

Antti Latvala

**Cognitive Functioning in Alcohol
and Other Substance Use
Disorders in Young Adulthood**
A Genetic Epidemiological Study

RESEARCH 53

Antti Latvala

Cognitive Functioning in Alcohol and
Other Substance Use Disorders in
Young Adulthood

A Genetic Epidemiological Study

Academic dissertation

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Helsinki, Finland

and

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*The brain is wider than the sky,
For, put them side by side,
The one the other will include
With ease, and you beside.*

*The brain is deeper than the sea,
For, hold them, blue to blue,
The one the other will absorb,
As sponges, buckets do.*

*The brain is just the weight of God,
For, lift them, pound for pound,
And they will differ, if they do,
As syllable from sound.*

Emily Dickinson (1830–1886)

*And inside every turning leaf
Is the pattern of an older tree
The shape of our future
The shape of all our history*

*And out of the confusion
Where the river meets the sea
Came things I'd never seen
Things I'd never seen*

Sting

To my family

Abstract

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Alcohol and other substance use disorders (SUDs) result in great costs and suffering for individuals and families and constitute a notable public health burden. A multitude of factors, ranging from biological to societal, are associated with elevated risk of SUDs, but at the level of individuals, one of the best predictors is a family history of SUDs. Genetically informative twin and family studies have consistently indicated this familial risk to be mainly genetic. In addition, behavioral and temperamental factors such as early initiation of substance use and aggressiveness are associated with the development of SUDs. These familial, behavioral and temperamental risk factors often co-occur, but their relative importance is not well known.

People with SUDs have also been found to differ from healthy controls in various domains of cognitive functioning, with poorer verbal ability being among the most consistent findings. However, representative population-based samples have rarely been used in neuropsychological studies of SUDs. In addition, both SUDs and cognitive abilities are influenced by genetic factors, but whether the co-variation of these traits might be partly explained by overlapping genetic influences has not been studied. Problematic substance use also often co-occurs with low educational level, but it is not known whether these outcomes share part of their underlying genetic influences. In addition, educational level may moderate the genetic etiology of alcohol problems, but gene-environment interactions between these phenomena have also not been widely studied. The incidence of SUDs peaks in young adulthood rendering epidemiological studies in this age group informative.

This thesis investigated cognitive functioning and other correlates of SUDs in young adulthood in two representative population-based samples of young Finnish adults, one of which consisted of monozygotic and dizygotic twin pairs enabling genetically informative analyses. Using data from the population-based Mental Health in Early Adulthood in Finland (MEAF) study (n=605), the lifetime prevalence of DSM-IV any substance dependence or abuse among persons aged 21–35 years was found to be approximately 14%, with a majority of the diagnoses being alcohol use disorders. Several correlates representing the domains of behavioral and affective factors, parental factors, early initiation of substance use, and educational factors were individually associated with SUDs. The associations between behavioral and affective factors (attention or behavior problems at school, aggression, anxiousness) and SUDs were found to be largely independent of factors from other domains, whereas daily smoking and low education were still associated with SUDs after adjustment for behavioral and affective factors.

Using a wide array of neuropsychological tests in the MEAF sample and in a subsample (n=602) of the population-based FinnTwin16 (FT16) study, consistent evidence of poorer verbal cognitive ability related to SUDs was found. In addition, participants with SUDs performed worse than those without disorders in a task assessing psychomotor processing speed in the MEAF sample, whereas no evidence of more specific cognitive deficits was found in either sample. Biometrical structural equation models of the twin data suggested that both alcohol problems and verbal ability had moderate heritabilities (0.54–0.72), and that their covariation could be explained by correlated genetic influences (genetic correlations -0.20 to -0.31). The relationship between educational level and alcohol problems, studied in the full epidemiological FT16 sample (n=4,858), was found to reflect both genetic correlation and gene-environment interaction. The co-occurrence of low education and alcohol problems was influenced by overlapping genetic factors. In addition, higher educational level was associated with increased relative importance of genetic influences on alcohol problems, whereas environmental influences played a more important role in young adults with lower education.

In conclusion, SUDs, especially alcohol abuse and dependence, are common among young Finnish adults. Behavioral and affective factors are robustly related to SUDs independently of many other factors, and compared to healthy peers, young adults who have had SUDs during their life exhibit significantly poorer verbal cognitive ability, and possibly less efficient psychomotor processing. Genetic differences between individuals explain a notable proportion of individual differences in risk of alcohol dependence, verbal ability, and educational level, and the co-occurrence of alcohol problems with poorer verbal cognition and low education is influenced by shared genetic backgrounds. Finally, various environmental factors related to educational level in young adulthood moderate the relative importance of genetic factors influencing the risk of alcohol problems, possibly reflecting differences in social control mechanisms related to educational level.

Keywords: Substance use disorders, alcohol, young adults, population-based sample, prevalence, cognitive functioning, verbal ability, educational level, twin study, heritability, genetic correlation, gene-environment interaction

Tiivistelmä

Antti Latvala. Cognitive Functioning in Alcohol and Other Substance Use Disorders in Young Adulthood. A Genetic Epidemiological Study [Kognitiiviset toiminnot nuorten aikuisten päihdehäiriöissä: Geneettis-epidemiologinen tutkimus]. National Institute for Health and Welfare (THL), Research 53/2011. 139 pages. Helsinki, Finland 2011.

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Alkoholin ja muiden päihteiden käytön häiriöt aiheuttavat huomattavaa kärsimystä ja haittoja niin yksilöille kuin perheillekin ja ovat merkittävä kansanterveydellinen ongelma. Useat erilaiset riskitekijät biologisista yhteiskunnallisiin tekijöihin ovat yhteydessä kohonneeseen päihdehäiriöiden riskiin, mutta yksi vahvimista yksilötason ennustajista on päihdeongelmien esiintyminen lähisukulaisilla. Geneettisistä vaikutuksista tietoa antavat kaksos- ja perhetutkimukset ovat johdonmukaisesti osoittaneet päihdehäiriöiden periytymisen johtuvan enimmäkseen geneettisistä vaikutuksista. Myös käyttäytymiseen ja temperamenttiin liittyvät tekijät, kuten päihteiden käytön varhainen aloittaminen ja aggressiivisuus, ovat yhteydessä päihdehäiriöiden kehittymiseen. Nämä perheittäiset sekä käyttäytymiseen ja temperamenttiin liittyvät tekijät esiintyvät usein yhdessä, mutta niiden merkitystä suhteessa toisiinsa ei tunneta hyvin.

