Department of Psychiatry
University of Helsinki
Finland

Predictors of violent reconvictions and mortality among impulsive alcoholic violent offenders: A prospective study

Roope Tikkanen, MD

ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in Christian Sibelius Auditorium, Department of Psychiatry on 25 September 2009, at 12 noon.

SUPERVISORS

Professor Matti Virkkunen, MD, PhD
Department of Psychiatry
University of Helsinki
Helsinki, Finland

Docent Matti Holi, MD, PhD
University of Helsinki
Helsinki, Finland

Docent Nina Lindberg, MD, PhD
University of Helsinki
Helsinki, Finland

REVIEWERS

Acting Professor Olli Kampman, MD, PhD
University of Tampere
Tampere, Finland

Docent Markku Eronen, MD, PhD
University of Turku
Turku, Finland

OPPONENT

Docent Hannu Lauerma, MD, PhD
University of Turku
Turku, Finland

ISBN 978-952-92-6094-2 (pbk.)
ISBN 978-952-10-5719-9 (PDF)

Helsinki University Printing House
Helsinki 2009

Abstract

Acts of violence lays a great burden on humankind. The negative effects of violence could be relieved by accurate prediction of violent recidivism. However, prediction of violence has been considered an inexact science hampered by scare knowledge of its causes.

The study at hand examines risk factors of violent reconvictions and mortality among 242 Finnish male violent offenders exhibiting severe alcoholism and severe externalizing personality disorders. The violent offenders were recruited during a court-ordered 2-month inpatient mental status examination between 1990—1998. Controls were 1210 individuals matched by sex-, age-, and place of birth. After a 9-year non-incarcerated follow-up criminal register and mortality data were obtained from national registers. Risk analyses were applied to estimate odds and relative risk for recidivism and mortality. Risk variables that were included in the analyses were antisocial personality disorder (ASPD), borderline personality disorder (BPD), a comorbidity of ASPD and BPD, childhood adversities, alcohol consumption, age, and monoamine oxidase A (MAOA) genotype. In addition to risk analyses, temperament dimensions (Tridimensional Personality Questionnaire [TPQ]) were assessed.

The prevalence of recidivistic acts of violence (32%) and mortality (16%) was high among the offenders. Severe personality disorders and childhood adversities increased the risk for recidivism and mortality both among offenders (OR 2.0–10.4) and in comparison between offenders and controls (RR 4.3–53.0). Offenders having BPD and a history of childhood maltreatment emerged as a group with a particularly poor prognosis. MAOA altered the effects of alcohol consumption and ageing. Alcohol consumption (+2.3%) and age (–7.3%) showed significant effects on the risk for violent reconvictions among the high activity MAOA (MAOA-H) offenders, but not among the low activity MAOA (MAOA-L) offenders. The offenders featured temperament dimensions of high novelty seeking, high harm avoidance, and low reward dependence matching Cloninger's definition of explosive personality.

The fact that the risk for recidivistic acts of violence and mortality accumulated into clearly defined subgroups supports future efforts to provide for evidence based violence prevention and risk assessments among violent offenders.

Tiivistelmä

Väkivalta kuormittaa ihmiskuntaa suuresti. Väkivallan moninaisia kielteisiä vaikutuksia pystyisi lieventämään parantamalla väkivallan ennustetarkkuutta. Epätietoisuus väkivallan perimmäisistä syistä vaikeuttaa väkivallan ennustamista.

Tämä tutkimus tarkastelee uusintaväkivallan ja kuolleisuuden riskitekijöitä suomalaisessa mies väkivaltarikollisaineistossa, joka kerättiin vuosina 1990—1998 mielentilatutkimusten yhteydessä. Aineiston 242 henkilöllä oli keskimäärin vaikea alkoholismi ja vakava persoonallisuushäiriö. Verrokkiryhmän muodosti 1210 sukupuoli, ikä- ja syntymäpaikkakunta vakioitua yksilöä. Yhdeksän vuoden seuranta-ajan jälkeen suoritettiin riskianalyysit saatujen rikosrekisteriotteiden (Oikeusrekisterikeskus) ja kuolleisuustietojen (Tilastokeskus) perusteella. Analyyseissä käytettiin riskitekijöinä antisosiaalista persoonallisuushäiriötä (ASPD), epävakaata persoonallisuushäiriötä (BPD), ASPD:n ja BPD:n samanaikaista esiintyvyyttä, lapsuuden kielteisiä olosuhteita, alkoholin kulutusta, ikää ja monoamiinioksidaasi A (MAOA) genotyyppiä. Riskianalyysien lisäksi arvioitiin temperamenttia (Tridimensional Personality Questionnaire [TPQ]).

Uusintaväkivallan (32%) ja kuolleisuuden (16%) esiintyvyys oli korkea väkivaltarikollisten parissa. Vaikeat persoonallisuushäiriöt ja lapsuuden kielteiset olosuhteet lisäsivät uusintaväkivallan ja kuolleisuuden riskiä sekä väkivaltarikollisten keskinäisissä vertailuissa (riskikerroin 2.0–10.4) että verratessa väkivaltarikollisia verrokkeihin (riskisuhde 4.3–53.0). Lapsena kaltoinkohdeltujen BPD henkilöiden ennuste oli erityisen huono. MAOA genotyyppi vaikutti alkoholin kulutuksen ja iän ennustekykyyn. Alkoholin kulutus (+2.3%) ja ikä (–7.3%) vaikuttivat uusintaväkivaltariskiin korkean MAOA aktiviteetin (MAOA-H) henkilöissä, mutta ei matalan MAOA aktiviteetin (MAOA-L) henkilöissä. Väkivaltarikollisten temperamentille oli tyypillistä korkea virikehakuisuus/impulsiivisuus/kaoottisuus (novelty seeking), korkea ahdistuneisuus (harm avoidance) ja matala sosiaalistuminen (reward dependence), mikä vastaa Cloningerin määritelmää eksplosiivisesta persoonallisuudesta.

Uusintaväkivallan ja kuolleisuuden riskit kasaantuivat selviin väkivaltarikollisten alaryhmiin. Vaikeiden persoonallisuushäiriöiden diagnostisointi, lapsuuden ympäristön arviointi, alkoholikulutuksen kartoitus ja MAOA genotyypin määritys saattavat tulevaisuudessa olla uusintaväkivaltaa ja kuolleisuutta ennaltaehkäiseviä sekä vaarallisuusarvioita tarkentavia keinoja.

Abstrakt

Våld utgör en stor belastning för mänskligheten. De mångahanda negativa återverkningarna av våldshandlingar kunde lindras genom att förbättra precisionen på förutsägelser om våldshandlingar. Ovisshet om de bakomliggande orsakerna till våld gör det emellertid svårt att förutsäga våldshandlingar.

Denna studie granskar riskfaktorer för upprepat våld och dödlighet bland 242 finska våldsbrottslingar, vilka led av svår alkoholism och svåra personlighetsstörningar. Materialet samlades i samband med sinnesundersökningar åren 1990—1998. Kontrollgruppen bestod av 1210 ålders- och födelseortstandardiserade män. Efter en uppföljningstid på 9 år genomfördes riskanalyser på basis av brottsregisterutdrag (Rättsregistercentralen) och dödlighetsuppgifter (Statistikcentralen). I de statistiska analyserna användes antisocial personlighetsstörning (ASPD), borderline personlighetsstörning (BDP), samtidig förekomst av ASPD och BPD, negativa barndomsvillkor, alkoholkonsumtion, ålder och monoaminoxidas A (MAOA) genotyp som riskfaktorer. Förutom riskanalyserna, bedömdes temperaments dimensioner (Tridimensional Personality Questionnaire [TPQ]).

Förekomsten av upprepad våldsbrottslighet (32%) och dödlighet (16%) var hög bland våldsbrottslingarna. Svåra personlighetsstörningar och negativa barndomsvillkor ökade risken för upprepat våld och dödlighet både internt bland våldsbrottslingar (OR 2.0–10.4) och vid en jämförelse av våldsbrottslingarna med kontrollgruppen (RR 4.3–53.0). Individer med BDP och vilka blivit illa behandlade som barn framstod som en grupp med en särskilt dålig prognos. MAOA genotypen påverkade alkoholkonsumtionens och ålderns prognosförmåga. Alkoholkonsumtionen (+2.3 %) och åldern (–7.3%) påverkade märkbart risken för upprepade våldshandlingar hos individer med hög MAOA aktivitet (MAOA-H), emedan det inte gjorde det hos individer med låg MAOA aktivitet (MAOA-L). Våldsbrottslingarnas temperament präglades av en hög benägenhet att söka stimulans/impulsivitet/kaotiskhet (novelty seeking), stor ångestfylldhet (harm avoidance) och låg socialisation (reward dependence), vilket motsvarar Cloningers definition av explosiv personlighet.

Risken för upprepade våldshandlingar och dödlighet skockade sig i vissa undergrupper av våldsbrottslingar. Diagnostisering av personlighetsstörningar, bedömning av barndomsmiljön, kartläggning av alkoholkonsumtionen och analys av MAOA genotyp kan därför i framtiden förebygga upprepat våld och dödlighet samt öka precisionen av farlighets bedömningar.

Contents

1 List of original publications

This thesis is based on the following publications:

I Tikkanen R, Holi M, Lindberg N, Virkkunen M (2007) Tridimensional Personality Questionnaire data on alcoholic violent offenders: specific connections to severe impulsive cluster B personality disorders and violent criminality. BMC Psychiatry 7:36.

II Tikkanen R, Holi M, Lindberg N, Tiihonen J, Virkkunen M (2009a) Recidivistic offending and mortality in alcoholic violent offenders: A prospective follow-up study. Psychiat Res 168:18–25.

III Tikkanen R, Sjoberg RL, Ducci F, Goldman D, Holi M, Tiihonen J, Virkkunen M (2009b) Effects of MAOA-genotype, alcohol consumption, and aging on violent behavior. Alc Clin Exp Res 33:428–434.

IV Tikkanen R, Ducci F, Goldman D, Holi M, Lindberg N, Tiihonen J, Virkkunen M. MAOA alters the effects of heavy drinking and childhood physical abuse on risk for impulsive violence. Alc Clin Exp Res, submitted.

The publications are referred to in the text by their roman numerals.

2 Abbreviations

5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
5-HT1A	a 5-HT receptor
5-HT2C	a 5-HT receptor
5-HT3B	a 5-HT receptor
5-HTT	5-HT transporter
ASPD	antisocial personality disorder
ASPD–BPD	comorbid antisocial and borderline personality disorder
AUC	area under the curve
BPD	bordeline personality disorder
CD	conduct disorder
CI	confidence interval
CPA	chidhood physical abuse
CRH-BP	corticotropin-releasing hormone-binding protein
CSF	cerebospinal fluid
DAT1	dopamine transporter
EEG	electroencephalography
FAAH	free acid amide hydroxylase
$GABA_A$	gamma-aminobutyric acid type A receptor
GABRA2	gene encoding $GABA_A$ alpha 2 subunit
GABRG1	gene encoding $GABA_A$ gamma 1 subunit
GAL	neuropeptide galanin
GALR3	galanin receptor 3 gene
GSK3β	glycogen synthase kinase 3β
HA	harm avoidance
HVA	homovanillic acid
MAOA	monoamine oxidase A
MAOA-H	high activity monoamine oxidase A genotype
MAOA-L	low activity monoamine oxidase A genotype
MAOA-LPR	MAOA linked plymorphic region
MHPG	3-methoxy-4-hydroxyphenylglycol
NS	novelty seeking
NTRK2	tyrosine kinase B neurotrophin receptor gene
OPRM1	μ-opioid type 1 receptor
OR	odds ratio
RD	reward dependence
ROC	receiver operating charasteristics
RR	risk ratio (relative risk)
TPH2	typtophan hydroxylase 2
TPQ	Tridimensional Personality Questionnaire

3 Introduction

The estimated global violence related death rate is 28.8 per 100 000 individuals (WHO, 2002). Homicide accounts for one-third, sucide for nearly half, and war related deaths for one-fifth of the deaths.

Reporting based on the current tenth edition of the International Classification of Diseases (ICD-10; WHO, 1992) to the World Health Organisation (WHO) suggests that 2.2 deaths occured per 100 000 Finnish inhabitants due to homicide (1.2 in Sweden and 21.6 in the Russian Federation) (WHO, 2002). The incidence of accidental poisonings (alcohol-intoxications as a major cause) was 15.2 per 100 000 inhabitants in Finland (3.3 in Sweden and 44.0 in the Russian Federation) (WHO Statistics).

The ultimate goal of violence research – including prediction of acts of violence – is to decrease the occurrence of violent behavior and its negative effects by means of preventive work and risk assessment. However, there is surprisingly limited clinically meaningful information available on predictive factors to support evidence based and cost-efficient secondary prevention of violent behavior. This lack of predictive information concerns also violent alcoholic populations with externalizing disorders – a population that commits the majority of the violent crimes in Finland. The unsolved etiology of violent behavior hampers predictions of violent behavior. Methodological obstacles such as difficulty collecting data, heterogeneous samples, definition of violence, usage of nonclinically significant statistical methods, and lack of prospective study settings limit the accuracy of violence prediction. Violence risk prediction has been claimed to be an inexact science (Dolan and Doyle, 2000).

A public awareness of the importance of predicting risk for acts of violence developed slowly during the 1960's and 1970's partly due to the appearance of some polemic judicial cases dealing with the release of patients from maximum security hospitals. *Thornberry and Jacoby* (1979) published a detailed study on the outcome of 586 mentally ill late-middle-aged criminal patients that were released from a Pennsylvania maximum security hospital after the ruling of the federal court according to which their commitment had been unconstitutional. The authors concluded that violent behavior was not frequent among the patients during the confinement or after release. Their text questions whether the average 14-year confinement had been purposeful or a misjudgement based on a "political prediction" founded in prejudged anticipation of violence, rather than facts.

