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Effects of *MAOA*-Genotype, Alcohol Consumption, and Aging on Violent Behavior

Roope Tikkanen, Rickard L. Sjöberg, Francesca Ducci, David Goldman, Matti Holi, Jari Tiihonen, and Matti Virkkunen

Institute of Clinical Medicine, Department of Psychiatry (RT, MH, MV), University of Helsinki, Helsinki, Finland; NIH / NIAAA, Laboratory of Neurogenetics (RLS, DG), Rockville, Maryland; Center for Clinical Research, Uppsala University (RLS), Västerås, Sweden; Department of Neurosurgery (RLS), University Hospital, Umeå, Sweden; King's College (FD), London, UK; and Department of Forensic Psychiatry and Clinical Physiology (JT), University of Kuopio, Niuvanniemi Hospital, Kuopio, Finland

Abstract

Background—Environmental factors appear to interact with a functional polymorphism (*MAOA-LPR*) in the promoter region of the monoamine oxidase A gene (*MAOA*) in determining some forms of antisocial behavior. However, how *MAOA-LPR* modulates the effects of other factors such as alcohol consumption related to antisocial behavior is not completely understood.

Methods—This study examines the conjunct effect of *MAOA-LPR*, alcohol consumption, and aging on the risk for violent behavior. Recidivism in severe impulsive violent behavior was assessed after 7 to 15 years in a sample of 174 Finnish alcoholic offenders, the majority of whom exhibited antisocial or borderline personality disorder or both, and featured impulsive temperament traits.

Results—The risk for committing new acts of violence increased by 2.3% for each kilogram of increase in yearly mean alcohol consumption ($p = 0.004$) and decreased by 7.3% for every year among offenders carrying the high activity *MAOA* genotype. In contrast, alcohol consumption and aging failed to affect violent behavior in the low activity *MAOA* genotyped offenders. *MAOA-LPR* showed no main effect on the risk for recidivistic violence.

Conclusions—Violent offenders carrying the high activity *MAOA* genotype differ in several ways from carriers with the low activity *MAOA* risk allele previously associated with antisocial behavior. Finnish high activity *MAOA* genotyped risk alcoholics exhibiting antisocial behavior, high alcohol consumption, and abnormal alcohol-related impulsive and uncontrolled violence might represent an etiologically distinct alcohol dependence subtype.

Keywords

Psychiatric Genetics; Alcoholism; Antisocial Personality Disorder; Borderline Personality Disorder; Violent Behavior

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Reprint requests: Roope Tikkanen, MD, Department of Psychiatry, University of Helsinki, PO Box 590, 00029 HUS, Finland; Fax: +358-9-471-63759; roope.tikkanen@helsinki.fi.

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Despite the immense burden of alcoholism and violence on society, their etiology remains largely unknown (Ducci and Goldman, 2008; Goldman et al., 2005; Nelson and Trainor, 2007). Alcoholism and violence frequently coexist particularly in early onset alcoholism with antisocial personality disorder (ASPD), which appears to represent a homogeneous subtype of alcoholism (Linnoila et al., 1989; Tiihonen et al., 1993).

Temperament traits have also been associated with alcoholism (Hesselbrock and Hesselbrock, 1992). Both novelty seeking (Gruza et al., 2006; Kampov-Polevoy et al., 2004)—including a subscale of impulsiveness—and harm avoidance (Cloninger, 1987) are robustly associated with alcoholism (Belfer et al., 2006; Ducci et al., 2007; Enoch et al., 2006). Alcoholism is thought to lead to increased impulsiveness and risk for impulsive violence (Babor, 1996; Brewer and Swahn, 2005; Johansson et al., 1999; Zhang et al., 1997). Trait impulsiveness, alcoholism, and violence form a vicious circle that may lead to habitual violence.