Päihdehäiriöistä kärsivien on raportoitu eroavan terveistä verrokeista myös monella kognitiivisten toimintojen osa-alueella. Yksi johdonmukaisimmista löydöksistä on ollut päihdehäiriöihin liittyvä heikompi kielellinen kyvykkyys. Päihdehäiriöiden neuropsykologisissa tutkimuksissa ei kuitenkaan ole juurikaan käytetty edustavia, väestöpohjaisia aineistoja. Lisäksi tiedetään, että geneettiset tekijät vaikuttavat sekä päihdehäiriöiden riskiin että yksilöiden välisiin eroihin kognitiivisissa toiminnoissa, mutta päihdehäiriöiden ja heikompien kognitiivisten kykyjen yhteisesiintymisen selittymistä osittain yhteisillä geneettisillä vaikutuksilla ei ole tutkittu. Päihdeongelmat ovat myös yleisempiä matalammin koulutetuilla, mutta ei tiedetä, vaikuttavatko osittain samat geneettiset tekijät sekä saavutettavaan koulutustasoon että päihdeongelmien kehittymiseen. Koulutustaso voi lisäksi toimia alkoholi-ongelmien geneettistä etiologiaa muokkaavana tekijänä, mutta geenien ja ympäristötekijöiden yhdysvaikutuksia näiden ilmiöiden välillä ei myöskään ole juurikaan tutkittu. Päihdehäiriöiden ilmaantuvuus on huipussaan nuorilla aikuisilla, mikä tekee tämän ikäryhmän epidemiologisista tutkimuksista informatiivisia.

Tässä väitöskirjassa tutkittiin kognitiivisia toimintoja ja muita päihdehäiriöihin liittyviä tekijöitä nuorilla aikuisilla kahdessa suomalaisessa väestöpohjaisessa aineistossa, joista toinen koostui mono- ja ditsygoottisista kaksosista mahdollistaneen geneettisistä vaikutuksista tietoa antavien menetelmien käytön. Minkä tahansa päihteen elämänaikaisen väärinkäytön tai riippuvuuden (DSM-IV) esiintyvyys 21–35-vuotiailla suomalaisilla oli väestöpohjaisessa Nuorten aikuisten terveys ja psyykinen hyvinvointi Suomessa -aineistossa (NAPS) (n = 605) noin 14 %, ja val-

taosa diagnooseista oli alkoholin käytön häiriöitä (nikotiiniriippuvuutta ei tutkittu). Useat tunne-elämään ja käyttäytymiseen liittyvät tekijät, vanhempiin liittyvät tekijät, päihdeiden käytön varhainen aloittaminen sekä koulutustasoon liittyvät tekijät olivat yksitellen yhteydessä päihdehäiriöihin. Aggressiivisuuden ja ahdistuneisuuden sekä kouluaikaisten tarkkaavaisuus- ja käytösongelmien yhteys päihdehäiriöihin oli enimmäkseen riippumaton muista tutkituista tekijöistä, kun taas päivittäinen tupakointi ja matala koulutustaso olivat yhteydessä päihdehäiriöihin myös vakioitaessa tunne-elämään ja käyttäytymiseen liittyvien tekijöiden vaikutus.

Käyttäen laajaa neuropsykologisten testien valikoimaa niin NAPS-aineistossa kuin väestöpohjaisen Nuorten kaksosten terveystutkimuksen (FinnTwin16) alotoksessa (n=602) tämä tutkimus tuotti johdonmukaista näyttöä päihdehäiriöihin liittyvästä heikommasta suoriutumisesta kielellistä kyvykkyyttä arvioivassa tehtävässä. NAPS-aineistossa päihdehäiriöihin liittyi myös huonompi suoriutuminen psykomotorista prosessointinopeutta arvioivassa tehtävässä, mutta merkkejä puutoksista muilla kognitiivisten toimintojen osa-alueilla ei havaittu kummassakaan aineistossa. Kaksosaineiston analysointi biometrisiä rakenneyhtälömalleja käyttäen tarjosi näyttöä niin alkoholiuongelmien kuin kielellisen kyvykkyyden kohtalaisen voimakkaasta periytyvyydestä (0.54–0.72) sekä näiden ilmiöiden yhteisesiintymisen selittymisestä osin yhteisellä geneettisellä taustalla (geneettiset korrelaatiot välillä -0.20 ja -0.31). Koulutustason ja alkoholiuongelmien yhteyttä tutkittiin käyttäen koko epidemiologista FinnTwin16-aineistoa (n = 4 858 henkilöä) ja saatiin näyttöä sekä geneettisestä korrelaatiosta että geeni-ympäristö -yhdysvaikutuksesta näiden ilmiöiden välillä. Matalan koulutustason ja alkoholiuongelmien yhteys selittyi osin yhteisillä geneettisillä tekijöillä. Korkeampi koulutustaso oli lisäksi yhteydessä geneettisten vaikutusten suhteellisesti suurempaan merkitykseen alkoholiuongelmien taustalla, kun taas matalammin koulutetuilla nuorilla aikuisilla ympäristötekijöiden vaikutus oli suurempi.