In a large register-based study *Eronen et al.* (1996) examined the incidence of homicides and frequency of mental status examinations performed in Finland during a 7-year period (1984—1991). They reported that 922 murders and manslaughters were committed (within a population of 5 029 000; 1 947 000 men and 2 113 000 women older than 15 years). The majority (91.6%) of the homicides were committed by males. The Finnish police force was able to solve 96.9% of the homicides. A court-ordered forensic psychiatric examination was conducted on 69.7% cases.

The typical Finnish homicide is committed under the influence of alcohol by males aged 20–29 with a low socioeconomic status (Kivivuori, 1999). The most common homicidal contexts are conflicts in marital relationships, conflicts among drunkards, and defending ones own honour or reputation (Kivivuori, 1999). The majority (85%) of the

Finnish recidivistic homicidees have a personality disorder (mostly antisocial personality disorder) combined with severe alcoholism (Tiihonen and Hakola, 1994). The odds to commit homicide have been shown to be 10 times higher among Finnish male homicidees as compared with the general population (Tiihonen et al., 1995).

The thesis at hand examines risk factors for recidivistic acts of violence and mortality among impulsive non-psychotic alcoholic violent offenders. The study is a quantitative follow-up study in which robust and clinically meaningful statistical methods were used.

4 Review of research related to violent behavior

4.1 Definitions of violence

Human aggression and violence can be defined in several ways. The World Health Organization defines violence as "the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation" (WHO, 1996). The intentionality of the act of violence is central. Laws judge in which case the harmful behavior is criminal. The ruling may depend on the intentionality of the act. Moreover, similar to its definition of violence, the World Health Organization has presented a typology of violence (WHO, 2002) according to which the victim-perpetrator relationship can be subtyped into self-directed, interpersonal, and collective violence. This typology suggests that violence can be inflicted in four "modes": physical, sexual, psychological, and deprivation. The occurrence of victimizations or acts of violence may be self-reported based on questionnaires or face-to-face interviews or observed in registers such as police registers, criminal records, and patient journals.

An accurate definition of violence is of great importance while examining clinically significant causes of violent behavior as a basis for prevention and risk assessment. One meaningful way to define violent behavior is a subdivision of violent behavior into impulsive and nonimpulsive since, hypothetically, these may have a distinct etiology. The etiologic puzzle of violent behavior comprises environmental, hereditary, and situational causes. These simple distinctions have, however, partly been blurred in violence research. Table 1 displays definitions of violent behavior, ranging from personality disposition toward violence and violent ideation to arrest information and criminal records, which have been used in some recent studies.

Table 1 Examples of definitions of violent behavior in studies examining genetic and environmental risk for violence.

	Definitions
Caspi et al. (2002)	a) Convictions of assault, aggravated assault with intent to injure with a weapon, domestic violence, manslaughter, and rape. b) Multidimensional Personality-Aggression scale (personality disposition towards violence). Violence was defined as the upper quartile.
Huizinga et al. (2006)	a) Arrest for simple assault, aggravated assault, homicide, rape, and domestic violence. b) Aggressive ideation between ages 24–28. Violence was defined as the upper quartile.
Reif et al. (2007)	"Predisposition toward overt and intentional physical aggressive behavior" in a forensic sample comprising acts of homicide, physical injury, and robbery, property offences and fraud, sexual offences, drug offences, and other offences.
Widom and Brzustowicz (2006)	A violence and antisocial behavior index (VASB) comprising arrest records (any cause), self-reported violent behavior, and DSM-III-R based conduct and antisocial symptoms.

4.2 Childhood environment

Similar to definitions of violent behavior, childhood adversities can be defined in several ways. The divergent definitions of childhood adversities (e.g., physical abuse [including or excluding sexual abuse], loss of caregiver, rejection of the child's emotions, inconsistent discipline) in violence research compromise the comparability of reports. Table 3 (under 4.8.1.5) displays definitions used in some studies. Despite the various definitions, childhood adversities have been shown to substantially predict violent behavior. Importantly, however, hampering the earlier consensus of the effects of childhood adversities on risk for violent behavior, some studies have suggested that individual genotype alters the effect of maltreatment on risk for violence and antisocial behavior (Table 3 under 4.8.1.5).

Well designed studies in large samples reporting OR figures have shown 4- to 14-fold increase in risk for violent behavior and/or other antisocial behavior after exposure to childhood adversities (Caspi et al., 2002; Nilsson et al., 2005; Reif et al., 2007). Studies reporting β-regression coefficients have shown figures of 0.07–0.81 as a an estimate of risk for violent and/or other antisocial behavior after exposure to childhood adversities (Caspi et al., 2002; Haberstick et al., 2005; Kim-Cohen et al., 2006; Prichard et al., 2008; Widom and Brzustowicz, 2006). Poor family conditions have been shown to explain 19–36% of the total variance of risk for alcohol related problem behavior (including

aggressive behavior) (R^2 = 0.19–0.362) (Nilsson et al., 2008). The severity and accumulation of adversities have been found to correlate positively with the risk for acts of violence (Caspi et al., 2002; Foley et al., 2004; Haberstick et al., 2005; Weder et al., 2009). Age at the time of exposure (childhood or adolescence) to adversities may also influence the effect sizes of risk (Huizinga et al., 2006).

Loeber et al. (2005) examined predictors of violent behavior and homicide in a prospective study setting among boys in a large school sample (n = 1 517). They reported that the violent boys, in comparison with nonviolent boys, were associated with low socioeconomic status overall, and more specifically, to variables such as family on welfare, African American, young mother, and bad neighbourhood. Other variables associated with violent behavior were bad friends, peer delinquency, peer substance abuse, low academic achievement, low school motivation, and old relative to grade. However, no effect sizes were reported for these variables separately but the odds for committing violent acts was 6-fold among boys with four or more risk factors in comparison with boys with fewer than 4 risk factors out of the 63 risk factors included in the study (domains: child behavior, parent's help seeking for child behavior problems, child's attitudes/cognition, child's psychiatric diagnoses, child's history of offending, birth factors, family, peer, school, and demographic factors including neighbourhood). A subset of the risk factors that were related to violent behavior also predicted homicide. Boys with 4 or more risk factors for homicide were 14 times more likely to later commit homicide as compared with violent individuals with fewer than 4 risk factors.

Sourander et al. (2006) showed in a large cohort of Finnish boys that living in nonintact families with low parental education level predicted a high level of criminal offences (including violence).

4.3 Personality disorders

A criterion for personality disorders is the presence of long-term maladaptation and inflexibility that are manifested as subjective distress or socioоccupational functional impairment, or both. The prevalence of antisocial personality disorder and borderline personality disorder has been estimated to be 1.4% (0.7% for both disorders separately) in the general population (Torgersen et al., 2001).

Antisocial personality disorder (ASPD), as defined by DSM-IV (APA, 1994), features pervasive disregard for and violation of rights of others occurring since 15 years of age and continuing into adulthood. A person has to be 18 years of age or older, and there has to be evidence of conduct disorder before 15 years of age. Individuals having ASPD typically break rules routinely, engage in criminal behavior, and have a strong tendency to be reckless, irresponsible, and deceitful. They burden and cause suffering to others but are also likely to be at an increased risk of premature death. The prevalence of ASPD in psychiatric outpatients has been estimated as 3.6% (Zimmerman M et al., 2005).

Borderline personality disorder (BPD), as defined by DSM-IV (APA, 1994), features impulsive behavior, emotional lability, inappropriate anger, and suicidal behavior. The

prevalence of BPD in psychiatric outpatients has been estimated as 9.3% (Zimmerman et al., 2005).

A similarity among cluster B personality disorders (ASPD, BPD, narcissistic personality disorder, and histrionic personality disorder) is the occurrence of "externalizing" symptoms including aggression, dramatic and fickle behavior, blaming others, and devaluation of others, and feeling of superiority or masked low self-esteem. These features capture the attention of others since the pathological features may take absurd dimensions even though the disordered themselves do not necessarily perceive themselves and their behavior as odd.

Individuals having ASPD frequently engaged in criminal activities. *Fazel and Danesh* (2002) reported that the prevalence of ASPD was 47% among male prisoners (n = 10 797) whereas 65% had "any personality disorder". The majority (85%) of the Finnish recidivistic homicidees have been reported to have a personality disorder (mostly ASPD) combined with severe alcoholism (Tiihonen and Hakola, 1994). Bordeline personality disorder was not separately reported in the studies by Fazel and Danesh (2002), and Tiihonen and Hakola (1994), and overall, BPD and a comorbid ASPD–BPD have been neglected in the criminal literature.

The specific etiology of ASPD and BPD is unclear. However, it has been shown that both ASPD and BPD have a high, but only partly overlapping, total heritability (0.41 and 0.37 respectively) (Kendler et al., 2008). The environmental causes of both ASPD and BPD explain approximately 0.60 of the etiology (Kendler et al., 2008).

Conduct disorder (CD) is a childhood or adolescence mental disorder that comprises behavioral symptoms such as rule breaking, lying, bullying, and injuring others (APA, 1994). Conduct disorder easily develops into adult ASPD (Simonoff et al., 2004), but attention has been given to the fact that not all aggressive children diagnosed with CD grow to become adults with ASPD (Moffitt et al., 2002). *Sourander et al.* (2006) reported that conduct problems at age 8 predicted violent behavior, property, traffic, and drunk driving offenses in late adolescence during a 4-year study period in a prospective population-based cohort comprising 2 713 Finnish boys.

4.4 Temperament

Temperament and personality are often used as interchangeable terms, but theoretically temperament describes a tendency to respond to stimuli in a certain way whereas personality is the manifest result of temperament, self-awareness, intelligence, and life-events, which results in a certain cognitive style and behavior.

Numerous dimensional personality and temperament assessment instruments have been developed. The study at hand uses the scientifically established Tridimensional Personality Questionnaire (TPQ) which offers a psychobiological frame to assess temperament dimensions. TPQ is based on the temperament theory suggested by *Cloninger* in the 1980's and holds that trait novelty seeking (NS) (including impulsivity) connects with dopaminergic, trait harm avoidance (HA) connects with serotonergic and gamma-aminobutyric, and trait reward dependence (RD) connects with noradrenergic

pathways in the brain (Cloninger, 1987a). Genetic data from 2 680 adult twin pairs showed that there is a significant genetic contribution (54–61%) to the variance of TPQ dimensions (Heath et al., 1994). All three traits are normally distributed. Specific extreme trait patterns correspond with personality disorders.

Antisocial personality, as suggested by Cloninger, features high NS, low HA, and low RD. The histrionic personality features high NS, low HA, and high RD. The passive-aggressive personality features high NS, high HA, and high RD. The explosive personality features high NS, high HA, and low reward dependence. All four types of personality connect with impulsive-aggressiveness and antisocial behavior. The antisocial personality resembles psychopathy as described by Hare (1991). The passive-aggressive and explosive personalities are frequently engaged in antisocial behavior when they are complicated with alcohol and other drugs (Cloninger, 1987a).

Individuals scoring high on NS are described as exploratory, impulsive, extravagant, and irritable whereas low scorers feature reservation and a stoical position. Individuals scoring high on HA are described as pessimistic, fearful, shy, and fatigable whereas low scorers feature optimism, energy, carelessness, and an outgoing attitude. Individuals scoring high on RD are described as sentimental, open, warm, and affectionate whereas low scorers feature detachment, coldness, and independence.

Cloninger's NS has been associated with alcoholism (Grucza et al., 2006; Hesselbrock and Hesselbrock, 1992; Kampov-Polevoy et al., 2004). High NS has also been suggested to predict early onset alcohol abuse and criminality and to discriminate alcoholics exhibiting antisocial behavior and persons with ASPD from their nonantisocial counterparts (Howard et al., 1997). Cloninger's high HA has also clearly been associated with alcoholism (Belfer et al., 2006; Ducci et al., 2007; Enoch et al., 2006). Low RD has been suggested to discriminate type 2 alcoholics from type 1 alcoholics (Howard et al., 1997) and alcoholic patients having high RD tend to have fewer relapses and greater attendance at self-help meetings as compared with alcoholic patients with low RD (Janowsky et al., 1999).

4.5 Addictions

4.5.1 Core symptoms and epidemiology

Three phenomena characterize addictions, namely, craving (preoccupation/anticipation), binge/intoxication, and withdrawal/negative affects (Koob, 2008). The prevailing classifications of mental disorders (DSM-IV and ICD-10), surprisingly, do not entirely include these features in the definition of addictions, but rather emphasize the negative social consequences. Although use of addictive agents is seemingly based on the free will of the individual, a central feature of addictions, as defined as mental disorders, is the subsequent loss of option and control, which amounts in compulsive habitual use.

The World Health Organization has estimated that 2 billion people consume alcoholic beverages and 76 million of these have an alcohol use disorder (WHO, 2004). The proportion of alcohol users is likely to increase when those areas of the world where alcohol availability is limited at the moment are better supplied and wealthier. Alcohol, tobacco, and illicit drugs contributed to 12.4% of deaths worldwide (WHO, 2004). The 1-year point prevalence of DSM-IV substance usage disorders in the U.S. general population has been shown to be 9.35% (alcohol use disorder 8.46%; alcohol abuse 4.65 and alcohol dependence 3.81%) (Grant et al., 2004). Addictive drugs also cause 590 000 deaths per year and cause injury or illness to almost 40 million individuals in the United States (McGinnis and Foege, 1999). Alcoholism subtracts an average of 4.2 disability adjusted life years per person while, for comparison, type I diabetes subtracts only 0.1 years (Merikangas and Risch, 2003).

