Violence in male patients with schizophrenia: risk markers in a South African population

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Objective: We investigate the role of functional variants in the catecholamine-O-methyl transferase gene (*COMT*) and the monoamine oxidase-A gene (*MOA-A*), as well as previously identified non-genetic risk factors in the manifestation of violent behaviour in South African male schizophrenia patients.
Method: A cohort of 70 acutely relapsed male schizophrenia patients was stratified into violent and non-violent subsets, based on the presence or absence of previous or current violent behaviour. Standardized violence rating scales were also applied and the *COMT/Nla*III and *MAO-A* promoter region variable number of tandem repeats (VNTR) polymorphisms were genotyped.
Results: A multiple logistic regression model based on the clinical, genetic and socio-demographic variables indicated that delusions of control (OR = 3.7, 95% CI = 1.21–11.61) and the combined use of cannabis and alcohol (OR = 6.89, 95% CI = 1.28–37.05) were two significant predictors of violent behaviour in this schizophrenia population. No association was found between the tested polymorphisms and violent behaviour.
Conclusions: Although the sample size may have limited power to exclude a minor role for these specific gene variants, such a small contribution would have limited clinical relevance given the strong significance of the non-genetic markers. These findings suggest that currently proactive management of violent behaviour in this schizophrenia population should continue to be based on clinical predictors of violence.
Key words: clinical, genetics, schizophrenia, violence.

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Many factors have been related to manifestations of violence among psychiatric inpatients. These include a history of previous violence [1,2], the level of violence at admission and a family history of violence [2]. Furthermore, studies have found associations with the presence of psychotic symptoms [3], demographic variables such as younger age of patients, or hospitalization variables, such as involuntary admission and the use of temporary nursing staff [4]. Additionally, schizophrenia specifically seems to be represented in involvement with violent incidents during hospitalization, as it is the diagnosis in 30–45% of all such cases [5,6].

A number of studies have focused specifically on violent behaviour in schizophrenia and have shown that previous violent behaviour was a strong predictor of current violence in the schizophrenia patient group [7]. In addition, a link between violence in schizophrenia and higher comorbidity for psychopathy [8], medication

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refusal [9], comorbid alcoholism [10] and number of previous hospitalizations [7,11], as well as male sex and alcohol abuse [11] has been suggested. Of further note is the research indicating that the prevalence of schizophrenia among prisoners convicted of violent crimes is substantially higher that would be expected in the general population [12].

The contribution of genetic versus environmental factors to the manifestation of aggressive behaviour associated with schizophrenia has been investigated in several twin and adoptive studies, with data suggesting that a moderate to substantial influence can be attributed to genetic factors, while environmental cues play a less significant role [13,14].

Several studies have implicated dysfunction in biogenic amine metabolism in violent behaviour and psychiatric disorders [15,16]. Consequently, as catechol-O-methyltransferase (COMT) is known to be pivotal to biogenic amine metabolism (serotonin and dopamine) [17], this enzyme has been regarded as a possible factor in regulating violent behaviour. Previous studies supported an association between homozygosity for the low activity allele (*L*) of a functional *Nla*III polymorphism in the COMT-encoding gene (*COMT*) and violent behaviour in schizophrenia [18–20]. However Jones *et al*. [21] demonstrated an association between homozygosity for the high activity allele (*H*) and the reported rate of aggression in schizophrenia suffers. This apparent contradiction could possibly be attributed to Jones' much larger sample size or the use of more extreme incidences of violence in the first studies.

Another enzyme involved in the dopaminergic pathways of neurotransmission is the flavin-containing monoamine oxidase A (MAO-A), which is responsible for the degradative deamination of a variety of biogenic amines, including the neurotransmitters dopamine and serotonin. Several lines of evidence suggest that MAO-A plays an important role in behaviour. A positive link between inactivation of the MAO-A-encoding gene (*MAO-A*), that is located on the X chromosome and violent behaviour in men has been reported by Brunner *et al*. [22] and Brunner [23]. Also, transgenic mice with a deletion of the *MAO-A* gene exhibit a wide variety of behavioural changes that include trembling, difficulty righting as pups and increased aggression in male adults [24].