Tämän tutkimuksen perusteella päihdehäiriöt, etenkin alkoholin väärinkäyttö ja alkoholiriippuvuus, ovat suomalaisilla nuorilla aikuisilla yleisiä. Tunne-elämään ja käyttäytymiseen liittyvät tekijät ovat vahvasti yhteydessä päihdehäiriöihin monista muista tekijöistä riippumatta, ja nuorilla aikuisilla, joilla on ollut päihdehäiriö elämänsä aikana, on terveitä verrokkeja heikompi kielellinen kyvykkyyttä sekä mahdollisesti psykomotorisen prosessoinnin hitautta. Yksilöiden väliset geneettiset erot selittävät huomattavan osan yksilöllisistä eroista alkoholiriippuvuuden riskissä, kielellisessä kyvykkyydessä ja koulutustasossa. Yhteinen geneettinen tausta selittää osittain myös alkoholiuongelmien yhteyttä heikompaan kielelliseen kyvykkyyteen ja matalaan koulutustasoon. Lisäksi koulutustasoon nuorilla aikuisilla liittyvät tekijät muokkaavat alkoholiuongelmien taustalla olevien geneettisten tekijöiden roolia, mikä saattaa heijastella koulutustasoon liittyviä eroja sosiaalisen kontrollin mekanismeissa.

Avainsanat: Päihdehäiriöt, alkoholi, nuoret aikuiset, väestöpohjainen otos, esiintyvyys, kognitiiviset toiminnot, kielellinen kyvykkyyttä, koulutustaso, kaksostutkimus, periytyvyys, geneettinen korrelaatio, geeni-ympäristö-yhdysvaikutus

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List of original publications

The thesis is based on the following original articles, which are referred to in the text by Roman numerals (I–IV).

- I Latvala A, Tuulio-Henriksson A, Perälä J, Saarni SI, Aalto-Setälä T, Aro H, Korhonen T, Koskinen S, Lönnqvist J, Kaprio J, Suvisaari J. Prevalence and correlates of alcohol and other substance use disorders in young adulthood: A population-based study. *BMC Psychiatry* 2009; 9:73.
- II Latvala A, Castaneda AE, Perälä J, Saarni SI, Aalto-Setälä T, Lönnqvist J, Kaprio J, Suvisaari J, Tuulio-Henriksson A. Cognitive functioning in substance abuse and dependence: a population-based study of young adults. *Addiction* 2009; 104:1558–68.
- III Latvala A, Tuulio-Henriksson A, Dick DM, Vuoksimaa E, Viken RJ, Suvisaari J, Kaprio J, Rose RJ. Genetic origins of the association between verbal ability and alcohol dependence symptoms in young adulthood. *Psychological Medicine* 2011; 41:641–651.
- IV Latvala A, Dick DM, Tuulio-Henriksson A, Suvisaari J, Viken RJ, Rose RJ, Kaprio J. Genetic correlation and gene-environment interaction between alcohol problems and educational level in young adulthood. *Journal of Studies on Alcohol and Drugs* 2011; 72:210–220.

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Abbreviations

A	Additive genetic variance component
ACE	A biometrical twin model containing additive genetic, common environmental and unique environmental variance components
ADE	A biometrical twin model containing additive genetic, dominant genetic and unique environmental variance components
ADHD	Attention-deficit hyperactivity disorder
AE	A biometrical twin model containing additive genetic and unique environmental variance components
AOR	Adjusted odds ratio
C	Common (shared) environmental variance component
CAGE	Cut-down, Annoyed, Guilt, Eye-opener questionnaire
CE	A biometrical twin model containing common and unique environmental variance components
CI	Confidence interval
CVLT	California Verbal Learning Test
D	Dominant genetic variance component
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DZ	Dizygotic
E	Unique (non-shared) environmental variance component
EDAC	Extremely discordant and concordant
FT16	FinnTwin16 study
GABA	Gamma-aminobutyric acid
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IQ	Intelligence quotient
Maxdrinks	Maximum number of alcoholic drinks consumed in a 24-hour period
MEAF	Mental Health in Early Adulthood in Finland study
MZ	Monozygotic
n (or N)	Number of participants
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NLAES	National Longitudinal Alcohol Epidemiologic Survey
r	Pearson product-moment correlation coefficient
rA	Additive genetic correlation
RAPI	Rutgers Alcohol Problem Index
SCID-I	Structured Clinical Interview for DSM-IV-TR
sd	Standard deviation
SSAGA	Semi-Structured Assessment for Genetics of Alcoholism

TMT	Trail Making Test
WAIS-III	Wechsler Adult Intelligence Scale, Third Edition
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WMS-R	Wechsler Memory Scale-Revised
χ^2	Chi-squared

1 INTRODUCTION

Psychoactive substances have been an integral part of human culture throughout history. The potential of these substances, when taken, to change an individual's state of consciousness, mood, thought and behavior guaranteed them a prominent role already in ancient societies where they were widely used for pleasure, medicine and ritual purposes. The ancient Egyptians, for example, are known to have made at least seventeen varieties of beer and 24 varieties of wine and to have warned against excessive drinking, while drunkenness was generally not regarded as a problem (Hanson 1995). Cannabis was used for its intoxicating effects by the ancient peoples of India and Nepal, as well as the ancient Assyrians (Booth 2003).

In the present day as well as historically, psychoactive substances are consumed largely for their expected beneficial effects, either in search of pleasure or to avoid negative emotional states. Despite these intended benefits, psychoactive substances have the potential for harm, and presumably all societies that consume them show related health and social problems (Rehm et al. 2009). Alcohol and nicotine are the two most widely used psychoactive substances (excluding caffeine, the use of which is relatively unproblematic) with an estimated 2 billion consumers of alcoholic beverages (WHO 2004a) and 1.2 billion smokers worldwide (Mackay and Eriksen 2002). The number of people who used illicit drugs—mainly cannabis, amphetamines, opiates and cocaine—at least once in 2007 was estimated to be between 172 and 250 million (United Nations Office on Drugs and Crime 2009). These figures correspond to a great contribution to the global burden of disease. Recently, an estimated 3.8% of all global deaths and 4.6% of global loss of disability-adjusted life-years were found attributable to alcohol use (Rehm et al. 2009). In 2000, these indicators of the global burden of disease for tobacco were 8.8% and 4.1%, and for illicit drugs 0.4% and 0.8% (WHO 2002). Overall, psychoactive substance use thus has a major effect on burden of disease, as well as great economic costs to societies. However, the full range of social harm and suffering caused by substance use is not captured by these measures.