4.5.2 Typology of alcoholism

Alcoholism is a complex disorder which holds a broad spectrum of symptoms and behavior, consequently, alcoholism has been described by a variety of typologies and classifications. *Babor* (1996) presented a review covering a 150-year perspective on the development of classification of alcoholics. According to this the time from the 1850's to the 1940's was a prescientific era comprising dozens of clinical speculative views. According to Babor (1996), *Bowman and Jellinek* (1941) formulated some foundations that may be considered the historical roots of the current typological ideas such as the existence of subtypes of alcoholics under a higher-order class (alcohol dependence) with the subtypes sharing some common characteristics. However, if the rigor of pure typology is put aside, then the early French, German, English, and American prescientific concepts of alcoholism do correspond with current views on alcoholism: a) dependence in terms of craving, tolerance, or withdrawal symptoms, b) continuous or intermittent drinking patterns, and c) the persistence of symptoms over time.

The prevailing scientific typologies of alcoholism are based on the separate works of Cloninger and Babor. *Cloninger* (1987b) suggested, based on his family studies among Swedish adoptees, a subdivision of alcoholism into type 1 – were environmental risk factors determine drinking patterns – and type 2 – were an family history of alcoholism determines vulnerability to alcoholism. Type 2 alcoholism features male gender, psychological vulnerability, and an early age of onset of problem drinking. Based on Cloninger's theory, *Babor et al.* (1992a,b) derived empirically a type A/B dichotomic classification after detailed analysis of family history and age of onset in a sample of 228 males and 85 females. Further, the type A/B classification includes assessment of lifetime patterns of drinking and other drug usage, medical health, withdrawal symptoms and "relief drinking", extent of psychosocial disruption, psychometric assessment of personality, and childhood and adult psychiatric status. In contrast to type A, type B comprises early onset, rapid course, more severe symptoms, greater psychological vulnerability, and poorer prognosis (Babor et al., 1992b).

By examining two general population samples (n = 8 643 and 664), and by comparing 5 previous studies (Babor et al., 1992a; Gilligan et al., 1988; Schuckit et al., 1995; Sullivan et al., 1990; von Knorring et al., 1987) *Carpenter and Hasin* (2001) confirmed that Cloninger's and Babor's typologies resemble each other. In the mixed population of nonsevere "problem drinkers" type 2 and type B alcoholics were less prevalent than type 1 and type A alcoholics. However, there was also a varying prevalence of "problem drinkers" that did not fit these categories. In addition to the replication of previous papers stating that type 2 and type B alcoholics feature male gender, antisocial behavior, and early onset of drinking, Carpenter and Hasin (2001) observed a number of more specific features among type 2 and type B alcoholics as compared with type 1 and type A: onset of drinking before age 25, less frequently married, lower average household income, current partner was more often alcoholic, 4-fold prevalence of DSM alcohol dependence (59% vs. 16%), 14-fold prevalence of DSM cocaine dependence (2.72% vs. 0.2%), 3-fold prevalence of depression (14.8% vs. 5.3%), 8-fold prevalence of fighting (28.6% vs. 3.6%), 8-fold prevalence of arrests (15.6 % vs. 2.0%), 4-fold prevalence of drinking and driving (59% vs. 16%), 6-fold increased risk of injury (34.4% vs. 6.3%), 3 times more drinking days during the past 12 months (97 vs. 31), 12 times more alcohol treatments during the past 12 months (97 vs. 31), and 4 times more "morning drinks" during the past 12 months (5.5 vs. 1.3). The estimates of the prevalence of type 2 and type B alcoholism among alcoholics has varied between 20–30% whereas two-thirds suffer from type 1 and type A alcoholism with a better prognosis. Specific changes in neurotransmission (Leggio and Addolorato, 2008; Storvik et al., 2009), brain structure (Laakso et al., 2000), and CSF 5-hydroxyindoleacetic acid (5-HIAA) levels (Fils-Aime et al., 1996) have also been found to distinguish type 1 and type 2 alcoholics.

In sum, a criterion that distinguishes two major types of alcoholism shared by most scientific classifications and typologies is the age of onset of drinking (Irwin et al., 1990). Early onset alcoholism seems to be a more severe disorder associated with ASPD and violent behavior as compared with late onset alcoholism (Fils-Aime et al., 1996; Hesselbrock and Hesselbrock, 1992). However, the major international classifications of mental diseases (DSM and ICD) do not account for age at onset of drinking, but rather describes the adverse social consequences of drinking, in their definitions of alcohol dependence. However, alcoholism conjunct to early onset of drinking and ASPD may become a distinct clinically acknowledged "disease" with a specific treatment in the future if the etiologic background and prognosis are found to be more distinct from other forms of alcoholism.

In the late 1970's and early 1980's continuous scales for alcoholism were developed. They anticipated Cloninger's type 2 alcoholism since they measured polydrug abuse, gregarious drinking style, young age, and antisocial attitudes (Horn et al., 1977; Skinner, 1981; Skinner and Allen, 1983). Moreover, these scales measure the quantity of drinking and account for loss of control while being under the influence, issues that are absent in the current DSM and ICD definitions of alcoholism.

4.6 Physiological factors

The majority of the Finnish violent crimes are committed impulsively under acute alcohol-intoxication by individuals who suffer from type 2 alcoholism, a condition that features antisocial behavior, early age at onset of drinking, and severe familial alcoholism. The strong hereditary component of type 2 alcoholism and the biological abnormalities found in type 2 alcoholics suggest that biological factors may be strong causal predictors of violent behavior. Distinct biological factors – apart from behavioral and environmental factors – may also explain why some individuals tend to be particularly irritable and aggressive during acute alcohol-intoxication. However, only a few prospective studies have examined purely biological causes of violent behavior. The studies by *Virkkunen et al.* (1989, 1996, 2007, 2009) have shown that cerebrospinal fluid (CSF) monoamine metabolites and non-oxidative glucose metabolism (low glycogen formation) are the strongest biological variables predicting recidivistic violent offending.

Low central serotonin levels have been argued to correspond with impulsive-aggressive behavior (Coccaro, 1989a,b; Virkkunen et al., 1995). Low monoamine levels in the CSF, particularly 5-HIAA, have been observed among impulsive-aggressive individuals (Brown et al., 1979, 1982; Linnoila et al., 1983; Virkkunen et al., 1989, 1996). Low CSF 5-HIAA levels have been observed to differentiate impulsive from nonimpulsive violence (Linnoila et al., 1983).

After a preliminary finding according to which low urinary free cortisol levels associate with habitually violent offenders having ASPD (Virkkunen et al., 1985) a line of research advocates that hypoactivity of the pituitary-adrenocortical axis (McBurnett et al., 2000; Brewer-Smyth et al., 2004) and high testosterone levels (Popma et al., 2007; Sjoberg et al, 2008) connects to antisocial behavior and aggressive CD. An inverse correlation between severity of psychopathic traits and serum cortisol levels in young adult male violent offenders has been observed (Holi et al., 2006).

Moreover, decreased perfusion and glucose metabolism in the frontal cortex (see Bufkin and Luttrel, 2005), increase in adult slow wave sleep (Lindberg et al., 2003a,b), and function of the amygdala and various other brain areas (New et al., 2007) have been associated to impulsive-aggressive ASPD and BPD. It is unclear how these scattered observations of abnormal physiology in impulsive-aggressive ASPD and BPD ties together. Integrative studies are needed. For instance, the finding that slow wave sleep seems to be connected with both growth hormone and cortisol levels, and their balance, in healthy men (Steiger, 2003; van Cauter et al., 2000) suggests that these physiologic functions should be studied as one entiety rather than in separate studies.

4.7 Brain structure

The German Physician Franz Joseph Gall (1758—1828) is considered the founding father of phrenology – a science hypothesizing that the shape of the skull correlates with personality and outcome in life. Phrenology assumed that the shape of the scull described variation in 27 areas of the brain of which one was the carnivorous instinct, a tendency to

murder. Later, Cesare Lombroso (1835—1909), an Jewish-Italian army surgeon and founder of the Italian School of Positivist Criminology, extended phrenology to serve criminology. Lombroso hypothesized that criminality was hereditary and visual signs of criminal tendencies were forward projection of large jaws, low sloping forehead, high cheekbones, flattened or upturned nose, handle-shaped ears, hawk-like nose, fleshy lips, hard shifty eyes, scanty beard, baldness, insensivity to pain, and long arms (Lombroso, 1887). Today, phrenology is considered a pseudo-science. Modern neuroimaging, however, could be argued to partly parallel forensic phrenology in that modern neuroimaging connects psychopathy, antisocial behavior, and violence with both neuroanatomical and neurofunctional abnormalities – findings inside the skull rather than outside the skull.

Modern neuroimaging has found variation in the structures and function of the brain in various criminality related phenomena. In a review *Yang et al*. (2008) concluded that antisocial individuals have abnormalities in the prefrontal cortex (particularly orbitofrontal and dorsolateral prefrontal cortex), superior temporal gyrus, amygdala-hippocampal complex, and anterior cingulated cortex. Despite significant brain abnormality findings among antisocial individuals in small samples, it is too early to make bold conclusions about criminal tendencies or legal responsibility based on these findings since the studies do not reveal causalities and the groups of criminals under examination have been heterogeneous.

4.8 Genes

4.8.1 Monoamine oxidase A (MAOA)

4.8.1.1 Genetics and enzyme activity

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 enzyme (Denney et al., 1999; Sabol et al., 1998). Alleles vary in the number of copies of a 30-bp repeat sequence (2, 3, 3.5, 4, or 5); the 4- (high activity [MAOA-H]) and 3-repeat (low activity [MAOA-L]) alleles are the most common. The 3.5-repeat allele is considered to be a MAOA-H allele whereas the 5-repeat allele belongs to the MAOA-L group. The MAOA activity is 3 times higher among the 4-repeat allele as compared with the 3-repeat allele (Denney et al., 1999). Although MAOA genotype has been widely considered to correspond with both MAOA enzyme activity and quantity (Denney et al.,

1999; Sabol et al., 1998), it has also been argued that brain MAOA activity does not correspond to MAOA genotype in healthy male subjects (Fowler et al., 2007).

The impact of MAOA genotype on serotonin metabolism is unclear but according to one hypothesis, MAOA activity is presumed to correlate inversely with central nervous system monoamine metabolites. To date, however, inverse correlations have been observed only between lumbar CSF homovanillic acid (HVA) and high activity MAOA (Ducci et al., 2006), and between CSF 3-methoxy-4-hydroxyphenylglycol (MHPG) and the low activity variant (Sjoberg et al., 2008), both findings in Finnish male alcoholic offenders. No robust association has been found 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-HT1A receptor availability measured by positron emission tomography indicating higher serotonergic level as compared to women with the high activity genotype (Mickey et al., 2008). However, a trend in the opposite direction was found among men (Mickey et al., 2008). Altogether, a prevailing hypothesis assumes that high MAOA activity associates with low central serotonin.

4.8.1.2 MAOA genotype and aggression

Brunner et al. (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 1–3 days, during which the affected male would suffer from insomnia. Some 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). Both MAOA genotypes may contribute to aggression and violence (Nelson and Trainor, 2007). The MAOA enzyme activity contingent on MAOA genotype has a wide inter-individual variance and it seems possible that MAOA activity displays a "U"–curve effect on human aggression: at the high MAOA activity extreme, aggression may surface as impulsive violence, and at the low MAOA activity extreme, as premeditated violence. In sum, a clearer distinction between impulsive and nonimpulsive violence may help to explain mixed results in research relating MAOA to violence.

4.8.1.3 MAOA genotype and alcohol dependence

Beyond descriptive typology and classification of alcoholism, some advance has been made in the search for genetic causes of alcohol dependence. An analysis based on a large sample of adult twins (n = 9 897) suggests that hereditability accounts for 50–60% of alcohol dependence (Goldman et al., 2005).

The serotonin catabolising enzyme MAOA has caught some attention in the field of alcohol research. The associative literature on the connection of MAOA with alcoholism has not, however, been able to reach a consensus whether the low or high MAOA activity genotype is the risk-genotype. Samples and study settings have varied greatly and confounding factors have rarely been accounted for. Table 2 summarizes the associative reports in the field and shows, importantly, that many studies have also failed to find a direct association of MAOA genotype with alcoholism. However, an association of the low activity MAOA genotype with alcoholism has been reported by some studies (Guindalini et al., 2005; Parsian and Cloninger, 2001; Samochowiec et al., 1999; Schmidt et al., 2000). Other studies found that the low activity allele increased risk for alcoholism only among subjects exposed to environmental stressors (Ducci et al., 2008; Nilsson et al., 2007; 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., 2008).

Table 2. Summary of MAOA-Alcoholism association studies.

Comparison groups	Result	Ethnicity	Gender
Controls vs. Pure-ALC			
Samochowiec et al. 1999	No	Ger	M
Lu et al. 2002	No	Chi	M
Parsian et al. 2003	No	C	M & F
Guindalini et al. 2005	No	C/A-B	M
Gade et al. 1998	Yes	C	M
Guindalini et al. 2005	Yes	C/A-B	Female
Controls vs. Anx/Dep-ALC			
Schmidt et al. 2000	No	Ger	M
Schmidt et al. 2000	No	Ger	Female
Controls vs. ASPD-ALC			
Parsian et al. 2003	No	C	M & F
Samochowiec et al. 1999	Yes	Ger	M
Schmidt et al. 2000	Yes	Ger	M
Parsian and Cloninger 2001	Yes	C	M & F
Controls vs. Pure-ALC and ASPD-ALC			
Parsian and Cloninger 2001	No	C	M & F
Parsian et al. 2003	No	C	M & F
Controls vs. Pure-ALC vs. ASPD-ALC			
Lu et al. 2003	No	Chi	M
Pure-ALC vs. ASPD-ALC			
Samochowiec et al. 1999	Yes	Ger	M
Controls vs. AB vs. ASPD vs. ASPD-ALC			
Lu et al. 2003	No	Chi	M
Anx/Dep-ALC vs. ASPD-ALC			
Schmidt et al. 2000	Yes	Ger	M

Controls=healthy controls, AB=antisocial behavior, ASPD=antisocial personality disorder, ALC=alcoholic, Anx/Dep=anxiety/depression, Ger=German descent, C=white Caucasian, Chi=Han Chinese, A-B=African-Brazilian, M=male, F=female.

