3 genotypes, allele frequencies, age and psychiatric diagnoses. There was a high prevalence of personality disorders and addiction in both violent and non-violent individuals (Fig. 1). No differences between the two groups were detected regarding mean scores of EIQ "impulsiveness" (non-violent: 8.3 (±4.6); violent: 8.3 (±4.2)), "venturesomeness' (non-violent: 8.3 (±4.0); violent: 8.3 (±3.8)), "empathy" (non-violent: 10.4 (±2.40); violent: 9.8 (±2.9)) and WURS-k ratings (non-violent: 26.7 (±14.2); violent: 27.1 (±14.8)). In the violent group nonparametric statistics revealed significant differences in EIQ mean scores of the three different genotypes ($\chi^2 = 8.09$; $p = 0.01$). This differences were not detected in the non-violent group (Fig. 2a). There was a somewhat lower EIQ mean score in the A2/A2 genotype compared A1/A1 but this difference was not statistically significant. Highest impulsivity measures were found in the violent heterozygous group (A1/A2). When the heterozygotes were compared to each homozygous group, the differences were statistically significant (A1/A1 vs A1/A2: $p = 0.01$; A1/A2 vs A2/A2: $p = 0.04$). The association of high impulsiveness with the A1/A2 genotype was even more accentuated after pooling of all homozygous individuals (A1/A2 vs. A1/A1 + A2/A2: $p = 0.005$; Fig. 2b). In the group of non-violent individuals no differences between genotypes regarding mean EIQ scores were detected.

When we evaluated mean scores on the WURS-k (Fig. 3a), nonparametric statistics showed a trend towards significance ($\chi^2 = 4.71$; $p = 0.09$) regarding differences between genotypes in the group of violent patients. Violent heterozygous individuals showed significant higher WURS-k rating scores compared to A1/A1 homozygotes ($p = 0.03$) and all homozygous patients (A1/A1 + A2/A2; $p = 0.03$; Fig. 3b), but not compared to carriers of genotype A2/A2. No differences of mean WURS-k scores between the three genotype groups have been detected in the subgroup of non-violent individuals.

Furthermore, in both non-violent and violent patients no significant associations were found between DRD3 genotypes and ICD10 diagnoses of antisocial personality disorder and addiction, respectively. There were also no

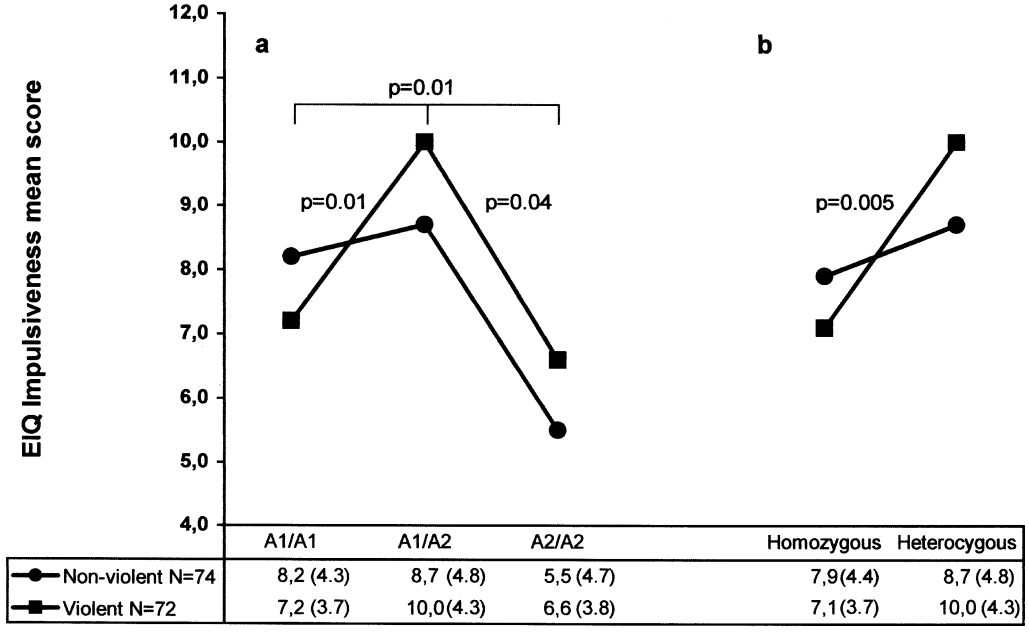


Fig. 2. Mean EIQ impulsiveness scores (±SD) in homozygous (A1/A1 and A2/A2) and heterozygous (A1/A2) individuals. Rating scores are given for violent and non-violent individuals. Significant different mean scores between genotype groups were found within the violent group ($\chi^2 = 8.09$; $p = 0.01$). Genotype A1/A2 showed significantly higher mean EIQ scores compared to genotype A1/A1 ($p = 0.01$) and A2/A2 ($p = 0.04$) (**a**) and compared to all homocygotes combined ($p = 0.005$) (**b**)