Sabol *et al.* [25] recently described a variable number of tandem repeats (VNTR) polymorphism in the promoter region of *MAO-A* (*MAO-A* u-VNTR), providing a genetic marker that can be used to assess the involvement of this gene in violent behaviour. Preliminary studies, using *in vitro* systems, indicated that this polymorphism demonstrated an allele-specific variation in promoter activity. However, no differences were found in transcriptional levels between specific alleles in the human brain [26]. Caspi *et al*. [27] who studied the same functional polymorphism (*MAO-A* u-VNTR) in a large male cohort (followed from birth to adulthood), concluded that this polymorphism moderated the effect of childhood maltreatment, in that those with higher levels of gene expression where less likely to develop antisocial problems.

In this study we assessed the possible association of selected clinical and genetic factors (*COMT, MAO-A*), with violent behaviour in a cohort of hospitalized South African schizophrenia patients. In order to limit confounding gender factors, only male subjects were included in the study.

Methods

Subjects

Patients were recruited from a male acute admissions ward at Stikland State Psychiatric Hospital in Cape Town, South Africa. Seventy consecutively admitted patients who had at least one prior admission with a DSM-IV diagnosis of schizophrenia were recruited. The ethnic composition of this sample included seven Caucasian, seven Xhosa [28] and 56 Coloured [29] individuals. The Coloured group was analyzed as to paternal and maternal grandparents' ethnic origin. Forty-seven of this group had four of the grandparents of Coloured origin, while the remaining nine patients had one grandparent of a different ethnic origin (six African and three Caucasian).

The study was approved by the ethics committee of the University of Stellenbosch and informed consent was obtained from patients or their guardians.

Evaluation

All patients were assessed on admission, before any medication was administered. For the purpose of the study, the definition of violent behaviour included at least one of the following preceding or present during this admission: physical violence against self, others or objects, or violent verbal threats as reported by family, or by staff or observed during interviews. Patients were divided into violent and non-violent groups based on these parameters.

The Corrigan Agitated Behaviour Scale – aggression component [30] and PANSS – excited factor items [31,32] were completed for each patient on admission, but was not used to stratify patients into violent and non-violent groups. The decision to use clinical assessment and history (patient, collateral, case notes) rather than assessment tools for primary group stratification was based on the fact that the tools used in previous studies have varied greatly and therefore, in order to make later comparisons easier, we opted for a method similar to that previously employed in the field of genetics [19,20].

A urinary drug screen was performed on each patient on the day following admission. On the fourth day of hospitalization, trained nursing staff completed the Overt Aggression Scale [33] recording inpatient behaviour for the preceding 4 days. A subsequent structured

clinical interview (Diagnostic Interview for Genetic Studies [DIGS]) [34] took place on day 8 after admission.

Genotyping

A blood sample was obtained from each subject by venous puncture for subsequent DNA extraction following standard protocols [35]. Polymerase chain reaction (PCR) amplification of the region spanning the *COMT/Nla*III polymorphism and subsequent restriction enzyme analysis was performed as previously described [36]. *H and L* alleles were size-separated by electrophoresis in 12% non-denaturing polyacrylamide gels and visualized by silver staining. The regulatory region of *MAO-A* containing the *MAO-A* u-VNTR polymorphism was PCR-amplified using published primer sequences and size-separated by electrophoresis in 12% non-denaturing polyacrylamide gels and then visualized by silver staining [26].

Statistical analysis

Genotype distribution of *COMT* and *MAO-A* alleles in the violent and non-violent patient subsets was analyzed for Hardy–Weinberg equilibrium. The association between *COMT* and *MAO-A* genotype distribution and allele frequency in the two groups was ascertained by means of χ^2 analysis using the SPSS software package. In addition, the association between demographic/clinical parameters in the two groups was ascertained by means of χ^2 or *t*-test analysis and finally a multiple logistic regression model based on the clinical, genetic and socio-demographic variables was constructed.

Results

Forty schizophrenia subjects (33 Coloured, 4 Caucasian, 3 African) were allocated to the violent group and 30 (23 Coloured, 3 Caucasian, 4 African) to the non-violent group. The two groups did not differ significantly regarding socio-demographic variables (Table 1). Significantly more patients from the violent subgroup (53%, $n = 21$), *vs.* the non-violent group (23%, $n = 7$, $p = 0.012$), reported alcohol abuse in the week prior to admission, but no withdrawal symptoms were noted during admission. No significant differences were observed between the groups regarding cannabis use (33% violent group *vs.* 27% non-violent group, $p = 0.597$) (Table 1). Three patients in the violent group and two in the non-violent group tested positive for other drugs of abuse (two methaqualone, one opiate and two methaqualone in each group, respectively).