4.8.1.4 MAOA genotype and impulsivity

Impulsivity has been shown to connect with the MAOA-H genotype in both healthy males (Cerasa et al., 2008; Manuck et al., 2000; Passamonti et al., 2006) and individuals with mental disorders (Gade et al., 1998; Manor et al., 2002; Ni et al., 2007, 2009). Borderline personality disorder, featuring impulsivity as a core symptom, has been associated with a high frequency of MAOA-H in comparison to healthy controls (Ni et al., 2007).

4.8.1.5 MAOA genotype and childhood maltreatment

Caspi et al. (2002) observed that even though childhood maltreatment has been considered a risk factor for later acts of violence, the risk was only increased among children carrying the MAOA-L genotype (OR 9.8 vs. nonsignificant figures for MAOA-H). Replication attempts have shown mixed results (Table 3).

Although the negative effects of childhood maltreatment are based on robust findings with various definitions of maltreatment, the definition of childhood adversities is particularly important in the examination of the relations between genes and environment since pure gene—environment interactions are difficult to discover and the possibility of spurious results is high (Eaves, 2006; Jaffee and Price, 2007). Possible gene—environment correlations (rGE) should be controlled for in statistical analyses. For instance, early onset conduct disorder may be an evocative rGE factor and parental problem drinking a passive rGE factor. The rationale behind this is that the pure environmental effect of maltreatment could be biased by parental aggression arousal caused by misbehavior of the child and, on the other hand, parental problem drinking (a putative genetic predisposal) could increase the level of physical abuse.

Despite the seemingly similar settings in studies examining gene—environment interactive effects on the risk for violence, antisocial behavior, and conduct disorder there is considerable variance between study settings. Table 3 summarizes study designs and results of some replication attempts of the study of Caspi et al. (2002).

Table 3 Summary of MAOA by maltreatment interaction studies.

	Maltreatment		Outcome measure	Main effect	Interaction
	Type	Exposure period			
Caspi et al. (2002)	a, e, d	C	CD, AB, V	M	L
Foley et al. (2004)	n, ipv, d	A	CD	M	L*
Haberstick et al. (2005)	a, n	C	CD, AB	M	-
Kim-Cohen et al. (2006)	a , ipv	C	AB, MH	M, H	L
Huizinga et al. (2006)	a	A	AB, V	M, H*	-
Nilsson et al. (2006)	ps	A	AB, V	M	L
Reif et al. (2007)	ps	C	V	M, L	-
Widom and Brzustowicz (2006)	a, n	C	AB, V	M	L
Young et al. (2006)	n, a	C	CD	M	-
Ducci et al. (2008)	a	C	AB, ALC	M	L
Prichard et al. (2008)	a, e, d, n	C, A	AB	M	-
Nilsson et al. (2007)	ps	A	APB	M	L
Nilsson et al. (2008)	ps	A	APB	M	H
Weder et al. (2009)	a	A, C	AG, AB	M	L

*a=physical or sexual abuse, e=emotional absence of parents due to rejection, loss, or divorce, n=parental neglect, ipv=interparental violence, d=inconsistent, erratic, or coercive discipline, ps=psychosocial measures, C=childhood, A=adolescence, CD=conduct disorder, AB=antisocial behavior, V=violence, APB = alcohol related problem behavior, AG = aggression, L= low activity MAOA, H=high activity MAOA. * A marginally significant result or trend.*

Altogether, variation in the definitions of maltreatment, outcome measures, samples, statistical power, and age of exposure to maltreatment between studies may explain the mixed results. *Kim-Cohen et al.* (2006), however, conducted a meta-analysis to summarize the results in the MAOA by maltreatment research field. The authors arrived at the conclusion that a MAOA genotype by maltreatment interaction exists so that children carrying the MAOA-L genotype are at a greater risk for later antisocial behavior.

These discoveries suggesting that genotype may determine vulnerability to childhood maltreatment lay important fundaments for preventive work and risk assessments in the future since they imply that one group of individuals are vulnerable to maltreatment and suffer from the negative effects while another group seems to be relatively indifferent to noxious environments.

4.8.2 Other candidate genes

The rapidly proceeding mapping of the human genome has generated new discoveries of genetic causes of diseases. DNA analyses have become cheaper and whole genome wide scans can be performed with moderate effort. Genome wide linkage, association, and expression analyses allow hypothesis-free mapping of disease loci. In addition to MAOA genotype, several other genetic abnormalities have been associated with aggression, alcohol-related disorders, and impulsivity.

The 5-HT3 receptor modulates dopamine release in mesolimbic dopaminergic neurons, mediate fast excitatory neurotransmission of serotonin, mediate reward, and the 5-HT3 receptors are also potentiated by acute alcohol exposure (Johnson, 2004b) – all facts that point in the direction that the 5-HT3 receptors are likely to be involved in the etiology of alcoholism. In line, *Ducci et al.* (2009) found, by using EEG signalling, that the 5-HT3B receptor gene is associated with type 2 alcoholism.

In samples similar to the sample under examination in the study at hand, a growing number of genes have been preliminarily associated with alcoholism: gamma-aminobutyric acid type A alpha 2 (GABRA2) (Edenberg et al., 2004; Enoch et al., 2006, 2009), gamma-aminobutyric acid type A gamma 1 (GABRG1) (Enoch et al., 2009), galanin (GAL) (Belfer et al., 2006), and galanin receptor gene GALR3 (Belfer et al., 2007).

Antisocial personality disorder in alcoholics has been associated with nucleotide sequence variations within the human tyrosine kinase B neurotrophin receptor gene (NTRK2) (Xu et al., 2007). Associated to BPD, *Ni et al.* (2009) discovered gene—gene interactions between 5-HT2C and TPH2, and among 5-HT2C, 5-HTT, MAOA and TPH2. Moreover, as described by *Hariri et al.* (2009), the endocannabinoid signalling may modulate trait impulsivity. The 9-repeat allele of dopamine transporter (DAT1) gene has recently been associated with angry-impulsive personality traits (Joyce et al., 2009).

Some preliminary evidence exists that the serotonin transporter (5-HTT) genotype associates with alcoholism. *Johnson et al.* (2008b) showed that carriers of LL and LS alleles of the 5-HTT gene consumed larger quantities of alcohol than did the carriers of the SS allele and that 5-HTT polymorphism predicts chronicity and severity of drinking in a racially and gender mixed sample of type 1 alcoholics. In line, *Nilsson et al.* (2005) showed that the LS allele had a main effect on risk for alcohol consumption and intoxications in a school sample of adolescent males and females. However, the S allele (corresponding to reduced central serotonin) has been associated with type 2 alcoholism among impulsive violent offenders in comparison to type 1 alcoholics and healthy controls (Hallikainen et al., 1999).

Tryptophan hydroxylase 2 (TPH2) is a rate-limiting enzyme for 5-HT synthesis in adult brain (Zhang et al., 2004) and a mutation in the gene encoding for TPH2 may result in a 80% reduction of central 5-HT levels (Zhang et al., 2005). Mild exploratory behavior and threatening postures have been associated with dysfunction of TPH2 in knockin mice (Beaulieu et al., 2008). There are some preliminary findings that TPH2 gene polymorphisms and MAOA functional variants are in gene—gene interactions among impulsive BPD individuals (Ni et al., 2009). The functional polymorphism in TPH2 gene, however, has not yet been found.

Glycogen synthase kinase (GSK3β) is a protein kinase that mediates the addition of phosphate molecules on certain serine and threonine amino aids in particular cellular substrates. Recently, the GSK3β gene has been shown to be involved in the dysregulation of 5-HT neurotransmission. *Beaulieu et al.* (2008) showed that GSK3β mediates signalling in 5-HT functions and the researchers claim that GSK3β is an important pathway through which brain 5-HT deficiency induces abnormal behavior. They showed that high GSK3β activity was associated with major central 5-HT deficiency in R439H Tph2 mice and that a reduction of GSK3β antagonizes behavior such as threatening postures and mild exploratory behavior.

Preliminary evidence exist that GSK3β is inhibited in the medial prefrontal cortex at acute alcohol challenge in alcoholic rats in a study setting where rat lines have been bi-directionally bred over 90 generations for high- and low-ethanol consumption, respectively, with the purpose of enriching alleles that affect alcohol preference and probably the vulnerability to abuse potential (Neznanova et al., 2009). These observations may, in the future, prove to be crucial in the understanding of the divergent morbidity associated with reduced central serotonin levels.

The enzyme free acid amide hydroxylase (FAAH) degrades fatty-acid amides (Cravatt et al., 1996) and regulates endocannabinoid signalling. A common single nucleotide polymorphism (C385A; rs324420) in the human FAAH gene putatively enhances endocannabinoid signalling by decreased degradation and has been associated with problem drug use (Chiang et al., 2004). Using imaging genetics *Hariri et al.* (2008) showed in 82 healthy adults that carriers of FAAH 385A had decreased threat-related amygdala reactivity but increased reward-related ventral striatal reactivity in comparison with C385 homozygotes. They showed that relative to C385 homozygotes, FAAH 385A carriers showed a diminished relationship between amygdala reactivity and trait anxiety, and that the 385A carriers exhibited marked increase in behavioral index of impulsivity

and reward sensitivity. The authors discuss that decreased threat-related amygdala reactivity and associated trait anxiety may contribute to the emergence of pathologies such as addiction and obesity by reducing the sensitivity of these individuals to potential environmental threat or harm, likewise, an increase in reward-related reactivity and associated impulsivity may contribute to disinhibitory psychopathologies through heightened reward sensitivity and impulsive decision making.

Other recent results show that impaired FAAH function may confer a phenotype of high voluntary alcohol intake (Hansson et al., 2007). Thus FAAH is both a potential susceptibility factor and a therapeutic target for alcohol dependence. Interestingly, FAAH function seems to be connected also with high GSK3β and coexistent low glycogen synthase activity (Neznanova et al., 2009).

Abnormalities in the corticotropin-releasing hormone-binding protein (CRH-BP) genotype and resting EEG have been associated with anxiety disorders and alcohol use disorders suggesting that stress-related alcoholism may be a distinct intermediate phenotype (Enoch et al., 2008). Genetic risk for poor stress-resiliency is likely mediated through a broad set of genes.

4.9 Risk assessment of violent behavior

4.9.1 Assessment of individual risk for violent behavior

One reason for the emergence of acutuarial instruments is that unaided clinical risk assessments have been considered poor (Gardner et al., 1996; Monahan et al., 2001). Actuarial instruments collect both clinical and historical data and aim at detecting risk for acts of violence on an individual case level. Structured clinical assessments (e.g., personality traits [impulsive control, affect regulation, narcissism, paranoid cognitive personality style, psychopathy], lifetime mental disorders [e.g., substance abuse], current mental health) is one method of estimating risk of acts of violence, but their long-term efficacy is unclear (Dolan and Doyle, 2000; Gray et al., 2004, 2008; Leistico et al., 2008; Monahan, 1984; Mossman, 1994; Nestor, 2002). Historical variables such as previous crime, previous violent behavior, and unemployment, however, have been stronger predictors of violent behavior as compared with clinical variables (Bonta et al., 1998; Gray et al., 2008; Mossman, 1994). A partly unacknowledeged issue is that ASPD diagnosis and psychopathy comprise a considerable amount of historical (anamnestic) data.

The numerous different actuarial instruments have limited and varying prediction accuracy due to the multi-factoral causes and complexity of violent behavior, changing clinical status, and accumulating life-events. For intance, actuarial instruments rarely account for childhood environments and do not directly describe biological variance, which both indisputably predict violent behavior.

The Revised Psychopathy Checklist (PCL-R) (Hare, 1991) is a risk assessment instrument that examines historical variables (previous criminality and other items closely related to ASPD diagnosis), assessment of personality features (e.g., superficial charm, pathological charisma, superficial emotional life, lack of remorse, lack of guilt, and lack of empathy; features similar to psychopathy as suggested by *Cleckley* in the 1940's [see Cleckley, 1976]), and inter-personal style (e.g., manipulativeness, deceitfulness, unpredictable commitment). *Leistico et al.* (2008) conducted a meta-analysis (n = 15 826) on the efficacy of PCL-R to predict antisocial conduct (including violence). They concluded that the effect size of PCL-R is moderate but it varied greatly between different samples (country, racial composition, gender, institutional setting, and type of information used for rating), and that the historical items tended to show greater efficacy than personality features.

The Historical, Clinical and Risk Management Scales (HCR-20) (Webster et al., 1997) is an actuarial instrument designed to assess risk among psychiatric patients. It offers the advantage of accounting for past, present, and future risk variables, with an emphasis on historical variables. Ten items relate to history (e.g., mental illness, employment problems), 5 to current clinical status (e.g., mental illness symptoms, lack of insight), and a further 5 to future risk variables (e.g., non-compliance, poor social network). *Gray et al.* (2008) examined a sample of 887 males, mean age 38, discharged from medium secure units. They arrived at the conclusion that there is an evidence base for the use of the HCR-20 for the prediction of acts of violence in male psychiatric patients discharged from secure units.

An ideal prediction instrument gives a correct yes/no answer to the question whether an individual is "dangerous" or not. A risk instrument comprising a continuous scale allows adjustment of the "cut-off" point which determines the false positive (overprediction) and false negative (underprediction) rates. An overprediction may be a concern for the legal right of the individual whereas an underprediction may worry the public. Reasonably, actuarial instruments should be applied to aid professional risk assessments of probability of future violent behavior rather than to arrive at "blind" absolute answers.