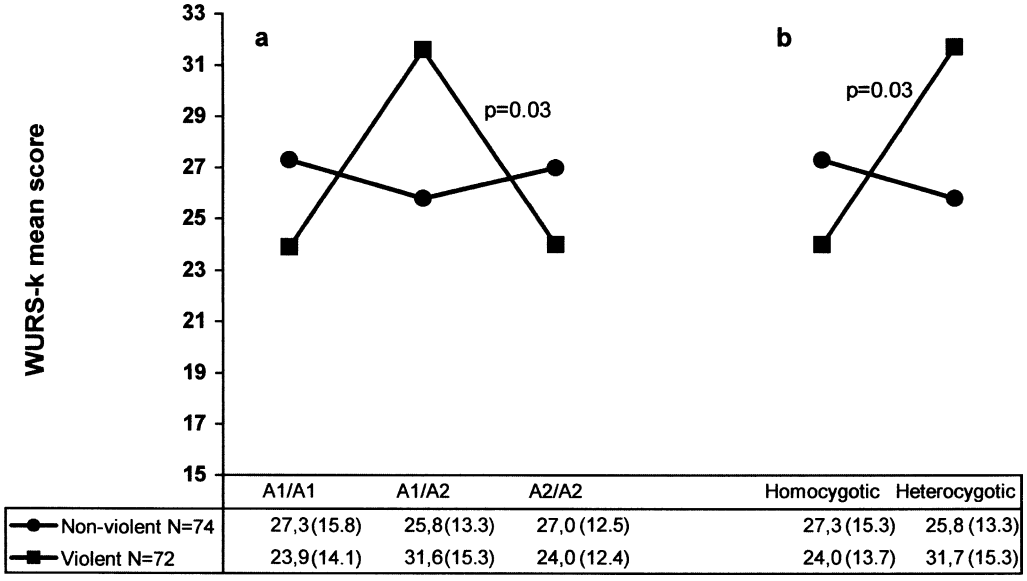
significant associations regarding the EIQ subscales "venturesomeness" and "empathy" in either patient group.

Using one-way ANOVA, the DRD3 polymorphism explained 5.2% ($\eta^2 = 0.052$) of the variance of the patients' EIQ "impulsiveness".

Discussion

In this study we showed an association of DRD3 polymorphism with psychometric measures of impulsivity. The association was detected in violent, but not in non-violent individuals. However, there was no association between DRD3 genotypes and violence per se. Therefore, the results may indicate an association with a specific varieties of impulsiveness and ADHD-related symptomatology comprising aggressive and physical violent behavior.

The results of this study support the hypothesis of an involvement of genetically determined dopaminergic mechanisms in impulsivity and violent behavior. Serotonin has been frequently associated with impulsive, violent and dangerous behavior (Lesch and Merschdorf, 2000). However, a certain role of additional neurotransmitters in the mediation of such complex traits can be assumed. Our results accord with previous reports that described an association between the DRD3 polymorphism with the personality trait of "novelty seeking" according to Cloninger's psychobiological model of person-



	A1/A1	A1/A2	A2/A2	Homocygotic	Heterocygotic
Non-violent N=74	27,3(15.8)	25,8(13.3)	27,0(12.5)	27,3(15.3)	25,8(13.3)
Violent N=72	23,9(14.1)	31,6(15.3)	24,0(12.4)	24,0(13.7)	31,7(15.3)

Fig. 3. Mean WURS-k scores (±SD) in homozygous (A1/A1 and A2/A2) and heterozygous (A1/A2) individuals. Rating scores are given for violent and non-violent individuals. In the violent group a trend towards significance regarding WURS-k mean score differences was detected ($\chi^2 = 4.71$; $p = 0.09$), significant different mean scores were found between A1/A1 and A1/A2 genotype ($p = 0.03$) (**a**) and between heterozygous and homozygous individuals ($p = 0.03$) (**b**)

ality (Cloninger et al., 1993), which shows some overlap with Eysenck's EIQ "impulsiveness" (Eysenck et al., 1990; Zelenski and Larsen, 1999). In bipolar patients, low "novelty seeking" scores were found in carriers of the allele A1 (Staner et al., 1998) and in a population of alcoholic patients those with the genotype A1/A2 showed significant higher "novelty seeking" scores than patients homozygous for the allele A1 (Thome et al., 1999). However, to our knowledge, this is the first study which demonstrates an association of impulsiveness measures and violent behavior with a DRD3 gene polymorphism and, therefore, underscores the importance of non-serotonergic mechanisms in such personality traits.