A major health and social consequence of psychoactive substance use is the potential development of addiction—a state characterized by impaired control over and volition about substance use (West 2006)—or substance use disorders, using the preferred term of the current diagnostic classification of psychiatric disorders. Recently, the global 1-year prevalence of alcohol use disorders was estimated at 3.6%, and alcohol use disorders comprised the disease class with the most detrimental effects on alcohol-attributable burden of disease (Rehm et al. 2009). In this estimation, the overall years of healthy life lost globally for disabilities for alcohol use disorders in 2004 were 22.0 million, and 36.4% of the disease-adjusted life years related to neuropsychiatric disorders were caused by alcohol (Rehm et al. 2009). Illicit drug use disorders are less prevalent than alcohol dependence or abuse,

but they cause considerable disease burden which is increasing in many countries (WHO 2002) and are associated with increased overall mortality, including that caused by HIV/AIDS, overdose and suicide.

Besides the notable preventable public health burden, substance use disorders result in great costs and suffering for individuals and families, urgently calling for improved strategies of effective prevention and intervention. From a more theoretical point of view, substance use and addiction are intriguing and important behavioral phenomena in need of explanation. The acute effects of psychoactive substances, mediated by neurochemical pathways in the brain, are a case in point of neurobiological explanations of mood, consciousness and perception (Breedlove et al. 2007). On the other hand, the developmental cascade from experimentation and regular substance use into addiction, sometimes described as a transition from impulsive to compulsive behavior (Koob et al. 2004), raises important questions about the mechanisms of self-regulation and behavioral control. From a more philosophical perspective still, addiction by itself—and the well-established genetic influence on the liability to develop addiction (Ducci and Goldman 2008) even more so—touches the perennial human dilemmas of free will and ethical and legal responsibility (Cashmore 2010, Haggard 2008, Kalivas and Volkow 2005, Leeman et al. 2009).

The present thesis is an exploration into alcohol and other substance use disorders and their correlates among Finnish young adults. Using two independently collected population-based samples from Finland, the present studies investigate the prevalence of substance use disorders in young adulthood, their several relevant correlates and risk factors, and the genetic and environmental background of these disorders and their correlates. A special focus of two of these studies is on cognitive functioning among people with alcohol and other substance use disorders, assessed with neuropsychological methods. This topic has rarely been studied with population-based or genetically informative samples. A theoretical and methodological framework for the present studies can be found at the intersection of three fields of epidemiological research, namely psychiatric (Susser et al. 2006), cognitive (Deary and Batty 2007) and genetic epidemiology (Thomas 2004), in combination and overlapping with three fields of psychological science: clinical psychology, neuropsychology, and behavior genetics.

2 REVIEW OF THE LITERATURE

2.1 Psychoactive substances and substance use disorders

This section gives an overview of the psychopharmacological effects of the most widely used psychoactive substances. After that, the concept and current definitions of substance use disorders are reviewed.

2.1.1 Major psychoactive substances

Psychoactive substances are chemical substances that have the potential to affect an individual's perception, mood, thinking and behavior. They exert their psychoactive influences by binding at specific target sites in the brain, reached via circulation as absorbed into the blood plasma (Meyer and Quenzer 2004). Binding at the binding sites initiates a cascade of cellular events causing changes in synaptic transmission between neurons and leading to complex alterations in the activity of a multitude of inter-related neural systems thus altering physiological and psychological functions. The range of psychoactive substances used by humans can be classified in several ways, of which biologically and psychologically most reasonable is a classification based on the chemical and functional properties of the substances. From a societal and public health perspective, classification by prevalence of use and legal status is also relevant. In the following, a short description of the most important classes of psychoactive substances is given, based on Koob & Le Moal (2006), Meyer and Quenzer (2004), McCrady and Epstein (1999), and WHO (2004b). Caffeine, the stimulating psychoactive compound of coffee, tea and many soft drinks, and as such probably the most widely consumed psychoactive substance in the world, is not covered in this thesis, however. Caffeine produces no intoxication and has a very low potential for addiction (Smith 2002).

Alcohol

Alcohol (ethanol) is a legal substance (for persons over a certain age), consumed throughout the world mostly for recreational purposes (Hanson 1995). It has a simple chemical structure and it is produced by fermentation and distillation of agricultural products. Alcohol is almost always taken orally in the form of various alcoholic beverages, and it is quickly absorbed in the bloodstream in the stomach and small intestine. The behavioral effects of alcohol vary somewhat between individuals but are in general dose-dependent such that low doses produce heightened activity (such as increased sociability and talkativeness) and disinhibition (release of inhibitions,

reduced tension), whereas higher blood alcohol levels produce increasingly more emotional instability and impairment in cognitive, perceptual and motor functions. Still higher doses cause ataxia, blackouts, impaired reaction time and sedation (Koob and Le Moal 2006). The impact of alcohol on the brain's neurotransmitter systems is somewhat atypical compared to many other psychoactive substances, as alcohol affects many different systems with no single one predominating. Two major brain effects are an increase of inhibitory activity mediated by the gamma-aminobutyric acid (GABA) receptors and a decrease of excitatory activity mediated by glutamate receptors, especially the N-methyl-D-aspartic acid (NMDA) receptors (Moak and Anton 1999). The reinforcing effects of alcohol are probably related to increased activity of dopamine neurons in the ventral tegmental area, but also the opioid and serotonin systems are influenced by alcohol (Moak and Anton 1999).