Hart et al. (2007) recently challenged the reliability of actuarial instruments by estimating the "margins of error" of group vs. individual predictions of violent behavior with rigorous statistics and concluded that the 95% CI were large for risk estimates at the group level in the first place, but on individual level they were so high as to render risk estimates virtually meaningless. The debate about the utility of actuarial instruments and prediction of violence will not end soon.

4.9.2 Meaningful statistical methods and study settings

The literature conveying prediction of violent behavior holds an important methodological bias – namely – the majority of factors that have been connected to criminality and violent behavior are constructed on associative/correlational statistical analyses. Consequently, results do not reliably describe actual risk on individual case level or even on group level.

Effect size analyses such as logistic regression analyses, receiver operating characteristic (ROC), attributable risk, and relative risk, on the other hand, are clinically meaningful statistical methods that describe actual risk, even though they carry a propensity to slight exaggeration (Talfryn et al., 1998). However, effect size analyses can also be misinterpreted. In the research field of efficacy of actuarial instruments, for instance, meta-analyses conclusively use effect size analyses to integrate results in the field, but still, the statistical methods may not allow accurate and fair application of results on an individual case level. Moreover, the base rate of violence in the population under examination robustly biases results if effect size analyses are not applied (Mossman, 1994).

The presentation of percentage figures in reports serve as an example of the advantage of follow-up settings over cross-sectional study designs, namely, even though point prevalence figures can be informative and easy to interpret they become significantly more important in a follow-up setting detecting cumulative incidence. High cumulative incidence figures in a distinct group with common characteristics may serve as a clue for effect size study settings that offer the possibility to account for confounding variables. Similarly, when a costly and inconvenient long-term follow-up is impossible to conduct, a cross-sectional study setting that uses logistic regression modelling (case-control study design) gives far more reliable information that corresponds with actual risk than mere associational statistics.

Mossman (1994) reanalysed 58 data sets presented in previous studies on violence prediction (comprising a multitude of different predictors) with rigorous statistical methods. He discovered that the accuracy (AUC figures) of short-term studies (0.70) has a propensity to be higher as compared with long-term studies (0.64) and that clinical predictions are better than chance (0.50). The average AUC in newer studies was clearly higher than the average for the older studies, but that may reflect a publication bias (negative results are liable to remain unpublished) which also biases the whole science of violence prediction. Retrospective studies arrived at higher mean AUC as compared with prospective studies.

There is a lack of prospective long-term outcome studies, especially non-incarcerated follow-ups. The roots of modern prospective studies on criminal populations were planted by L. N. Robins, who presented a study in 1966 on the outcome of young delinquents (Robins, 1966). She suggested that adolescents with conduct symptoms and an antisocial father were at a high risk for mental disorders and adulthood criminality (including violence).

In sum, effect size statistical approaches and long-term follow-up study settings are able to reveal which correlates of violent behavior are true causes and risk factors of violence.

5 Aims of the study

5.1 Study I

Temperament profiles (TPQ) within a violent offender population and healthy controls were compared. The associations of violent crime types to severe personality disorders were also examined.

5.2 Study II

The odds and relative risk for reconviction or death were examined. The risk factors under examination were a) a diagnosis of ASPD, BPD, or both, b) adverse childhood environments including violence both involving and not involving the child, and c) combination of maltreatment and ASPD or BPD diagnosis.

5.3 Studies III and IV

The effects of MAOA genotype on alcohol consumption, ageing, and childhood physical abuse (CPA) were examined.

6 Methods

6.1 Subjects

6.1.1 Study I

The sample comprised 198 males and formed a subsample of the sample examined in study II. Originally 242 offenders were asked to complete a TPQ, but eventually 198 returned a completed questionnaire. The subjects had been convicted of 11 crimes (including nonviolent crimes) at average at the time of inclusion.

Controls were 170 healthy volunteers matched by age and gender. They were recruited through newspaper advertisements and they underwent the same TPQ and lifetime DSM-III-R evaluation as the offenders. Originally 181 responders were interviewed. Eleven (6%) were excluded due to diagnosed major depression, dysthymia, panic disorder, or BPD. The occupations of the controls were dockworkers, fire fighters, mail carriers, police officers, vocational students, and a few university students.

Mean age was 30.7 years in the ASPD group (SD 8.6, 18–52), 35.7 in the non-ASPD group (SD 10.4, 18–67), and 30.7 in the control group (SD 9.9, 18–59); $F = 6.387$, $p = 0.002$.

6.1.2 Study II

Subjects comprised 242 habitually violent alcoholic male offenders recruited between 1990 and 1998 during a court-ordered 2-month inpatient mental status examination at the Department of Forensic Psychiatry of Helsinki University Central Hospital. The sample included many subjects who had participated in recent studies concerning Finnish 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. The majority of the offenders belonged to lower socioeconomic groups. Their occupational status included mainly semi-skilled workers. Many subjects were unemployed at the time of recruitment in the study. The controls were 1210 individuals matched by sex, age, and place of birth who were randomly included from a national register (Statistics Finland) with five controls for each violent offender.

Recidivists or deceased offenders as a group were aged 32.4 (SD 10.3) and nonrecidivists 33.4 (SD 9.3) at inclusion. The difference was nonsignificant ($F = 0.674$, $df = 1$, $p = 0.413$). However, a small difference in mean age emerged between recidivists (30.2, SD 9.0) and nonrecidivists (33.3, SD 9.3); $F = 5.245$, $df = 1$, $p = 0.023$.

Recidivists or deceased offenders as a group had an intelligence quotient of 95.4 (SD 13.3) and nonrecidivists had an intelligence quotient of 98.2 (SD 15.1). The difference was nonsignificant; $F = 2.182$, $df = 1$, $P = 0.14$. Neither was there a difference in

intelligence quota between recidivists 95.1 (SD 13.1) and nonrecidivists; F = 2.936, df = 1, p = 0.09.

6.1.3 Study III and IV

Study III and IV included 174 Finnish violent alcoholic offenders. It was a MAOA genotyped subsample of the sample in study II (including recidivistic and nonrecidivistic offenders, excluding deceased offenders). Mean age at the time of evaluation was 32.5 (SD ± 9.7), and mean IQ (WAIS) was 97.2 (SD ± 14.5).

6.2 Personality disorders

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, USA. The distributions of mental disorders in the samples were essentially equal.

Study I: The SCID I and SCID II diagnoses, and a comparison of them between ASPD and non-ASPD participants are presented in Table 1 in study I. The ASPD group (114 out of 198; 58%) seemed to comprise more BPD than the non-ASPD group but the difference was non-significant (p=.06). The sample comprised 50 (25%) participants with an ASPD-BPD comorbidity.

Study II: The most prevalent Axis II diagnoses were ASPD (136; 56%), BPD (94; 39%), and ASPD–BPD comorbidity (60; 25%). All subjects received a diagnosis of alcohol dependence or alcohol abuse. Conduct disorder was diagnosed in 62% (151) of the subjects.

Study III and IV: Axis II diagnoses were pure ASPD (61; 36%), pure 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.

6.3 Tridimensional personality questionnaire (TPQ)

The assessment of temperament dimensions was performed with Cloninger's TPQ, a 100-item questionnaire that measures three hereditary and genetically distinct personality dimensions: novelty seeking (NS), harm avoidance (HA), and reward dependence (RD), each of which consists of four lower-order dimensions (Cloninger 1987a). The TPQ is a self-report questionnaire that takes 20-30 minutes to complete. In order to decrease mitigating answers the total question-set contains 17% non-scored questions. The validity

of the questionnaire seems to be good according to a large psychometric investigation in the Finnish general population (Miettunen et al., 2004). The present study gives information of the relevance of TPQ in Finnish alcoholic offenders.

6.4 Assessment of violent behavior, mortality, and follow-up

6.4.1 Index and outcome crimes

6.4.1.1 Study I

The frequency distribution of offenses was as follows: homicide (n = 99; 50%), attempted homicide (39; 20%), assault-battery-robbery as a group (18; 9%), arson (34; 17%), and rape (8; 4%).

6.4.1.2 Study II

The index crimes were generally serious, impulsive, and committed under the influence of alcohol. The frequency distribution of index offences was as follows: homicide (n = 119; 49%), attempted homicide (50; 21%), assault-battery-robbery as a group (22; 9%), arson (42; 17%), and rape (9; 4%).

The outcome crimes (n = 77) were homicide (32; 41.5%), attempted homicide (19; 24.7%), assault-battery-robbery taken as a group (13; 13.9%), arson (9; 11.7%), and rape (4; 5.2%).

6.4.1.3 Study III and IV

The index crimes 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 were 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 frequently occurring subjective experience reported by the offenders was that of amnesia and loss of behavioral control during the act of violence. The grouping of crimes was different from the grouping in study I and II with the rationale to display the mainly impulsive nature of the crimes (manslaughter, assault, or battery vs. premeditated murder). The index crimes were manslaughter, attempted manslaughter, assault, or battery (61%), murder or attempted murder (19%), arson (16%), and rape (4%).

The distribution of the outcome acts of violence (n = 69) was manslaughter, attempted manslaughter, assault, or battery (56; 81.2%), murder or attempted murder (5; 7.3%), arson (5; 7.3%), and rape (3; 4.3%).

6.4.2 Register data and follow-up time

6.4.2.1 Study II

Register data were obtained in august 2005. Criminal records, provided by the Legal Register Centre were examined for violent crimes. Statistics Finland contributed with mortality data. The end point of the follow-up for recidivists was the time of the first reconviction, for nonrecidivists august 2005, and for the deceased the time of death.

The total follow-up period (from inclusion until the examination of criminal register in August 2005) lasted 11.3 years (135 months, range 82–182). We subtracted time spent in prison from the total follow-up time for those with this information available (n = 178). For the deceased offenders (n = 39) time spent in prison was unavailable due to register policy of destroying criminal records after death, which holds a slight bias such that the actual non-incarcerated follow-up was shorter. The deceased offenders may have committed a recidivistic offence before death, which was a rationale for examining the recidivistic offenders and the deceased offenders as one "poor prognosis" group.

The Legal Register Centre's register policy also sees to it that in cases of minor sentences (less than two years) register records are expunged after a 10-year conviction-free period, which partly limited the accuracy of our follow-up time since time spent in prison was unknown in 25 nonrecidivistic cases. Those 25 nonrecidivistic offenders whom were examined 1990–1994 (convicted of assault, battery, or arson) were followed from the initial examination to august 2005, which gave them a slightly longer follow-up than the actual non-incarcerated time. Altogether, the actual mean non-incarcerated follow-up period was 8.7 years (104 months, range 3–182) for the whole sample.

The offenders were divided into three comparison groups: recidivistic offenders, deceased offenders, and non-recidivistic offenders. The primary comparison was between recidivists or deceased offenders ("poor prognosis group") vs. the nonrecidivistic offenders. The secondary comparison was between the recidivists and nonrecidivists.

6.4.2.2 Study III and IV

Recidivism in violent behavior was assessed in the same manner as in study II. The total follow-up period was 11.7 years (140 months, range 85–182). The non-incarcerated follow-up period was 8.1 years (97 months, range = 3–182).

6.5 MAOA

The MAOA polymorphism (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, USA). A detailed description of the genotyping method appears elsewhere (Ducci et al., 2006).

As the study sample composed only males, the genotypes were grouped based on relative transcriptional activity into two categories: high-activity (4- repeats) vs. low-activity (3-repeats). These two alleles accounted for 97% of the MAOA-LPR variety among the offenders (4-repeats, 0.56 and 3-repeats, 0.44). The distribution of MAOA-H and MAOA-L alleles was similar to those in other Caucasian male samples (Caspi et al., 2002; Gade et al., 1998; Manuck et al., 2000; Ni et al., 2007; Reif et al., 2007; Weder et al., 2009).

6.6 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. *Heavy drinking* was defined as alcohol consumption ≥ 70 kg per year matching the upper quartile of the sample (n = 43).

6.7 Childhood adversities

6.7.1 Childhood maltreatment and familial adversity (Study II)

The definition of childhood maltreatment was similar to that by Caspi et al. (2002). The childhood history was obtained from multiple face-to-face interviews (each participant was interviewed by a psychiatrist, psychologist, psychiatric nurse, and social worker as part of a standard mental examination), by structured questionnaires about family history sent to first-degree relatives, and through collateral information collected from health-care and social service documents. The primary source of information was the face-to-face-interviews and the family members' assessment of the offender. In uncertain cases the classification was completed with the collateral information. To define childhood maltreatment (before age 13) we used three specific exposure components: (1) major

emotional absence of either parent due to divorce, separation, or death, (2) considerably inconsistent/irresponsible parenting, and (3) physical abuse. A continuous variable were a "yes" answer to any specific exposure scored as one point and a "no" answer scored as zero was formed, resulting in a scale of 0–3. Further, a total exposure score of 0 or 1 points was termed as "no maltreatment" (177/242; 73%) whereas an exposure score of 2 or 3 points was termed "maltreatment" (65/242; 27%). The classification was carried out independently by RT and MV with an interrater reliability of 0.90 (Spearman's rho correlation coefficient, $p<0.01$). In the few cases where the classification differed a consensus was reached by an open re-evaluation.

Familial adversity was defined as a childhood environment comprising both excessive substance abuse and violence not directly involving the child. Data collection was performed in the same manner as information on childhood maltreatment.

6.7.2 Childhood physical abuse (CPA) (Study IV)

Information on childhood exposure to physical abuse was obtained from the same multiple sources as in study II. CPA was defined as exposure to physical abuse before age 13 (n = 51; 29%). Sporadic abuse was not classified as an exposure event. The abuse had to be pronouncedly traumatic (assessment by the subjects or relative) or reported as a recurrent problem. Blinded to MAOA genotype, the classification was carried out independently by RT (all cases) and MV (20 cases) with an interrater reliability of 0.90 (Spearman's rho correlation coefficient, $p < 0.01$). All subjects received a classification. The classification of two subjects was determined through an open re-evaluation.