Monoamine oxidase A (*MAOA*) is an outer membrane mitochondrial enzyme that catabolizes monoamines such as serotonin, noradrenalin, and dopamine (Shih et al., 1999). The *MAOA* gene is located on the X chromosome (Xp11.23-11.4) (Levy et al., 1989). A common polymorphism in the *MAOA* gene's transcriptional control region ["*MAOA*-linked polymorphism region" (*MAOA-LPR*)] affects transcriptional activity, resulting in high activity or low activity *MAOA* (Denney et al., 1999; Sabol et al., 1998). Alleles (2, 3, 3.5, 4, 5 or 6) vary in the number of copies of a 30-bp repeat sequence; the 4- (high activity) and 3-repeat (low activity) alleles are the most common. The impact of *MAOA* genotype on serotonin metabolism is unclear but according to one hypothesis, *MAOA* activity is presumed to correlate inversely with CNS monoamine metabolites. To date, however, inverse correlations has been observed only between lumbar cerebrospinal fluid homovanillic acid (CSF HVA) and high activity *MAOA* (Ducci et al., 2006) and between CSF 3-methoxy-4-hydroxyphenylglycol and the low activity variant (Sjoberg et al., 2008), both findings in Finnish male alcoholic offenders, but not between 5-hydroxyindoleacetic acid (5-HIAA) and *MAOA-LPR*. Recently, women carrying the low activity allele at the *MAOA-LPR* locus have been found to display lower 5-HT_{1A} receptor availability measured by positron emission tomography indicating higher serotonergic level as compared to women with the high activity genotype. However, a trend in the opposite direction was found among men (Mickey et al., 2008).

Brunner and colleagues (1993) reported a rare point mutation of the *MAOA* gene in a Dutch family that affected several males by a syndrome of borderline mental retardation, abnormal sexual behavior, and aggressive behavior that tended to cluster in periods of 1 to 3 days, during which the affected male would suffer from insomnia. Later research supports the hypothesis that low activity *MAOA* (a hyperserotonergic state comparable to Brunner's point mutation finding) is linked to aggression and violent behavior (Buckholtz and Meyer-Lindenberg, 2008; Caspi et al., 2002; Widom and Brzustowicz, 2006). Some other research, on the other hand, supports an association of the high activity *MAOA* genotype and impulsive aggression (Beitchman et al., 2004; Manor et al., 2002; Manuck et al., 2000). Altogether, both *MAOA* genotypes may contribute to aggression and violence (Nelson and Trainor, 2007).

The role of *MAOA* in determining vulnerability to alcoholism is also unclear due to contradictory results obtained in widely differing samples. An association of the low activity *MAOA* genotype with alcoholism has been reported by some studies (Guindalini et al., 2005; Parsian and Cloninger, 2001; Parsian et al., 2003; Samochowiec et al., 1999; Schmidt et al., 2000). Other studies failed to find a genotype main effect, but found that the low activity allele increased risk for alcoholism only among subjects exposed to environmental stressors (Ducci et al., 2008; Nilsson et al., 2007a; Vanyukov et al., 2007). On the other hand, other studies have reported an association of the high, rather than low, activity *MAOA* genotype with

alcoholism (Gade et al., 1998) and alcohol-related problem behavior after exposure to psychosocial stressors (Nilsson et al., 2007b).

The sample at hand comprises impulsive-aggressive alcoholics, the majority of whom committed impulsive homicides. Their psychiatric morbidity and their violent acts match those of the majority of Finnish violent offenders (Tiihonen and Hakola, 1994).

The primary aim of the current report was to evaluate the role of *MAOA-LPR*, alcohol consumption, and their conjunct effect on risk for committing new acts of violence among risk alcoholics. We hypothesized that heavy drinking associates with increased risk for recidivistic violent behavior especially among high activity *MAOA* genotyped violent offenders as the disinhibitory effect of alcohol might increase the risk of impulsive-aggressive behavior associated with low CSF 5-HIAA in similar samples (Linnoila et al., 1983; Virkkunen et al., 1989, 1994). Secondly, we examined the conjunct effect of *MAOA-LPR* and age on risk for recidivistic acts of violence. We failed, however, to find studies examining a possible connection between *MAOA-LPR*, age, and violence but it has been suggested that *MAOA* expression may decrease over time in mice (Vitalis et al., 2002). Assuming that high activity *MAOA* genotyped subjects have low central serotonin levels with corresponding low CSF 5-HIAA levels then a decrease in *MAOA* activity over time might elevate central serotonin levels and decrease impulsive-aggressive behavior among these subjects.