Cannabinoids

Cannabis is the most widely used illegal substance in the world (United Nations Office on Drugs and Crime 2009). Cannabinoids are derived from the hemp plants *Cannabis sativa* and *Cannabis indica* which both have numerous chemical constituents, but the major active constituent responsible for their pharmacological effects is delta-9-tetrahydrocannabinol (THC). The two most common forms of cannabis preparations are marijuana and hashish. Marijuana consists of a mixture of the flowering tops, leaves and stems of the dried cannabis plant, and it is usually administered by smoking. Hashish is a potent cannabis preparation created by extracting resin from the flowering tops of the plant, which is then dried and smoked in a pipe or baked in cookies for oral consumption (Stephens 1999). When smoked, THC is absorbed rapidly from the lungs into the bloodstream, whereas absorption is much slower if taken orally. The acute effects of cannabis vary widely as a function of the dose, the setting, the current state of the user and the user's prior experience with the drug, but for most users cannabis produces a mild state of euphoria or relaxation. It may enhance other experiences such as those related to music, food and sex, and the perception of time is slowed. Acute toxicity of cannabis is minimal, but some users may experience anxiety and panic reactions as unwanted effects. The psychoactive effects of cannabis are produced by the binding of THC on specific cannabinoid receptors, which exist in high densities in the cerebral cortex, hippocampus, cerebellum and basal ganglia (the endocannabinoid system). The euphoric effects of cannabis appear to be related to the cannabinoid receptor's modulation of the mesolimbic dopaminergic pathways (Stephens 1999).

Opioids

Opiate drugs are compounds extracted from the opium poppy plant. The term "opioids" includes these natural or semisynthetic narcotics—e.g. opium, morphine and heroin—as well as fully synthetic compounds with similar properties, such as methadone. "Endorphins" is a term referring to the opioid subclass of endogenous opioid peptides, consisting of the enkephalins, the dynorphins, and the beta-

endorphins (Stine and Kosten 1999). These ‘morphine-like’ molecules that exist naturally in the brain were discovered after it was observed that opiates interact with specific binding sites in the brain, namely the opioid receptors. The three opioid receptors (mu, delta and kappa receptors) mediate the activities of both exogenous opioid drugs and endogenous opioid peptides. Opioid drugs are usually administered intravenously or by smoking. Their intoxicating effects include a profound euphoria which occurs about 10 seconds after the beginning of the injection. After the euphoria comes a general feeling of well-being that can last several hours. After that, there is a state of escape from reality that can range from sleepiness to virtual unconsciousness (Koob and Le Moal 2006). Overall, opioids have euphorogenic, analgesic, sedative, and respiratory depressant effects, and opioid overdose is a life-threatening medical emergency. Worldwide, opioid addiction is a major medical problem, with highest levels of heroin and other opioid use in Europe and Asia (United Nations Office on Drugs and Crime 2009).

Stimulants

Stimulants are substances that stimulate the central nervous system to produce increased psychomotor activity such as increased alertness, arousal, energy, motor and speech activity, as well as an overall feeling of well-being. The most prevalent stimulant drugs are amphetamines and cocaine. Amphetamines include e.g. D-amphetamine, metamphetamine and methylenedioxymetamphetamine (MDMA, also known as Ecstasy). Cocaine is structurally and neuropharmacologically different from amphetamines, but both classes of stimulants are indirect sympathomimetic drugs, i.e. they mimic the effects of the sympathetic nervous system. Stimulants can be administered intravenously, intranasally, orally, or inhaled. They act neuropharmacologically to enhance the amount of monoamines available within the synaptic cleft of monoamine synapses in the central nervous system (Koob and Le Moal 2006). They block the reuptake of norepinephrine, dopamine and serotonin, and also enhance their release. The primary action responsible for their psychomotor stimulant and reinforcing effects appears to be on the dopamine systems of the brain. While most users do not become addicted, the addiction potential of the stimulants is probably the highest of all psychoactive substances (Goldstein and Kalant 1990).

Other substances of abuse

Hallucinogens constitute a broad group of substances that have an ability to produce sensory distortions and hallucinations. They are among the least toxic psychoactive substances, have a relatively low addiction potential and are among the illicit substances least frequently used in the Western world (Stephens 1999). There are over 100 different hallucinogens with substantially different molecular structures, some of the most widely used being d-lysergic acid diethylamide (LSD), psilocybin, mescaline and ketamine. Despite their chemical diversity, these substances produce similar hallucinogenic effects such as visual hallucinations of geometric patterns, landscapes or symbolic objects. LSD and other hallucinogens block serotonin

receptors or otherwise alter serotonergic activity. Another class of substances of abuse is comprised of sedatives, hypnotics and anxiolytics, such as benzodiazepines. These drugs have an ability to produce widespread depression in the central nervous system, resulting in calming, anxiolytic effects (sedation) at low doses and drowsiness and sleep (hypnosis) at higher doses. Most of their actions are a result of potentiation of neural inhibition mediated through the GABA neurotransmitter system. Problematic use of these substances often occurs comorbidly with other substance use disorders (McCabe et al. 2008).

Nicotine

Nicotine is the main, but not sole psychoactive component of tobacco (Villegier et al. 2006). Tobacco products are legal commodities, aggressively marketed by the transnational tobacco industry. Nicotine has mild stimulating effects and it may subjectively relieve stress. Its effects are mediated by the nicotinic acetylcholine receptors of the brain, which are prominent e.g. in the cortex, thalamus and ventral tegmental area. They are situated in presynaptic terminals and thus modulate neurotransmitter release. Nicotine stimulates dopamine transmission in both nigrostriatal and mesolimbic dopamine pathways of the brain, a major mechanism underlying its reinforcing properties. Among psychoactive substances, nicotine can be regarded as a special case because its reinforcing effects and potential for addiction are high, equaling those of heroin, although it does not produce intoxication (Goldstein and Kalant 1990, West 2006). Due to the lack of intoxicating effects, the social and personal consequences of tobacco addiction are very different from those of alcohol and many illicit substances, although the adverse health effects are grave. Importantly, tobacco smoking co-occurs frequently with alcohol and other substance use and disorders (Li et al. 2007, Schuckit 2009). In the present thesis, smoking and nicotine dependence are not studied as main outcomes, but their role as comorbidities and correlating factors for alcohol and illicit substance use disorders is addressed.