6.8 Statistical analyses

6.8.1 Study I

The variance analysis of TPQ mean scores was performed with the Kruskal-Wallis test and pairwise comparisons with the Dunn's test. These conservative non-parametric methods were applied to reduce the possibility of type I error, as all dimensions were skewed or kurtotic, or both. The Kolmogorov-Smirnov method served to test the normality of the data. The Pearson Chi-Square and Fisher's exact tests were applied in frequency distribution comparisons of diagnoses and types of crimes. ANOVA was applied to compare the variance of age. Analyses were performed with SPSS 14.0.

6.8.2 Study II

Pearson's Chi-Square test was applied for frequency distribution comparisons. Spearman's correlations coefficients were calculated for predictor-pairs prior regression analyses to examine the independence of variables (Table 1 in study II). For odd ratios, the following age-adjusted forced entry multinomial logistic regression analyses were run with outcomes a) recidivistic violence or death, or b) recidivistic violence: I. ASPD, BPD, maltreatment, and familial adversity as independent variables; II. CD, maltreatment, and familial adversity as independent variables; and III. comorbid ASPD and BPD, maltreatment, and familial adversity as independent variable. The effect of age on risk for outcomes was examined using binary logistic regression analysis. ROC analysis allowed examination of the variables' ability to correctly classify outcome. Variance and relative risk calculations were applied to assess further effect sizes. Kaplan-Meier survival analysis was run to show the incidence of outcome observations over time. The significance level was set at 95% CI. The analyses were performed with SPSS 14.0 software for Windows.

6.8.3 Study III

Bonferroni- and age-corrected general linear model univariate analyses were conducted for comparison of alcohol consumption means for the whole sample, recidivistic vs. non-recidivistic 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 ageing as independents. The level of significance was set at 95% CI. Analyses were performed with SPSS 15.0 for Windows.

6.8.4 Study IV

The Pearson Chi-Square and Fisher's exact tests were applied for frequency distribution comparisons. Correlations were examined with the Pearson and Spearman's rho tests. Univariate analysis of covariance (ANCOVA) was used to examine interaction between MAOA genotype and CPA for alcohol consumption. Analyses were adjusted for age and Bonferroni correction was used in post hoc multiple comparisons

Four logistic regression models were constructed to examine risk for impulsive acts of violence (dependent). The first model, adjusted for age, included MAOA genotype, *heavy drinking* and CPA as independents and interaction terms were tested. The same procedure was applied for both MAOA genotypes separately. To avoid spurious results caused by possible gene—environment correlations (rGE), we included early onset conduct disorder (evocative rGE factor) and parental problem drinking (passive rGE factor) as covariates in the logistic regression analyses. The rationale behind this, on one hand, was that the pure environmental effect of CPA could be biased by parental aggression arousal caused by the

misbehavior of the child and on the other hand, parental problem drinking could increase the level of physical abuse. The fourth regression model was constructed to assess the effect of different exposure and covariate combinations on risk for acts of impulsive violence among MAOA-H offenders. The level of statistical significance was set at 0.05 and analyses were carried out with SPSS 16.0.

6.9 Ethics and permission

Written informed consent was obtained from all subjects after the procedure had been fully explained. Procedures for appropriate protection of human rights were employed. The study was approved by the Ethical Committee of Helsinki University Central Hospital, Finland.

7 Results

7.1 Temperament and violent crimes (Study I)

7.1.1 TPQ scores and pairwise comparisons

The TPQ higher-order means of the entire offender sample were as follows: NS 18.7 (SD 4.8), HA 17.9 (SD 6.8), and RD 15.5 (SD 4.9), which showed importantly different in comparison with controls. TPQ mean scores and contrasts of the ASPD, non-ASPD, and control groups are displayed in Additional file 1 (Study I).

The significant differences (p-values) in a pairwise comparison between ASPD vs. non-ASPD offenders were as follows: NS 0.000; NS2 0.006; NS4 0.000.

The significant differences between ASPD offenders and controls were: NS .000; NS2 0.000; NS3 0.004; NS4 0.000; HA 0.000; HA1 0.000; HA2 0.000; HA3 0.000; HA4 0.000; RD 0.005; RD3 0.000; RD4 0.001.

The significant differences in pairwise comparison between non-ASPD offenders and controls were as follows: NS1 0.005; NS3 0.008; HA 0.000; HA1 0.000; HA2 0.000; HA3 0.000; HA4 0.000; RD1 0.036; RD3 0.002.

7.1.2 Groups of high and low harm avoidance

Trait HA was particularly non-normally distributed. A scatter-plot displayed a two-peaked curve with a kurtosis of –0.766 (SE 0.346) (unpublished). Subsequently, a notable over-representation of scores between 5 and 10 and between 25 and 30 appeared on the HA scale (0–34). Figure 1 shows the TPQ profiles of high and low HA offenders, ASPD offenders, and controls.

The frequency distribution of the ASPD diagnosis showed no difference ($\chi 2 = 0.367$, $p = 0.55$) between high- (60%) and low (55%) HA offenders. Nineteen low HA offenders lacked an ASPD diagnosis (19/42; 45%). There were more ASPD and BPD co-morbidities in the high HA group compared with the low HA group ($\chi 2 = 6.039$, $p = 0.009$). No difference in alcohol dependence occurred between the HA extremes ($\chi 2 = 0.98$, $p = 0.23$).

7.1.3 Crime comparisons

There were no significant differences in homicide, attempted homicide, assault-battery-robbery, or rape offences between the ASPD and non-ASPD groups, but arson was more frequent in the non-ASPD group ($\chi 2 = 16.388$, $p < 0.0004$).

Murder convictions were more frequent in the low HA offenders as compared with high HA offenders ($\chi 2 = 4.025$, $p = 0.04$). Assault-battery-robbery convictions were more

frequent among high HA offenders than among low HA offenders ($\chi 2 = 4.07$, $p = 0.03$. No other differences emerged in comparisons of offence types between high and low HA offenders.

7.2 Recidivism and mortality (Study II)

7.2.1 Risk for poor outcome and reconviction

Table 2 (in study II) shows the odds ratios for pooled outcome recidivistic offending or death, and recidivistic offending alone. The average variance of the multivariate logistic regression analyses explained 13% ($R^2 = 0.13$) of recidivistic offending or death and 19% ($R^2 = 0.19$) of the recidivistic offending on its own. The mean value of area under the curve (AUC) obtained from ROC analyses for the significant predictors were 0.61 for recidivistic offending or death and 0.62 for recidivistic offending. Table 3 (in study II) displays the relative risk for outcomes among the offenders and their subpopulations as compared with 1210 controls matched by age-, sex-, and place of birth.

7.2.2 Incidence of recidivism and mortality

The frequency of recidivism was 32% (77/242) in the whole sample, which equals an incidence of 3.7%. For controls, the cumulative incidence of violent offending was 5% (65/1210). Recidivism occurred on average within 2.3 years (28 months, median = 21 months) among the offenders. Offenders were aged 32 (SD = 9.0) at the time of the recidivistic offence.

A significant difference in mortality surfaced between offenders (39/242, 16%) and controls (52/1210, 4%); $\chi 2 = 47.98$, $p = 0.0004$. The incidence of death among the offenders was 1.8% (16%/8.7 years). The pooled death category comprising alcohol-related diseases, poisoning, and violence was greater among the offenders as compared with controls (19/39, 49% vs. 11/52, 21%; $\chi 2 = 7.66$, $p = 0.007$). Outcome death occurred on average at 5.9 years (71 months, median = 76) of follow-up among the offenders. Offenders were aged 43 (SD = 12.0) at death.

Maltreated BPD offenders protruded as a group of high risk with a cumulative incidence of 88% for recidivistic acts of violence or death as compared with 48% in the total offender population. A significant increase in risk for a poor outcome over time was observed in both maltreated BPD offenders and maltreated offenders (Fig 1 and 2 in study II).

7.3 Age as a predictor of reconvictions (studies II and III)

Study II suggested – not accounting for genotype – that ageing decreases the risk of violent reconvictions by 3.7% for every year (b = –0.037, SE = 0.02, W = 5.1, p = 0.025).

Study III replicated the finding of study II and suggested a 4.9% decrease in risk for every year in the whole sample (b = –0.049, SE = 0.21, W = 5.7, p = 0.017). Importantly, study III extended the finding of study II by showing that ageing decreased the risk only among MAOA-H offenders, not among the MAOA-L offenders. The decrease in risk among MAOA-H offenders was 7.3% for every year (b = –0.073, SE = 0.03, W = 6.0, p = 0.015).

7.4 MAOA and alcohol consumption (study III)

The MAOA genotype showed no main effect on risk for violent behavior in the first multivariate logistic regression model but the model suggested that a one kilogram increase in yearly mean consumption of ethanol increased the risk for reconvictions with 1.4% (b = 0.014, SE = 0.01, W = 8.1, p = 0.004) (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 which was performed in the subsample comprising MAOA-H offenders augmented the pattern observed in the first analysis suggesting that a one kilogram increase in yearly mean consumption of ethanol increased the risk with 2.3% (b = 0.023, SE = 0.01, W = 8.5, p = 0.004) . 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 MAOA-L group, but found no effect (b = 0.003, SE = 0.01, W = 0.4, p = 0.542).

The all-offender mean yearly alcohol consumption was 52 kg (SD ± 38). 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 non-recidivists: 61 kg (SE = 4.7) vs. 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) vs. 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 offences for alcohol consumption. Fig. 1 (in study III) displays that the high activity MAOA genotyped recidivists emerged as heavy drinkers (72 kg) with significantly greater consumption than that of the other groups. No other pairwise group comparisons were significant.

Alcohol consumption showed independent and additive effects on reconvictions. Fig. 2 (in study III) shows a clinical risk assessment implication of this finding.

7.5 MAOA, heavy drinking, and childhood physical abuse (study IV)

MAOA genotype altered the effects of *heavy drinking* and CPA (Tikkanen et al., unpublished results). *Heavy drinking* and CPA seem to be independent and additive risk factors for recidivistic acts of violence (Tikkanen et al., unpublished results).

Heavy drinking and CPA showed main effects on risk for recidivistic acts of violence whereas MAOA genotype showed no main effect in a logistic regression model (intercept, b = -2.50 se = 0.82, W = 9.3, p = 0.002; model fitting information, χ^2 = 26.3, df = 6, p < 0.001; predictive power 71%) explaining 19% of the variability of outcome (Nagelkerke = 0.190). On stepwise inclusion of interaction terms both MAOA**heavy drinking* (b = -2.90, se = 0.88, W = 10.9, p = 0.001) and MAOA*CPA (b = -3.16, se = 0.93, W = 11.6, p = 0.001) added risk to the model whereas *heavy drinking**CPA showed nonsignificant (b = -0.79, se = 0.54, W = 2.1, p = 0.144).

Both *heavy drinking* (OR 5.2, p = 0.004) and CPA (OR 5.3, P = 0.003) increased the risk for acts of violence among MAOA-H offenders (intercept, b = -3.90 se = 1.22, W = 10.3, p = 0.001; model fitting information, χ^2 = 26.5, df = 5, p = 0.001; predictive power 73%; nagelkerke = 0.320) whereas these exposures showed no effect among MAOA-L offenders (intercept, b = -0.12 se = 1.30, W = 0.008, p = 0.928; model fitting information, χ^2 = 7.5, df = 5, p = 0.183; predictive power 68%; nagelkerke = 0.131). Entry of the *heavy drinking**CPA interaction term into the MAOA-H offender model failed to add risk to the model even though an interaction occurred (b = -3.45, se = 1.25, W = 7.6, p = 0.006).

8 Discussion

8.1 Temperament and violent crimes

The temperament profile of the offenders differed significantly from the controls. The offenders had high NS, high HA, and low RD, which suits Cloninger's original proposal of explosive personality. However, the comparison of profiles between ASPD vs. non-ASPD offenders suggested that ASPD differs only in the temperament dimensions higher total NS, impulsivity (NS2) and disorderliness (NS4) – all pathognomonic for ASPD. Crime types showed no difference between ASPD and non-ASPD offenders except for arson, which was more frequent among non-ASPD offenders.

Further, we observed that the continuum of trait HA was not normally distributed among the offenders. Two distinct subpopulations exhibiting high or low HA scores emerged. The frequency of ASPD showed no difference between the groups of high and low HA offenders, but a comorbid ASPD and BPD was more frequent among high HA offenders. The ASPD–BPD offenders were associated with impulsive assaults and batteries rather than premeditated acts of violence. Interestingly, the protruding impulsivity as a central diagnostic criterion in both ASPD and BPD resembles the diagnosis of intermittent explosive disorder, which is classified as an impulse control disorder in DSM-IV (APA, 1994). Results suggest that the trait HA may describe a propensity to commit impulsive violent crimes and subdiagnostic BPD symptoms in offenders with a primary ASPD diagnosis.

8.2 Violent reconvictions and death

8.2.1 Incidence and risk

Results showed that the frequency of violent reconvictions and mortality was high in this 9-year non-incarcerated follow-up setting. However, most reconvictions had already occurred after 2.3 years and deaths after 5.9 years. Certain risk factors may determine which individuals have a propensity to commit a new violent crime or die soon after release for prison. Our analyses suggest, for instance, that maltreatment and a combination of BPD and maltreatment will lead to violent reconviction or death sooner than in the rest of the offender population. The literature on recidivistic acts of violence and mortality among violent offenders lacks reports on risk factors for rapidly developing poor outcome.