MATERIALS AND METHODS

Subjects

The sample under study included 174 Finnish violent alcoholic offenders recruited between 1990 and 1998. These subjects, due the violent nature of their crimes, were remanded to a mental status examination and spent 2 months in the inpatient care unit of the Department of Psychiatry, Helsinki University Central Hospital. This sample included many subjects who participated in several genetic studies on violent alcoholic offenders, mainly with ASPD (Belfer et al., 2006, 2007; Enoch et al., 2006; Xu et al., 2007). Psychosis and an IQ of less than 70 served as exclusion criteria. Mean age at the time of evaluation was 32.5 years ($SD \pm 9.7$), and mean IQ (WAIS) was 97.2 ($SD \pm 14.5$). The majority of the offenders belonged to lower socio-economic groups. Their occupational status included mainly semi-skilled workers, and many were unemployed at the time of recruitment in the study.

Psychiatric Assessment

Each subject was interviewed with the Structured Clinical Interview for DSM-III-R (Spitzer et al., 1990) to detect lifetime mental disorders (APA, 1987). Interviewers were experienced licensed psychiatrists, and diagnoses were double-checked by psychiatrists at the National Institute of Alcohol Abuse and Alcoholism in Bethesda, Maryland. Axis II diagnoses were as follows: ASPD (61; 36%), borderline personality disorder (BPD) (21; 12%), ASPD and BPD comorbidity (46; 26%), narcissistic personality disorder (8; 5%), paranoid personality disorder (24; 14%), and others (21; 12%). Alcohol dependence was diagnosed in 134 subjects (77%) and alcohol abuse in 40 (23%). Early onset conduct disorder was diagnosed in 42% (73/174) of the subjects. Alcoholics included in this study displayed high level of impulsivity and novelty seeking (as measured with Tridimensional Personality Questionnaire) (Tikkanen et al., 2007).

Alcohol Consumption

Alcohol consumption was measured before the follow-up with the Lifetime Drinking History (Skinner and Sheu, 1982) questionnaire, which is a structured interview where subjects are asked about patterns of alcohol consumption from the first year of regular drinking to the

present. We divided the subject's lifetime alcohol exposure by the number of years of drinking to form a variable describing the lifetime yearly mean alcohol consumption.

Assessment of Violent Behavior

The base line violent offenses were generally serious, impulsive, and committed under the influence of alcohol [alcohol-intoxication occurred in 155/174 cases (89%)]. Impulsive-aggressive behavior was assessed from mental status examination reports, where the offender's ability to control his behavior during the violent act was thoroughly discussed. One-hundred fifteen (66%) crimes were clearly impulsive and unexpected. A common subjective experience reported by the offenders was that of amnesia and loss of behavioral control during the act of violence. The most common offenses were manslaughter, attempted manslaughter, assault, or battery (61%), murder or attempted murder (19%), arson (16%), and rape (4%). Recidivism in violent behavior was assessed using register data provided by the Legal Register Centre in August 2005. The distribution of the outcome acts of violence was manslaughter, attempted manslaughter, assault, or battery (81.2%), murder or attempted murder (7.3%), arson (7.3%), and rape (4.3%).

The total follow-up period (from enrolment in the study to the examination of criminal records) was 11.7 years (140 months, range 85–182). We subtracted the time spent in prison from the total follow-up time, which resulted in a nonincarcerated follow-up period of 8.1 years (97 months, range = 3–182).

MAOA-LPR Genotyping

The *MAOA-LPR* was genotyped with PCR primer sequences: Forward 5'-(CCC AGG CTG CTC CAG AAA CATG 3)-3' and Reverse 5'-(GTT CGG GAC CTG GGC AGT TGT G)-3'. Owing to the high GC content in the region where the *MAOA-LPR* is located, amplification was performed using Invitrogen's PlatinumTaq and PCRX Enhancer System kits according to the manufacturer's protocol (Invitrogen, Carlsbad, CA). A detailed description of the genotyping method appears in the paper by Ducci and colleagues (2006).