2.1.2 Common neurobiological mechanisms of drug action and addiction

Although each class of psychoactive substances has its unique pharmacological mechanisms, they all share common effects, especially those related to the mesolimbic dopamine system of the brain (Figure 1) and its role underlying reward or pleasurable experiences. Directly or indirectly, administering any psychoactive substance acutely enhances dopamine transmission, especially intrasynaptic levels of dopamine in the nucleus accumbens (Goodman 2008). This is a property shared with more natural rewards such as sex, eating (especially sweet foods), or pleasurable social interactions (Berridge and Kringelbach 2008). However, psychoactive substances differ from these conventional reinforcers in that their effects on dopamine release

are significantly greater in magnitude—at least five- to tenfold—and in duration than those induced by natural rewards (Volkow and Li 2004).

Despite this consistent pattern of activation, mesolimbic dopamine stimulation does not appear to be necessarily required for the acute reinforcing effects of all substances, and there is evidence of dopamine-independent reinforcement in the nucleus accumbens (Koob and Volkow 2010). Further, the relationship between the mesolimbic dopamine system (also termed the “reward system” of the brain) and reward, as well as the components of the reward process itself, are not straightforward. Increases in dopamine may in fact not be directly related to reward *per se*, but rather to the prediction of reward and to salience, i.e. stimuli or environmental changes that are arousing or elicit an attentional-behavioral switch (Volkow and Li 2004). Evidence also suggests that reward has separate and partly independent components, such as “liking” and “wanting”, which may have a partly non-overlapping neurochemical background (Berridge et al. 2009). This separation is compatible with reports of some addicted individuals, that they seek the drug even though its effects are no longer pleasurable (Volkow and Li 2004).

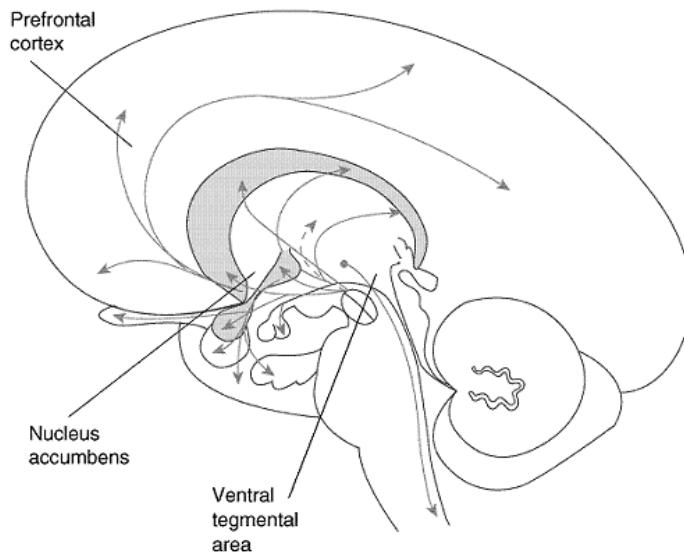


FIGURE 1. Dopaminergic pathways in the brain, including the mesolimbic dopaminergic system, which consists of the ventral tegmental area, the nucleus accumbens, and the prefrontal cortex.

(Source: <http://pubs.niaaa.nih.gov/publications/arh26-2/136-142.htm>)

Addiction, or substance dependence (reviewed in more detail in the next chapter), is a pathology of motivation and choice (Kalivas and Volkow 2005) which arises due to “usurpation” of neural processes that normally serve reward-related learning and memory (Hyman et al. 2006). Addictive psychoactive substances are reinforcing, meaning that behaviors aimed at obtaining and taking these substances tend to increase in frequency with experience. After repeated use both humans and animals tend to seek and self-administer these substances in preference to pursuing other goals, and obtaining them often becomes a priority which is not compromised despite severe obstacles. The major substrates of persistent compulsive substance use are likely to be molecular and cellular mechanisms that underlie long-term associative memories in several forebrain circuits that receive input from midbrain dopamine neurons (Hyman et al. 2006). Synapses of the brain have a ubiquitous ability to undergo activity-dependent changes in their synaptic strength. Two basic mechanisms underlying this synaptic plasticity are activity-dependent strengthening and weakening of synaptic transmission, termed long-term potentiation (LTP) and long-term depression, which can occur both at excitatory and inhibitory synapses. Exposure to addictive substances is known to trigger LTP especially in the ventral tegmental area but also e.g. in the amygdala, and hijacking these basic mechanisms of synaptic plasticity in key brain circuits seems to be a crucial element underlying addictive behavior (Hyman et al. 2006, Kauer and Malenka 2007, Russo et al. 2010). The role of dopamine may be most important for progressively shaping substance use into drug-seeking behaviors that are difficult to control, whereas the enduring vulnerability to relapse seems to arise from long-lasting adaptations in the corticostriatal glutamatergic circuitry in which the dopamine axon terminals are embedded (Kalivas 2009, Kalivas and Volkow 2005, Kalivas et al. 2009, Vengeliene et al. 2009). All in all, the transition to addiction seems to begin with changes in the mesolimbic dopamine system, followed by a cascade of neuroadaptations from the ventral striatum to dorsal striatum and orbitofrontal cortex, and eventually dysregulation of the prefrontal cortex, cingulate gyrus and extended amygdala (Koob and Volkow 2010).

2.1.3 What are substance use disorders?

Although intuitively we have a good grasp of what “addiction” and “being addicted” mean, scientific attempts to classify problems related to alcohol and drug use have been problematic both contemporarily and historically. Contemporary conceptualizations of substance use disorders are formulations of the “disease model” of addiction, which has its origins in the late 18th and early 19th centuries (Ferentzy 2001, Leshner 1997, Levine 1978, Meyer 1996). The term “alcoholism” was probably first used in 1849, whereas the early drug epidemics of the late 19th century gave rise to terms such as “morphism” and “narcomania” (Grant and Dawson 1999). However, the origins of the disease concept are often credited to Benjamin Rush

(1745-1813) who conceptualized excessive alcohol use as a disease in which alcohol was the causal agent, loss of control over drinking the characteristic symptom, and total abstinence the only effective cure (Meyer 1996). This focus on loss of control links the contemporary concept of substance dependence with this early description. Two other notable historical developments were Jellinek's formulation of a classification that included a disorder that did not involve dependence (Jellinek 1960), and development of the concept of alcohol dependence syndrome by Edwards and Gross (1976). These developments have had an evident impact on the history and current forms of psychiatric classification of substance use disorders (Grant and Dawson 1999).