The annual incidence of recidivistic non-incarcerated acts of violence was 3.7%, which is slightly lower than the extrapolated 4.9% annual recidivism incidence of homicides during a 3-year period in the studies by Tiihonen et al. (1994, 1995). Results suggest that the majority of the Finnish violent offenders are not prone to commit recidivistic acts of violence. The cumulative proportion of recidivism was 32% after the 9-year follow-up. In comparison, the 5% cumulative occurrence of violent crimes among the controls (n =

1210) was relatively high as compared to the general population in Finland, but still, it was 6 times less than among the violent offenders.

The 4 times higher mortality among the violent offenders as compared with controls is in line with an observed 3-fold mortality risk among individuals with personality disorders and criminality in a Northern Finland 1966 birth cohort followed to age 27 (Rasanen et al., 1998). Moreover, our mortality incidence is in line with a 20-year follow-up study that suggested a 3.3 times higher mortality rate among assaultive alcoholics than among the general population (Berglund and Tunving, 1985).

The cause of death was more often alcohol-related diseases, poisoning, and violence among offenders as compared with the controls and the offenders died at an early age (mean 43). The high quantity of drinking (5-fold as compared with the general population) likely explains the deaths due to alcohol-related diseases and poisoning. *Rydelius* (1988) examined the mortality among 832 Swedish boys (mean age 16) referred to a probationary school after an 18-year follow-up. He concluded that a link exists between the development of antisocial behavior and "sudden death" at an early age. Eighty-eight percent of the boys had died in accidents, suicides, death from uncertain causes, murder/manslaughter, or alcohol/drug abuse (Rydelius, 1988).

The risk for recidivism (5-fold) or a "poor prognosis" (outcome recidivism or death) (4-fold) was high in comparison with 1210 controls matched by sex-, age-, and place of birth.

8.2.2 Personality disorders

Not surprisingly, externalizing disorders predicted a poor outcome and recidivism. Antisocial personality disorder exhibited a 2-fold risk increase for recidivism but did not predict recidivism or death as a group. BPD, on the other hand, exhibited a 2-fold risk increase for both recidivism and recidivism or death as a group. In comparison to controls, BPD had a higher risk for both recidivism and recidivism or death as a group (9–11-fold) than ASPD (7–8-fold).

It is important to note that the study at hand examines ASPD and BPD as separate risk factors but still not excluding each other. In other words both ASPD and BPD variables in the risk analyses included also the ASPD–BPD cases. A rationale for this procedure was that in clinical settings one of the diagnoses is likely to become the primary diagnosis and the symptoms of the other diagnosis may be on a subdiagnostic level or even unrecognized. Antisocial personality disorder and BPD as "pure" diagnoses, excluding the other diagnosis, may have a slightly different prognosis as to the figures displayed in this study. However, we also examined ASPD–BPD comorbidity as a distinct risk factor; results showed that the prognosis of this group was slightly poorer as compared with ASPD or BPD separately. The ASPD–BPD comorbid condition has not previously been examined in follow-up risk analyses even though both diagnoses include impulsivity and uncontrolled behavior, which may have an additive effect on recidivistic acts of violence and premature death.

In our study, ASPD including BPD diagnoses was observed in 56% of the subjects, which is higher than the 47% prevalence of ASPD in a large prison population study (Fazel and Danesh, 2002). However, "pure" ASPD in the study at hand was only observed in one-third, ASPD–BPD in one-fourth, and BPD in one-eight of subjects. The fact that the Finnish courts order particularly impulsive-aggressive violent offenders to undergo a mental status examination may explain the discrepant prevalence of ASPD in the prison populations examined by *Fazel and Danesh* (2002) and that of the study at hand.

A history of conduct disorder showed no risk increase in the comparison between offenders, but it surfaced as a significant risk factor in comparison to controls (6–8-fold increase). The lack of effect of CD in the comparison within the offenders probably depends on that the frequency of CD was high and it naturally robustly correlated with ASPD.

8.2.3 Childhood maltreatment

As expected, childhood maltreatment (including physical abuse of the child) increased the risk for poor prognosis but familial violence and substance abuse (not including physical abuse of the child) failed to predict a poor prognosis. However, both childhood maltreatment and familial adversity (violence and substance misuse) exposures separately increased the relative risk (comparison to controls) for a poor prognosis (4–21-fold).

Maltreatment among ASPD offenders showed no significant risk increase as compared with maltreatment as a separate risk factor. However, maltreatment among BPD offenders significantly increased the risk for a poor outcome. This may indicate that ASPD individuals are more indifferent to childhood maltreatment whereas BPD subjects have a greater vulnerability to the exposure of maltreatment.

8.3 MAOA-H and outcome impulsive violent crimes

8.3.1 MAOA-H rather than MAOA-L

It is unlikely that one gene explains complex behavior or mental disorders (Kendler, 2005). In line, the results of the study at hand suggest that the MAOA gene shows no main effect on the risk for violent behavior. Only one study to date has shown a main effect of the MAOA gene on the risk for violent crimes (Reif et al., 2007).

One of the main findings of the study at hand was that even though alcohol consumption and ageing seemingly increased the risk for reconvictions in the whole sample, at the end, only MAOA-H offenders, rather than the MAOA-L offenders, were at an increased risk. Results imply that Finnish MAOA-H risk alcoholics exhibiting antisocial behavior, high alcohol consumption, and abnormal alcohol-related impulsive

and uncontrolled acts of violence might represent an etiologically distinct alcohol dependence subtype.

Studies using correlational/associative statistical methods have shown divergent results in the effort to determine which MAOA genotype, if any, links with alcoholism. Age at onset of drinking was not part of the study design, but most of the offenders had started drinking as teenagers, which is a fact, in combination with the highly prevalent ASPD that suggests that the sample comprised mainly type 2 alcoholics with severe alcohol dependence and impulsive-aggressive antisocial behavior. Thus, our result according to which the MAOA genotype alters the effect of alcohol consumption on risk for recidivistic acts of violence should be interpreted in the context of type 2 alcoholics rather than alcoholism at large. Apart from most other studies we established a link between alcohol consumption (not the alcohol diagnosis) and applied robust effect size statistics.

A fundamental fact, for a meaningful interpretation of the role of MAOA-H in the sample at hand, is that impulsive-aggressive behavior has been argued to associate with dysfunction of the serotonergic pathways (Coccaro et al., 1989a,b; Virkkunen et al., 1995). Our finding according to which the MAOA-H genotype – resulting in a highly efficient serotonin catabolization that causes a state of low central serotonin – connects with an increased risk for impulsive acts of violence probably links with an inextricable association of low CSF metabolites with impulsive and aggressive behavior (Brown et al., 1979, 1982; Linnoila et al., 1983; Placidi et al., 2001; Virkkunen et al., 1989, 1996), as well as, type 2 alcoholism (Fils-Aime et al., 1996).

The Finnish population may be considered an isolate population carrying a highly conserved genome (Kere, 2001) and our sample probably differs genetically from other Caucasian samples, which may explain as to why we observed alteration of risk contingent on genotype. Moreover, within the Finnish isolate, the sample at hand was highly narrowed to a group of individuals with a history of acts of violence, severe psychopathology, and familial alcoholism.

8.3.2 Impulsive acts of violence

Several facts illustrate that we measured specifically impulsive acts of violence. The majority of the index crimes were committed under alcohol-intoxication. Alcohol is a potent neurotoxic substance that 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 Luttrel, 2005; Volkow et al., 1994) among alcoholics, which may predispose to loss of behavioral control. Impulsive habitually violent Finnish alcoholic offenders also have an abnormal energy substrate metabolism, and especially low glycogen formation (Virkkunen et al 2007, 2009). Alcohol dependent individuals tend to neglect nutrition during alcohol abuse relapses, which may increase the risk for uncontrolled impulsive violent behavior particularly among offenders with an abnormal glucose metabolism – a distinct subgroup among violent offenders (Virkkunen et al 2007, 2009).

Moreover, the index crimes in the cohort were impulsive assessed by both crime types (61–81% manslaughter, attempted manslaughter, assault, or battery) and mental status examination reports. The mental status examination reports hold detailed discussions whether the violent crime was impulsive and uncontrolled or committed after premeditation. We had less information on the outcome violent crimes than on the index-crimes. However, the majority of the outcome crimes also belonged to impulsive crime categories. We have no reason to doubt that the outcome crimes would have been essentially different from the index crimes.

The fact that we observed mainly impulsive acts of violence may explain as to why the effects of alcohol consumption and ageing were important among MAOA-H offenders. An increasing body of evidence suggests that the MAOA-H genotype associates with impulsivity in healthy males (Cerasa et al., 2008; Manuck et al., 2000; Passamonti et al., 2006), impulsivity related disorders such as BPD (Ni et al., 2007, 2009), ADHD (Manor et al., 2002), Tourette syndrome (Gade et al., 1998), and substance abuse (Gade et al., 1998).

Human aggression could meaningfully be divided into impulsive and premeditated subcategories. The role of MAOA in human aggression is not completely understood and even though the literature lacks a consistent classification of impulsive and premeditated aggression, a trend is discernable according to which the MAOA-H genotype connects with impulsive aggression whereas the MAOA-L genotype links to more premeditated aggression. The MAOA-H genotype has been associated to dispositional aggression with impulsive features (Manuck et al., 2000) whereas the MAOA-L genotype has shown a main effect on aggression defined as predisposition toward intentional physical aggression against another person (Reif et al., 2007).

Likewise, after exposure to childhood adversities, MAOA-H individuals have presented impulsivity/aggression in terms of alcohol-related problem behavior (Nilsson et al., 2008), and inattention (after extreme trauma) (Weder et al., 2009) whereas maltreated MAOA-L individuals have shown antisocial behavior and attitudes that accept usage of inter-personal violence (Caspi et al., 2002). *Weder et al.* (2009) showed that the level of childhood adversities may determine which MAOA genotype associates with aggression, rule breaking, and inattention. Moreover, an increasing level of maltreatment seems to correlate positively to the risk for antisocial behavior (Caspi et al., 2002) and conduct disorder (Foley et al., 2004).

8.3.3 Gene—gene interactions and physiology

Gene by gene interactions may also explain as to why we observed a mediation of risk among MAOA-H offenders rather than among MAOA-L offenders. A growing number of genes have been preliminarily associated with alcoholism in Finnish alcoholic cohorts, namely, gamma-aminobutyric acid type A alpha 2 (GABRA2) (Edenberg et al., 2004; Enoch et al., 2006, 2009), gamma-aminobutyric acid type A gamma 1 (GABRG1) (Enoch et al., 2009), galanin (GAL) (Belfer et al., 2006), and galanin receptor GALR3 (Belfer et al., 2007), tyrosine kinase B neurotrophin (NTRK2) (Xu et al., 2007), and serotonin receptor 3B (5-HT3B) (Ducci et al., 2009). Especially the genes NTRK2 and 5-HT3B

have been connected with antisocial alcoholism. The genes GABRA2, GAL, GALR3 may also, however, be important in ASPD alcoholism because they are connected with high HA, which is a feature that has been shown to be typical among ASPD alcoholics (Ducci et al., 2007; Tikkanen et al., 2007).

Recent research also suggests that MAOA-H genotype may be a marker of a wider serotonergic dysfunction in BPD (Ni et al., 2009). Results would be more comprehensible if the MAOA-H genotype links to other specific genotype abnormalities underlying physiological abnormalities such as energy expenditure and non-oxidative glucose metabolism as observed in impulsive habitually violent Finnish alcoholic offenders with ASPD (Virkkunen et al., 2007, 2009). In addition to the deviant energy expenditure several other physiological changes may potentially connect with the MAOA-H genotype.

8.3.4 Alcohol consumption, childhood physical abuse, and ageing

Study III shows that alcohol consumption correlates positively with the risk for acts of violence among MAOA-H offenders (±2.3% for each ± kilogram change in yearly average consumption). This may be a crucial change in risk since there is considerable variance in the quantities of alcohol consumption within the offenders (mean 52 kg, [SD ± 38]).

Ageing decreased the risk for new acts of violence with 7.3% for every year among the MAOA-H offenders. Ageing may decrease impulsive-aggressive behavior particularly among MAOA-H genotyped offenders for several reasons. If ageing will show to decrease expression of MAOA in future human studies, as suggested in mice (Vitalis et al., 2002), then the risk for impulsive-aggressive behavior and violent reconvictions would possibly decrease due to a correction of low central serotonin levels over time. Animal models have also suggested that other genetic variations such as endocannabinoids may cause differences in age-dependent alcohol consumption (Wang et al., 2003). Another possibility to examine in the future is that the MAOA-H genotype may connect with various physiological abnormalities that will be moderated by ageing.

Moreover, not accounting for genotypes, an examination of nation-wide statistics in Finland revealed that the frequency of homicide is 61% lower among 50-year old males than among 30-year old males and the difference was still 43% when the 4.9-fold mortality of habitually violent offenders was accounted for (Paanila et al., 2000). Convictions in general, including both nonviolent and violent convictions, have been negatively correlated with age after addiction treatment (Gossop et al., 2005). Age has also been found to be a moderate predictor with a negative correlation to violent offences (effect size –0.18) (Bonta et al., 1998).

Study IV replicated the finding that alcohol consumption increases the risk for violent behavior among MAOA-H offenders, but importantly, *heavy drinking* and childhood physical abuse (CPA) showed independent and additive effects on the risk for recidivistic acts of violence. The fact that we observed independent effects of *heavy drinking* and CPA means that the effect of alcohol consumption observed in study III is not likely biased by the distribution of CPA.

8.4 Implications

8.4.1 Prevention and treatment

8.4.1.1 Background

In contrast to a generalizing argument that an individual who has committed a violent crime will commit another crime in the future, results strongly suggest that different subgroups of violent offenders (all have committed a violent crime) are at considerably different risks for violent reconvictions and premature death. The accumulation of risk into clearly defined subgroups supports the development of evidence based and cost-efficient allocations for secondary prevention and risk assessment.