As the study sample comprised only males, genotypes were grouped by relative transcriptional activity into 2 categories: high activity (4 repeats, 56%) versus low activity (3 repeats, 44%). These 2 alleles accounted for 97% of the *MAOA-LPR* variety among the offenders.

Statistical Analyses

Bonferroni- and age-corrected general linear model univariate analyses were conducted for comparison of alcohol consumption means for the whole sample, recidivistic versus nonrecidivistic offenders stratified by *MAOA-LPR*, and for the examination of interactive effect between *MAOA-LPR* and recidivism. The risk for acts of violence in the whole sample and in the *MAOA-LPR* groups was assessed separately by applying forced multivariate logistic regression analyses with *MAOA-LPR*, alcohol consumption, and aging as independents. The level of significance was set at 95% CI. Analyses were performed with SPSS 15.0 for Windows.

RESULTS

Alcohol Consumption

A bonferroni- and age-corrected general linear univariate model with a good fit (Levene's statistics $F = 2.0$, $df = 3$, $df = 151$, $p = 0.125$) suggested that the recidivistic offenders drank 36% more than did the nonrecidivists: 61 kg (SE = 4.7) versus 45 kg (3.8), mean difference 16 kg ($p = 0.008$). Comparison between the high and low activity *MAOA* genotyped offenders showed borderline significance ($F = 3.7$, $df = 1$, $p = 0.056$) toward greater alcohol consumption among high activity *MAOA* genotyped offenders: 59 kg (SE = 3.9) versus 47 kg (4.5), mean

difference 12 kg. This model suggested an interaction ($F = 4.2$, $df = 3$, $p = 0.043$) between *MAOA-LPR* and recidivistic offenses for alcohol consumption.

Figure 1 displays that the high activity *MAOA* genotyped recidivists emerged as heavy drinkers with significantly greater consumption than that of the other groups. No other pairwise group comparisons were significant. The all-offender mean consumption was 52 kg ($SD \pm 38$).

The Effect of *MAOA-LPR*, Alcohol Consumption, and Aging

MAOA genotype showed no main effect on risk for violent behavior in the first multivariate logistic regression model, whereas alcohol consumption and aging both influenced the risk in opposite directions (Table 1). This model explained 12% ($R^2 = 0.117$) of the risk and no interaction occurred ($b = 0.58$, $SE = 0.67$, $W = 0.76$, $df = 1$, $p = 0.385$). The second analysis carried out among the high activity *MAOA* offenders augmented the pattern observed in the first analysis (Table 1). This model explained 24% ($R^2 = 0.244$) of the risk, and no interaction emerged ($b = 0.84$, $SE = 0.91$, $W = 0.85$, $df = 1$, $p = 0.357$). Finally, we applied the original regression model to the low activity *MAOA* group, but found no effect.

Because both alcohol consumption and aging predicted acts of violence in the high activity *MAOA* genotyped offenders, we attempted to describe the united risk by creating a risk index (Fig. 2). Moreover, because the second logistic regression model failed to show any interaction between these variables and the mean values used to define the index score were centered, we judged that the united risk of drinking and aging was additive.

DISCUSSION

Our results show that *MAOA-LPR*, alcohol consumption, and aging may play an important role in the prediction of impulsive violence. Our results suggest that the high activity *MAOA* genotype modulates the effect of alcohol consumption and aging on risk for recidivistic acts of violence in a sample of violent Finnish criminal alcoholics.

The group of violent offenders that committed a new violent offense in the 8 year follow-up had a history of significantly larger alcohol exposure than the nonrecidivists. That alcohol exposure correlated with recidivistic violence may depend on the fact that this potent neurotoxic substance causes loss of behavioral control, which has been suggested as a core symptom of addiction (Baler and Volkow, 2006; Goldstein and Volkow, 2002). Research has suggested dysfunction of the inhibitory pathway (Taber et al., 2000; Volkow et al., 1993) and glucose metabolism of the frontal cortex (Bufkin and Luttrell, 2005; Volkow et al., 1994) among alcoholics, which may predispose to loss of behavioral control. Antisocial alcoholic offenders also have an abnormal energy substrate metabolism (Virkkunen et al., 2007) and they tend to neglect nutrition during relapses, which may worsen the glucose metabolism disturbance and increase the risk for uncontrolled impulsive violence.