The current major psychiatric diagnostic classification systems, *The ICD-10 Classification of Mental and Behavioural Disorders* (WHO 1992) and *The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)* (APA 2000), do not use the term addiction but instead describe a condition termed substance dependence. In addition, both of these systems describe a less severe form of problematic substance use not including addiction-like symptoms, termed harmful use in ICD-10 and substance abuse in DSM-IV. Together, substance dependence and abuse/harmful use make up the diagnostic class of substance use disorders, further divided into disorders of specific substances, such as alcohol use disorders and cannabis use disorders, and into current and lifetime disorders (APA 2000, WHO 1992). The DSM-IV and ICD-10 diagnostic criteria for substance dependence are shown in Table 1, and those for substance abuse/harmful use in Table 2.

Both DSM-IV and ICD-10 conceptualize substance use disorders as syndromes that include a heterogeneous collection of symptoms. Thus, a large number of different profiles of symptoms lead to the diagnosis of substance dependence or abuse/harmful use. The symptoms of substance dependence in both classification systems rely heavily on the alcohol dependence syndrome set out by Edwards and Gross (1976), including withdrawal and tolerance (reduced effect with repeated use, leading to increasing amounts of use) as possible symptoms. These symptoms of "physiological dependence" are not required for diagnosis, and DSM-IV differentiates two subtypes of dependence based on whether these symptoms are met. However, their inclusion in the list of diagnostic criteria for substance dependence is significant because, as has been strongly argued, at the core of addiction is the compulsive and uncontrolled nature of substance use behaviors rather than normal physiological adaptation, which can also result from controlled use of medical drugs (O'Brien et al. 2006, Sellman 2010, West 2006). Tolerance and withdrawal notwithstanding, the current conceptualization of substance dependence clearly describes a state of addiction, characterized by impaired control over substance use, neglect of other activities because of substance use, and continued substance use despite problems evidently related to it. Recently, this notion of addiction being "fundamentally about compulsive behavior" featured as No.1 in the list of "the 10 most important things known about addiction", intended as an eye-opener for both the general public and health professionals (Sellman 2010).

TABLE 1. DSM-IV and ICD-10 diagnostic criteria for substance dependence.

	DSM-IV	ICD-10
Clustering criterion	A. A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by three or more of the following occurring at any time in the same 12-month period:	A. Three or more of the following have been experienced or exhibited at some time during the previous year:
Tolerance	(1) Need for markedly increased amounts of the substance to achieve intoxication or desired effect; or markedly diminished effect with continued use of the same amount of the substance	(1) Evidence of tolerance, such that increased doses are required in order to achieve effects originally produced by lower doses
Withdrawal	(2) The characteristic withdrawal syndrome for the substance or use of the substance (or a closely related substance) to relieve or avoid withdrawal symptoms	(2) A physiological withdrawal state when substance use has ceased or been reduced as evidenced by: the characteristic substance withdrawal syndrome, or use of substance (or a closely related substance) to relieve or avoid withdrawal symptoms
Impaired control	(3) Persistent desire or one or more unsuccessful efforts to cut down or control substance use	(3) Difficulties in controlling substance use in terms of onset, termination, or levels of use
	(4) Substance use in larger amounts or over a longer period than the person intended	
Neglect of activities	(5) Important social, occupational, or recreational activities are given up or reduced because of substance use	(4) Progressive neglect of alternative pleasures or interests in favor of substance use; or
Time spent	(6) A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of the substance used	A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of substance use
Continued use despite problems	(7) Continued substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by use	(5) Continued substance use despite clear evidence of overtly harmful physical or psychological consequences
Compulsive use	None	(6) A strong desire or sense of compulsion to use substance
Duration criterion	B. No duration criterion separately specified, but several dependence criteria must occur repeatedly as specified by duration qualifiers associated with criteria (e.g. "often", "persistent", "continued")	B. No duration criterion separately specified
Criterion for subtyping dependence	With physiological dependence: Evidence of tolerance or withdrawal	None
	Without physiological dependence: No evidence of tolerance or withdrawal	

(Sources: APA 2000, WHO 1992, Grant and Dawson 1999)

TABLE 2. DSM-IV and ICD-10 diagnostic criteria for substance abuse/harmful use.

<p>DSM-IV Substance abuse</p> <p>A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following occurring within a 12-month period:</p> <ol style="list-style-type: none"> (1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (2) recurrent substance use in situations in which use is physically hazardous (3) recurrent substance-related legal problems (4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance <p>B. The symptoms have never met the criteria for substance dependence for the same class of substance.</p>
<p>ICD-10 Harmful use of substances</p> <p>A. A pattern of substance use that is causing damage to health. The damage may be physical or mental. The diagnosis requires that actual damage should have been caused to the mental or physical health of the user.</p> <p>B. No concurrent diagnosis of the substance dependence syndrome for the same class of substance.</p>

(Source: APA 2000, WHO 1992, Grant and Dawson 1999)

Psychometric validity and reliability of the substance use disorder diagnoses have been found to be good, based on evidence from clinical samples, general population samples and samples of participants and their relatives in genetic studies, conducted in many countries around the world (Grant and Dawson 1999, Grant et al. 2007, Hasin and Paykin 1999, Hasin 2003, Hasin et al. 2006). This is especially true for substance dependence, whereas evidence is more mixed for abuse/harmful use, and it has been suggested that future classifications should describe this diagnostic entity more clearly as referring to consequences of heavy use, assessed independently of dependence (Hasin et al. 2006). Although substance abuse has often been conceptualized as a prodrome to dependence, only a small minority of those diagnosed with alcohol abuse in fact seem to go on to develop alcohol dependence (Grant et al. 2001a, Lemke et al. 2005, Schuckit et al. 2001), lending some support to their categorization as two different diagnoses. However, due to problems identified with the DSM-IV division between abuse and dependence, the DSM-5 Substance Use Disorders Workgroup has recommended combining abuse and dependence into a single disorder of graded clinical severity in the upcoming fifth edition of the DSM, DSM-5, expected to be released in 2013 (<http://www.dsm5.org/>).