A general caveat for any treatment is lack of mutual motivation. However, it is possible that the treatment of personality-disordered individuals and addictions has partly sunk into unjustified pessimism. The work of motivation to participate in treatment should be intensive among the group of violent, psychopathological, and addicted individuals – a group of individuals who have a decreased ability to make enduring decision to participate in treatment due to the inherent nature of their mental disorders.

The means of prevention, risk assessment, and treatment of violent offenders – all aiming at decreasing the incidence of violent behavior and prevent premature death – involves ethical and political perspectives. For instance, the issues of including socioeconomic benefits (e.g., an apartment with affordable rent at release from prison) or early supervised parole as a reward for participation in treatment and successful treatment (e.g., achieved and enduring abstinence) is disputable. However, a debate based on facts and research results, rather than prejudices, is the path to decision making that will decrease the incidence of acts of violence.

Moreover, focusing on the causes of violent behavior, rather than to explain violent behavior with previous violent behavior and other historical variables, may be a key to efficacious prevention. Treatment of addictions, aggression/impulsivity and personality disorders exist but an extensive review of these is beyond of the scope of this study.

8.4.1.2 Neuropsychopharmacological treatments

Some evidence exists according to which neuropsychopharmacological treatment of impulsive-aggressive behavior may be motivated, but the use of medication has been limited. Lithium is the first psychotropic agent that has been approved by U.S. Food and Drug Administration (FDA) for treatment of aggression. Lithium was originally found to be efficacious in prevention of impulsive violent behavior in prisons (Sheard et al., 1976) and later among impulsive adolescents with conduct disorder (Campbell et al., 1984; Malone et al., 2000). These findings were observed in incarcerated settings but there is a dearth of studies examining the efficacy of lithium among antisocial subjects in non-

incarcerated settings. Non-incarcerated studies are challenging to conduct due to non-compliance to pharmacological treatments and chaotic life-style among antisocial individuals (e.g., irregular eating, sleeping, and uncontrolled alcohol consumption). Sodium valproate has also been shown to improve self-reported impulse control and self-restraint in conduct disorder (Steiner et al., 2003).

One potential neurocellular mechanism of the antiaggressive effect caused by lithium and sodium valproate is the inhibition of glycogen synthase kinase 3β (GSK3β) (Beaulieu et al., 2007; De Sarno et al., 2002; Rayasam et al., 2009). Closely related, it has been hypothesized that high GSK3β activity downregulates insulin-mediated glycogen synthesis and glucose homeostasis (Rayasam et al., 2009), which putatively leads to low non-oxidative glucose levels – a factor that has been associated with impulsive violent recidivism under the influence of alcohol (Virkkunen et al., 2007, Virkkunen et al., 2009). Both incarcerated and non-incarcerated study settings are needed in the future to examine whether MAOA-LPR alters the efficacy of antiaggressive agents. Not only pharmacological agents, but also supplementary vitamins, minerals, and essential fatty acids have been associated with decrease in antisocial behavior among young adult prisoners in a double-blind controlled study setting (Gesch et al., 2002). It is unclear, however, how the MAOA gene variants are connected with these nutritional variables.

Naltrexone, acamprosate, and supervised intake of disulfiram have shown moderate efficacy in different populations in the treatment of alcohol dependence. The recent advance in treatment of alcohol dependence underlines the need to identify specific subtypes of alcohol dependence (Alho and Hyytia, 2009; Johnson, 2008a). On one hand, serotonin reuptake inhibitors (SSRI) have shown general efficacy in the treatment of depression in alcohol dependent patients, but on the other hand, SSRI treatment has shown limited efficacy in the treatment of alcoholism (Angelone et al., 1998; Tiihonen et al., 1996) and induced a significant negative impact among type 2 alcoholics (Kranzler et al., 1996). Early onset alcoholics (type 2 and type B) have, on the other hand, benefited from ondansetron treatment (action via serotonin receptor 3B) more than late onset alcoholics (type 1 and type A) (Johnson, 2008a; Roache et al., 2008).

The alpha-amino-3-hydroxy-5-methylioxazole-4-propionic acid and kainate glutamate receptor antagonist topiramate has shown promising results in the treatment of alcohol dependence (Johnson et al., 2003, 2004a; 2008a,c). Randomized controlled trials (n = 150–371) have shown that topiramate may significantly improve physical health and quality of life of alcohol dependent individuals (Johnson et al., 2004a; 2008c). Topiramate has not yet been examined specifically among type 2 alcoholics.

Oral baclofen treatment, examined in small samples, has been associated with abstinence in 64–71% cases among alcohol dependent subjects (Addolorato et al., 2000, 2007; Leggio et al., 2008), amelioration of withdrawal symptoms, and a significant decrease in craving (Leggio et al., 2008).

Inter-individual variance in genotype and environmental exposure may play a larger role in neuropsychopharmacological treatments in the future (Bevilacqua and Goldman, 2009; Humphrey, 2009). For instance, an asparagine-to-aspartate amino acid substitution in the μ-opioid type 1 receptor (OPRM1) at the 40 position (Asn40Asp) alters the efficacy

of naltrexone treatment in addition to functional changes of the clinical effects of alcohol and cell function modulation (Anton et al., 2008; Oroszi et al., 2009).

Moreover, some potential neurobiological sites of neuropsychopharmacological treatments have been identified in animal models (See review by Heilig and Egli, 2006). Endocannabinoids seem to have a role in alcohol consumption (Wang et al., 2003). The cannabinoid CB1 receptor antagonist rimonabant is currently examined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) for its ability to reduce alcohol consumption. The manipulation of the function of stress-related neuropeptides such as corticotrophin-releasing factor, neuropeptide Y, and nociceptin are also potential sites of neuropsychopharmacological treatment of alcoholism (Heilig and Egli, 2006).

Altogether, all neuropsychopharmacological treatments – particularly combined medications (Stella et al., 2008) – that reduce alcohol consumption and alcohol dependence related symptoms may decrease the risk for violent reconvictions even though complete abstinence would not be achieved. Alcohol dependence evolves over several years, which supports the importance of early intervention. Lifetime neuropsychopharmacological treatments are not necessarily needed since ageing and other protective variables may also decrease the risk for acts of violence. Participation in addiction treatment programs in prisons should be strongly encouraged. The effect of focused neuropsychopharmacological treatments of early onset alcoholism (type 2) among violent offenders (for instance with ondansetron) needs to be studied because it may eventually significantly decrease the occurrence of violent reconvictions.

8.4.1.3 Psychotherapy, intervention, and endurance

Dialectic behavioral therapy has shown efficacy in treatment of BPD (Linehan et al., 1993, 2006). Although there is a paucity of randomized controlled reports on therapy for ASPD, there likely exist subpopulations within ASPD that can benefit from dialectic behavioral therapy or integrative and eclectic psychotherapy. For instance, group based cognitive and behavioral interventions focused on reducing offending and other antisocial behaviors in an optimistic and trusting context (Kendal et al., 2009) may show successful, rather than a punitive approach, whereas surely other subpopulations such as psychopaths will have limited or no benefit from psychological treatments. Moreover, spontaneously intervening constructive life-events such as valued opportunities (stable marriage, work-related progress, and religious conversion) may enhance psychological maturation and improve the prognosis of ASPD. Putative brain maturation over time may also increase the possibilities to benefit from psychotherapy and to perceive constructive life opportunities as rewarding.

Prevention of a harmful event that has already occurred such as childhood maltreatment is obviously impossible. However, it may be possible to decrease the negative effects concerning the exposed individual and also stop the passing of such noxious exposure to the next generation. A study by *Olds et al.* (1998) presented promising results in primary prevention of ASPD and substance abuse. Supportive therapy-like interventions aimed at young mothers in households with a low

socioeconomic status were performed. The children of the young mothers that had received supportive interventions were significantly less antisocial or substance addicted as adolescents.

A basic goal of any treatment is to keep the patient alive. Our results suggest that time will work to the benefit of this goal since ageing decreases impulsive-aggressive behavior particularly among MAOA-H genotyped offenders. Thus, the endurance of treatment is important. Moreover, ageing may modulate the effects of some other risk factors especially among the MAOA-H genotyped offenders. The core symptoms of BPD, for instance, have been shown to decrease over time (Zanarini et al., 2007, 2008) and BPD has been associated with MAOA-H (Ni et al., 2007, 2009).

8.4.2 Risk assessment and ethics

The accuracy of risk assessments for violent reconvictions will improve if the results of this study are replicated. However, the increased accuracy of risk assessments holds strong undercurrents of ethical issues on how to take advantage of the knowledge.

For instance, when an offender is identified as being at a high risk for recidivism there is the possibility to "lock him in and throw the key away". A more human approach, however, would be treatment or conditional release after the risk has been reassessed as being diminished as compared to the original situation. Furthermore, public fear may prevent the release of a low risk individual from prison with the rationale that a violent reconviction can never definitely be ruled out.

Identification of high-risk individuals holds the possibility to focus secondary prevention resources upon them. Another issue that is affected by the increased risk assessment accuracy is that keeping prisoners incarcerated for decades is costly. If the risk for reconvictions decreases over time it is worthwhile to consider increasing the number of prisoners released on parole to decrease to costs of incarceration. An increasing body of knowledge on the causes and risk for acts of violence and death among violent offenders will hopefully stimulate the political debate and direct the discussion from arguments based on prejudices towards arguments supported by facts.

A fundamental issue in the ethics debate is that acts of violence and severe substance addictions may be seen, on one hand, to spring from the free choice of an individual, but on the other hand, acts of violence and severe addictions may be seen as handicapping, partly inherited biological liabilities present among some unfortunate individuals.

8.5 Critical assessment of the study

The statistical methods that have been applied are central in the assessment of the results. In study I associations were examined which is a less robust method than effect size analyses. However, the non-normality of the temperament dimensions was accounted for by choosing conservative association examination methods to avoid type I errors. The majority of the results of the study originate from robust and conservative effect size

analyses, which should direct results to correspond with actual risk. However, no power analyses were performed at the time of collection of the sample and post hoc power analyses are not to be relied on. Still, the possibility of type II error is small due to the large sample size, which is one of the largest in this field of research.

The high quality of Finnish register data, the high-standard mental status examination, and the stringent scientific diagnosing of mental disorders used in this study adds confidence in the reliability of results. However, the file based assessment of childhood adversities was retrospectively performed, which is a potential source of bias. To avoid spurious results we included three definitions of childhood adversities.

It is difficult to account for all possible risk factors when assessing the risk for a multi-causal outcome. The fact that the risk factor repertoire was relatively broad (personality disorders, childhood environments, alcohol consumption, and genotype), and the setting was a prospective follow-up, favor the possibility that results approach actual risk.

This study has focused on risk factors for recidivistic impulsive acts of violence. Protective factors, however, were not examined which may be a source of bias and partly explain why some groups have a better prognosis. Identification of protective factors would be important to support strategies for preventive work.

8.6 Conclusions

Results indicate that temperament traits among violent offenders differ from traits among controls. Temperament traits also seem to associate with personality disorders among violent offenders and distinguish a propensity to commit impulsive or non-impulsive violent crimes. Severe personality disorders, childhood maltreatment, a combination of these, and alcohol consumption increased the risk for reconvictions and death. Ageing decreased the risk for violent reconvictions.

We note that results indicate that some risk factors only apply for high activity MAOA offenders, not the low activity MAOA offenders, in this Finnish alcoholic violent offender sample. However, the slight minority of offenders having MAOA-L likely have different risk factors that were not revealed in the study at hand. However, in light of the novel connection of MAOA-H to impulsivity and MAOA-L to premeditated aggression it is likely that MAOA-L offenders may have a propensity to commit premeditated, rather than impulsive, acts of violence either with different or similar risk factors as those examined in the present study.

To avoid over simplified or false interpretations of the results, it is important to understand that the MAOA-H genotype is not a rare allele prevalent only among violent offenders, but rather, the distribution of MAOA-H and MAOA-L allele frequencies are similar also in Caucasian community samples. Moreover, the sample under examination was a selected sample comprising violent offenders therefore results should not be applied to the general population.

The incidence of recidivistic acts of violence and mortality was generally high but results suggest that the risk accumulates into a small minority of violent offenders. The majority of the offenders did not commit a new act of violence in the follow-up. The fact

that genotype alters the effects of risk factors may have profound consequences for preventive work and risk assessments in the future. Identification of specific risk groups gives support for evidence based and cost-efficient secondary prevention, which may substantially decrease the incidence of violent crimes overall. Risk assessments may simultaneously gain benefit from identification of both high and low risk groups.

9 Acknowledgements

Much gratitude is to be directed to professor Matti Virkkunen for giving the opportunity to participate in his work in the field of antisocial alcoholism and violence research and for teaching both a deductive and inductive methodological approach during the process of this thesis (2005—2009). The authorship of Dr. David Goldman and his staff at the Laboratory of Neurogenetics at NIAAA in studies III and IV has supported the quality of this study. Moreover, the following persons have contributed to the scientific contents of this study: Markku Eronen, Olli Kampman, Matti Holi, and Matti Virkkunen.

Hannu Laurema is involved as the opponent at the public examination of the dissertation. Monica Eggert and Hannu Naukkarinen performed the SCID-interviews when the original material was collected. Niall Chorell and Inka Tikkanen-Pietikäinen served as language consultants and reviewed the text from the layman's perspective.

Countless hours of academic work by numerous anonymous persons have been put into reviewing the original publications. Dr. Cloninger was one reviewer of study I. Aija Räsänen, Helvi Numminen, Kuutti Mujunen, and Viivi Mujunen have assisted in various ways. This reseach was supported by many Finnish non-profit organisations.

With deep gratitude I sincerely thank you all.

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