Analyses suggest that alcohol consumption predicts violent behavior. However, alcohol exposure predicted violence only among high activity *MAOA* offenders. This result may find support from research claiming that high activity *MAOA* individuals are more impulsive as compared with low activity *MAOA* genotyped individuals (Gade et al., 1998; Manor et al., 2002; Manuck et al., 2000). Recent task-related brain imaging studies in healthy males also suggest that high activity *MAOA* allele carriers exhibit impulsive behavior associating to focal brain activation (Cerasa et al., 2008; Passamonti et al., 2006) and self-reported impulsivity (Passamonti et al., 2006). The high *MAOA* activity associated impulsive-aggressive violent behavior observed in our alcoholic sample matches indirectly previous consistent research that links low CSF 5-HIAA to impulsive-aggressive behavior (Linnoila et al., 1983; Virkkunen et al., 1989, 1994), suicides (van Praag, 1983; Traskman et al., 1981), and type II alcoholism

(Fils-Aime et al., 1996). However, our finding contrasts research that links low activity *MAOA* with violence and aggression (Brunner et al., 1993; Buckholtz and Meyer-Lindenberg, 2008; Caspi et al., 2002; Widom and Brzustowicz, 2006). This discrepancy may depend on the difference in impulsivity, alcohol consumption, and environmental effects.

The low activity *MAOA* carriers in our sample entirely comprising violent offenders may have developed aggressive antisocial behaviors for reasons other than those of the high activity *MAOA* individuals. For instance, the low activity *MAOA* individuals seem to be vulnerable to adverse childhood experiences (Caspi et al., 2002; Nilsson et al., 2006; Widom and Brzustowicz, 2006). It is thus possible that the effects found amongst high activity *MAOA* individuals in the present study should be interpreted as representative of individuals who (unlike *MAOA* low activity individuals) develop alcoholism and antisocial behaviors for reasons other than childhood adversity (Baler et al., 2008). Information on early-life events could possibly have shed further light on this but such data were not available. Low activity *MAOA* has been associated with personality traits of anger, aggression, hostility, hypersensitivity to social exclusion, and increased neural activity in emotion processing areas of the brain (Alia-Klein et al., 2008; Buckholtz and Meyer-Lindenberg, 2008; Buckholtz et al., 2008; Eisenberger et al., 2007). Such traits may lead to some form of aggressive and violent behavior. For instance, Alia-Klein and colleagues (2008) described the low activity *MAOA* associated self-reported aggression as "... attitudes, values, and beliefs that are consistent with approval of the use of physical violence." However, when this aggression tendency, linked to the low activity *MAOA* genotype, leads to violent behavior it may be different from the mainly impulsive, unexpected, and uncontrolled violence observed in the current report.

Possible gene by gene interactions may explain as to why the high activity *MAOA* recidivists in our sample featured persistent heavy drinking, as emerging evidence shows that antisocial alcoholism associates with abnormal genotypes (Belfer et al., 2006, 2007; Enoch et al., 2006; Xu et al., 2007). Recently, single nucleotide polymorphisms in the GABA receptor alpha2-subunit have been associated with variance in body sway and motor coordination during alcohol-intoxication (Lind et al., 2008). It is conceivable that such polymorphisms, affecting motor control, may interplay with *MAOA-LPR* if a subpopulation of high activity *MAOA* alcoholics exhibit impulsive and uncontrolled violence under the influence of alcohol as suggested in the current report. Moreover, epigenetic influence may moderate the conjunct effect of *MAOA-LPR* and excessive alcohol exposure as various physiological functions are altered in impulsive-aggressive ASPD and BPD (Brewer-Smyth et al., 2004; Lindberg et al., 2003a,b; McBurnett et al., 2000; New et al., 2007; Popma et al., 2007; Sjoberg et al., 2008; Virkkunen et al., 2007).