The incidence of paranoid and grandiose delusions, as documented in the DIGS, did not differ significantly between the two patient groups, but delusions of control were significantly more common in the violent group ($p = 0.028$). No significant difference was found between the two groups for the presence of perceptual disturbances. (Table 1).

Seven incidents of inpatient violence were reported on the Overt Aggression Scale, all by patients already stratified to the violent group. No significant difference was found between the history of non-compliance with medication ($p = 0.480$) or the average number of admissions to a psychiatric hospital ($p = 0.822$) between the two patient groups. Seventy-nine percent of the study population presented with a history of non-compliance (80% violent group *vs.* 77% non-violent group). The average number of admissions to a psychiatric hospital was 5.33 ± 3.88 for the violent group and 5.5 ± 1.96 for the non-violent group.

The five PANSS – excited component items (poor impulse control, tension, hostility, uncooperativeness and excitement) and the total of the Corrigan Agitated Behaviour Scale – aggression component scores were significantly higher in the violent group ($p < 0.001$).

Both patient subsets were in Hardy–Weinberg equilibrium for the *COMT* and *MAO-A* polymorphisms. There was no statistically significant difference between the observed genotype distribution (*COMT/Nla*III, $p = 0.74$; *MAO-A* u-VNTR, $p = 0.72$) of the tested polymorphisms in the two groups (Tables 1,2). Stratification based on the presence or absence of high/low activity alleles (COMT *H* or *L*, MAO-A 1 + 4 or 2 + 3) also showed no significant difference in the two groups ($p = 1$). The majority of the patients were of Coloured origin and ethnic stratification did not change the lack of significant association (Table 2).

The multiple logistic regression model based on the clinical, genetic and sociodemographic variables indicated that delusions of control (OR = 3.7, 95% CI = 1.21–11.61) and the combined use of cannabis and alcohol (OR = 6.89, 95% CI = 1.28–37.05) were two significant predictors of violent behaviour in this schizophrenic population.

Table 1. Clinical and sociodemographic variables in the violent and non-violent subgroups

	Violent group		Non-violent group		Significance
	%	n	%	n	χ^2, p
Employment status at first diagnosis (unskilled)	60	24	77	23	2.21, 0.14
Employment status at present (unemployed)	75	30	77	23	0.03, 0.87
Marital status (married)	35	14	27	8	0.56, 0.46
Alcohol abuse	53	21	23	7	6.27, 0.012
Cannabis use	33	13	27	8	0.28, 0.597
Paranoid delusions	63	25	63	19	0.01, 0.94
Grandiose delusions	43	17	43	13	0.005, 0.944
Delusions of control	73	29	47	14	4.84, 0.028
Auditory hallucinations	73	29	70	21	0.05, 0.82
Visual hallucinations	8	3	20	6	2.38, 0.12
Total n		**40**		**30**	

Table 2. Genotype distribution

	Violent group		Non-violent group	
	All subjects*	**Coloured subjects****	**All subjects***	**Coloured subjects****
COMT/*Nla*III polymorphism				
COMT genotype				
H/H	17 (0.48)*	14 (0.46)**	12 (0.43)*	10 (0.48)**
H/L	9 (0.26)*	8 (0.27)**	10 (0.36)*	8 (0.38)**
L/L	9 (0.26)*	8 (0.27)**	6 (0.21)*	3 (0.14)**
MAO-A u-VNTR polymorphism				
Number of repeats				
1	2 (0.06)***	1 (0.03)****	1 (0.04)***	1 (0.05)****
2	14 (0.40)***	12 (0.40)****	8 (0.28)***	7 (0.33)****
3	11 (0.31)***	10 (0.33)****	12 (0.43)***	8 (0.38)****
4	8 (0.23)***	7 (0.24)****	7 (0.25)***	5 (0.24)****

*$\chi^2 = 0.6894$, df = 2, p = 0.74; **$\chi^2 = 1.43$, df = 2, p = 0.489; ***$\chi^2 = 1.33$, df = 2, p = 0.7225; ****$\chi^2 = 0.29$, df = 2, p = 0.9615; genotype frequencies shown in brackets.