Regarding the association between the DRD3 polymorphism and rating scores of ADHD symptoms on the WURS-k, the results parallel those of impulsiveness measures. This finding was not unexpected, since high impulsivity is one of the key symptoms of ADHD. Highest WURS-k ratings were found in the heterozygous group of violent offenders. In contrast, non-violent homozygotes showed low ratings on the WURS-k, suggesting minor problems regarding impulsivity, inattentiveness, and other conduct problems in childhood. However, this association reached only significance when heterozygotes were compared to all homocygotes and carriers of the A1/A1 genotype. It has to be considered that the WURS-k was not constructed to distinguish between psychiatric disorders which may present with prominent attentional problems, hyperactivity and high impulsivity, but to assess the severity of these behavioral abnormalities in childhood. Therefore, the results might be not specific

for ADHD, but they indicate that impulsivity and violence in ADHD is likely influenced by DRD3 mediated dopaminergic mechanisms. Recent publications reporting a lack of association of the DRD3 polymorphism with a diagnosis of ADHD in children (Barr et al., 2000; Payton et al., 2001; Muglia et al., 2002) together with our results may also suggest that DRD3 polymorphism is associated only with a subgroup of ADHD patients exhibiting high impulsivity and violent behavior. However, further studies are needed to confirm or refute these hypotheses.

Heterozygous patients exhibited significantly higher scores on the impulsiveness subscale of the EIQ when compared to either the A1/A1 genotype or the A2/A2 genotype. Conversely, low scores of impulsiveness were associated with homozygosity of either allele. The same correlation was found regarding ratings of ADHD-related symptomatology. While this appears counterintuitive to the expectation of gene-dosage effects, molecular heterosis may offer an explanation. Molecular heterosis occurs when subjects heterozygous for a specific genetic polymorphism show greater or lesser effect for a quantitative or dichotomous trait than subjects homozygous for either allele. This effect has been described for several non-psychiatric disorders (Beckman and Fröhlander, 1990). Comings and MacMurray (2000) have reviewed molecular heterosis at different neurotransmitter genes and concluded that up to 50% of all gene associations show a heterosis effect. The differential effect of heteozygosity and homozygosity of either allele of the DRD3 polymorphism has been also reported in association studies of schizophrenia (Crocq et al., 1992; Spurlock et al., 1998), Tourette's syndrome and cocaine dependence (Comings et al., 1993, 1999). However, in light of functional studies (Lundstrom and Turpin, 1996), the association of DRD3 heterozygosity with impulsiveness and violence is difficult to explain: Those studies have revealed that receptor binding assays show a significantly higher dopamine binding affinity in A2/A2 homozygotes, if cDNAs for the homozygotes A1/A1 and A2/A2 and the heteroxygote A1/A2 were introduced and expressed in Chinese hamster ovary cells. The heterozygote binding did not differ from the wildtype A1/A1. More functional studies are needed in order to fully understand the complexities of dopaminergic neurotransmission and to elucidate the possible relevance of DRD3 heterozygosity for personality traits and psychiatric disorders.

Since there was a high prevalence of personality disorders and addiction, the question arises whether these disorders are directly associated with the DRD3 polymorphism. In this study we did not detect a direct correlation between DRD3 genotypes and alcoholism, drug addiction, and antisocial personality disorder according to ICD10 criteria. In accordance with the majority of association studies focusing on the DRD3 gene, our results do not support the notion of an association of this polymorphism with psychiatric disorders, but suggest an association with certain personality traits and behavioral abnormalities in the sense of shared psychopathological "endophenotypes".

In our study the A1 and A2 allele frequencies within the entire study population was similar to those described by Spurlock et al. (1998) in 306

control subjects in a multicenter association study of schizophrenia (A1: 0.68 vs. 0.62). However, there was a somewhat lower prevalence of heterozygous individuals in our forensic male study population (47.3% vs. 54.2%). Therefore, a cautious interpretation of our study results is needed, since stratification effects cannot be ruled out.

Another limitation of our study are the unavoidable problems concerning construct validity of impulsiveness and violence, since such conduct is heterogeneous and differs in origins and mechanisms. We relied on the construct of impulsiveness according to the EIQ (Eysenck et al., 1990) and a definition of violence as overt and intentional physically aggressive behavior against another person according to the concept used by Volavka (1999) and accepted by expert consent (Filley et al., 2001). It should be emphasised, that the DRD3 polymorphism accounted for only 5.2% of the variation in impulsiveness within the investigated population. Thus, only a small but statistically significant contribution of this gene to every individual's impulsivity must be assumed. This underlines the probably important contributions of other genes and environmental factors to this complex trait. Nevertheless, our work gives a rationale for further investigations regarding the genetic background of impulsivity and violent behavior, and also for psychopharmacological studies focusing on possible therapeutic effects of drugs interacting with the dopaminergic neurotransmitter system. Presently, we are planning further studies in order to confirm this association and to clarify whether DRD3 mutation potentially is in a linkage disequilibrium with another gene variant of functional significance.

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