Aging showed a 7.3% decrease in the risk for recidivism among high activity *MAOA* offenders for every year, but failed to affect the risk among low activity genotyped offenders. Aging may decrease impulsive-aggressive behavior particularly among high activity *MAOA* genotyped offenders, if aging decreases *MAOA* expression in humans, as suggested in mice (Vitalis et al., 2002), possibly resulting in a correction of low central serotonin levels over time which would decrease impulsive-aggressive behavior. Moreover, aging may modulate the effects of some other risk factors especially among the high activity *MAOA* genotyped offenders. It is possible that our results are biased because we lack data on participation in addiction treatment programs that the Finnish prisons offer. Finding a firm spouse, embracing a religious faith, or attending Alcoholics Anonymous meetings could also decrease alcohol consumption and the risk for uncontrolled impulsive violent behavior over time.

A considerable limitation of our study-setting is that we assessed impulsivity and acute alcohol-intoxication of the index crimes, and lifetime alcohol exposure at the beginning of the follow-up, but we had no data on these variables related to the outcome violent crimes. However, our

sample comprises violent offenders and violent crimes that match the bulk of Finnish violent offenders and violent crimes, which are mainly committed under the influence of alcohol, which argues for the alcohol-intoxication related impulsivity of the recidivistic offenses. Moreover, even though we had no access to detailed police reports on the recidivistic offenses, the criminal records revealed that the outcome violent crimes were even more frequently impulsive (manslaughter, attempted manslaughter, assault, or battery) than the index crimes preceding the follow-up (an increase from 61% to 81%). Despite the limitations of this study, we present preliminary results of the conjunct effects of *MAOA-LPR*, alcohol consumption, and aging on the risk for violent behavior. The main strengths of our study were its large sample size, long prospective follow-up, and reliable register-based outcome measure of dominantly impulsive violence. Results imply that for secondary prevention of violence, the high activity *MAOA* offenders in particular, should be supported to abstinence and possibly psychopharmacological treatment to increase central serotonin levels. Results are preliminary and need replication in similar populations.

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Fig. 1.

The yearly mean consumption of alcohol (ETHO kilograms per year) in recidivistic and nonrecidivistic offenders stratified by monoamine oxidase A (*MAOA*) genotype. *MAOA-H* = high activity genotype, *MAOA-L* = low activity genotype. Bonferroni corrected comparisons between groups were performed with a general linear univariate model where age served as a covariate. Comparisons between *MAOA-H* recidivists and other groups separately: a, $p = 0.036$; b, $p = 0.002$; c, $p = 0.002$.

Fig. 2.

A risk index for recidivistic violent behavior among high activity *MAOA* genotyped offenders. The index composes the variables age and alcohol consumption. The index score 100 was defined as the all-offender means of the variables (age 33 and an alcohol consumption of 52 kg pure alcohol per year). According to the results (Table 1), a 1 unit change in drinking showed a +2.3% effect, and a 1 unit increase in age showed a -7.3% effect on the risk for recidivistic offenses. The pure alcohol load (kg per year) equivalents in terms of daily dose of 40% liquor: 110 kg = 0.75 l (25 drinks), 52 kg = 0.36 l (12 drinks), and 10 kg (the average Finnish consumption) = 0.07 l (2 drinks).

The Effect of Alcohol Consumption and Aging on the Risk for New Acts of Violence Among Alcoholic Violent Offenders

Table 1

	<i>b</i> (SE)	W	<i>p</i>	OR	CI
All offenders (<i>n</i> = 174)					
Alcohol consumption	0.014 (0.01)	8.1	0.004	1.014	1.0–1.02
Aging	–0.049 (0.21)	5.7	0.017	0.952	0.91–0.99
MAOA	–0.321 (0.34)	0.9	0.353	0.725	0.37–1.43
MAOA- <i>H</i> group (<i>n</i> = 97)					
Alcohol consumption	0.023 (0.01)	8.5	0.004	1.023	1.01–1.04
Aging	–0.073 (0.03)	6.0	0.015	0.930	0.88–0.99
MAOA- <i>L</i> group (<i>n</i> = 77)					
Alcohol consumption	0.003 (0.01)	0.2	0.624	1.003	0.99–1.02
Aging	–0.018 (0.03)	0.4	0.542	0.982	0.93–1.04