Discussion

The data generated did not support previous reports of an association of the *COMT/Nla*III polymorphism with the incidence of violent behaviour in schizophrenia. This discrepancy may be caused by a number of factors. It may reflect differences in the population groups studied, the earlier investigations having been undertaken in North American subjects of Caucasian origin [19,20]. In the South African patients studied, *MAO-A* was also not implicated in playing a major role in the manifestation of violence in schizophrenia. Although the strategy of including only male patients in the analysis had the advantage of controlling for confounding gender factors, it inevitably limited the sample size. This may have reduced the statistical power to detect a minor contribution from *COMT* and/or *MAO-A* in the incidence of violent behaviour in these schizophrenics. Thus, a type II error, that would negate a minor role for either of the tested genes, cannot be dismissed.

Schizophrenia patients in the violent group were significantly more likely to abuse alcohol, and combining this with cannabis use significantly increased the odds ratio (OR = 6.89) for violent behaviour. This finding concurs with previous community studies that showed an association between increased alcohol consumption [37] or cannabis use [38], and increased incidence of violence and would therefore predict a higher risk of violence in schizophrenia patients.

Certainly, previous studies have identified alcohol abuse to be a major contributing factor in violent behaviour in the Western Cape [39,40], although the nature of the association between alcohol abuse and violent behaviour is complex, and not specific to patients with schizophrenia [41]. While alcohol abuse may contribute directly to violent behaviour in patients with schizophrenia, in our study this was unlikely to be an intoxication effect, as the violent incidents usually occurred some days after admission to the ward. Furthermore, the violence does not appear to be associated with withdrawal phenomena, as no other withdrawal symptoms were observed in the subjects. It is also possible that the alcohol abuse and violent behaviour are both manifestations of disturbed impulse control, which is further exacerbated by the use of cannabis and the presence of psychotic symptoms.

The presence of delusions and hallucinations has previously been linked to violence [3] and our study found delusions of control (OR = 3.7) to be a significant predictor of violence in this sample. This suggests that a more detailed analysis between the content of psychotic symptoms and its association with violent behaviour could prove useful in identifying patients at risk for such behaviour. Both groups had more auditory than visual hallucinations, with no significant differences between the groups (Table 1).

In this study, a significant difference was found between the two patient groups in terms of the mean scores on the five PANSS – excited component items (poor impulse control, tension, hostility, uncooperativeness and excitement) and the total of the Corrigan Agitated Behaviour Scale – aggression component ($p < 0.001$ for both). Therefore, while the assessment tools were not used to stratify the groups, they supported our sample stratification as based on a history of violence preceding or at admission. Although our clinical assessment specifically included questions with regard to both lifetime physical and verbal violence against self, others

and objects, the use of a tool such as the Life History of Aggression Assessment [42] should be considered for future studies to further increase the validity of stratification.

The sociodemographic variables assessed showed no significant difference between the two patient groups, which is similar to the findings of Rossi *et al*. [43] and Miller *et al*. [44].

Undeniably, defining violence in any setting, and specifically with the aim of using it to predict incidents of further violence in different patient groups, remains a dilemma and many criteria have been proposed to address this problem [45]. It is therefore clear that this is an ongoing issue and needs to be acknowledged as a possible confounding factor with regards to the division of the two groups and specifically determining the violent phenotype. Of note though, is the fact that the stratification of the groups correlated significantly with known non-genetic markers of violence.

Conclusion

The findings of the study encourage attention being given to a history of alcohol and cannabis abuse, the presence of delusions of control and previous violent behaviour, in order to proactively manage inpatients at greater risk for violent behaviour. Although the study was unable to exclude a minor role for *COMT* and *MAO-A* in the occurrence of violence in schizophrenia, it can be concluded that any such contribution would, currently, have limited clinical implications, given the strong correlation of the clinical parameters of alcohol/cannabis abuse and delusions of control. However, further studies of other plausible candidate genes may identify risk markers that may consistently predict violent behaviour in schizophrenia and other psychoses.

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