Despite evidence of generally good reliability and validity, several studies have questioned the categorical nature of two distinct substance use disorder diagnoses. Some studies examining the latent factor structure of DSM-IV substance use disorder criteria have found support for two dimensions bearing a strong resemblance to the diagnoses of abuse and dependence (Blanco et al. 2007, Harford and Muthén 2001), whereas many more have argued for a single underlying continuum of risk (Gillespie et al. 2007, Hasin et al. 2006, Hasin and Beseler 2009, Saha et al. 2006),

and some for a combination of categorical and dimensional criteria (Helzer et al. 2006, Muthén 2006). While diagnoses are clearly necessary for clinical decision-making, a dimensional indicator of risk for substance dependence might provide more information for research purposes (Hasin et al. 2006).

A further issue of validity is related to the cross-cultural variability of the conceptualization of substance use disorders. For example, Room (1985, 2006) has argued that the concept of dependence can be interpreted as culture-bound, with a specific history and cultural inception starting with the early American temperance movement (Levine 1978). On the other hand, empirical evidence does lend support to cross-cultural commonality and generalizability of the concept of substance dependence and factors associated with it, one near-universal feature being the high level of social disapproval and stigma related to both alcohol and drug addiction in many different cultures (Room 2006). More theoretically, the concept of mental disorders in general—of which addiction is one—has been difficult to define, and there have been extreme accounts claiming e.g. that mental disorders only exist in the eye of the psychiatrist, are moral rather than medical problems, or depend too radically on social context (Cooper 2007). While some of these concerns may have some validity, on balance it seems clear that substance use disorders are indeed real phenomena with a family of core symptoms, often predictable course of progression, and meaningful psychological and biological underpinnings (Cooper 2007, Finney et al. 1999, Thagard 2008, Volkow and Li 2004, West 2006).

In the present thesis, alcohol and other substance use disorders were defined according to the DSM-IV criteria (Studies I and II) and in one study (III) according to an earlier version of the DSM, DSM-III-R (APA 1987). DSM-III-R was the first diagnostic classification to reflect the concept of the alcohol dependence syndrome by Edwards and Gross (1976), and only minor changes in the categorization of substance use disorders were made in the transition to DSM-IV seven years later (Hasin 2003). Compared to the current DSM-IV criteria (APA 2000), the DSM-III-R criteria for substance dependence are broader (also including inability to fulfill roles, and hazardous use) and those for substance abuse narrower (continued use despite knowledge of problems, or recurrent use in hazardous situations) (APA 1987), but overall these two classifications are in good agreement (Grant 1996, Hasin 2003). In addition to diagnostic classification and symptoms, questionnaire-based indicators of problems related to alcohol use, correlated with alcohol dependence, were utilized in two of the present studies (III and IV).

2.2 Epidemiology of alcohol and other substance use disorders

This section reviews key epidemiological issues related to alcohol and other substance use and disorders. A special focus of this review is on substance use disorders among young adults. With respect to correlates and risk factors of substance use disorders, the focus is on familial and individual factors. Individual differences in cognitive functioning as a potential risk factor for substance use disorders, and the contribution of genetic factors underlying risk are discussed separately in chapters 2.3 and 2.4, respectively.

2.2.1 Alcohol and other substance use

In order to develop substance abuse or dependence, it is necessary to initiate substance use and make a transition into (more or less) regular use. However, most people who consume alcohol or illicit substances do not have problems and are not dependent on the substance they use (Goldstein and Kalant 1990, Schuckit 2009). Further, although early initiation of use is a robust risk factor for substance use disorders (see below), experimentation with alcohol and other substances in adolescence, and even binge drinking, is common and can be perceived as socially normative in some contexts (Clark 2004, Kuntsche et al. 2004, Perkins 2002).

An estimated 80% of men and 60% of women in developed countries drink alcohol at some time during their lives, and between half and two-thirds of those who ever drank are likely to consume alcohol in any year (Grant and Dawson 1999, Schuckit 2009). The prevalence of illicit substance use is more difficult to estimate, particularly for some substances (e.g. opioids), but known estimates of any use during the lifetime range from a few per cent for stimulants to more than 20% for cannabis among European adults, with notable variation between countries (EMCDDA 2008). Estimates for North America are overall fairly similar, but the prevalence of lifetime cannabis use is higher, probably in the range of 30-40% (United Nations Office on Drugs and Crime 2009). In Finland, alcohol use is common, with almost 90% of the adult population reporting having consumed alcohol during the previous year (Helakorpi et al. 2009). In contrast, the prevalence of illicit drug use—especially that of cannabis—is somewhat lower than in many other European countries (EMCDDA 2008).

Alcohol and other substance use is typically initiated in mid-adolescence. Regarding alcohol, the usual age of first drink independently of the family is around 14–16 years in many different countries, including Finland (Eliassen et al. 2009, Patton et al. 2007, Pitkänen et al. 2005, Prescott and Kendler 1999, Rose et al. 1999, Rose et al. 2001, Young et al. 2002). The period of heaviest drinking is usually from late adolescence to early adulthood, approximately between 18 and 22 years of age (Chen

and Kandel 1995, Clark 2004, Grant and Dawson 1999, Kandel and Logan 1984, Schuckit 2009). Complementing and contrasting these normative trends, however, several studies have found notable individual variation in the developmental course of alcohol use, suggesting distinct prototypical courses of alcohol involvement, such as a stable low-user course, a stable high-user course, or a late-onset course (Chassin et al. 2002, Clark 2004, Jackson et al. 2008, Sher et al. 2005, Tucker et al. 2003, Windle et al. 2005). Also gender differences in alcohol use and drinking progression begin to emerge in late adolescence (Schulte et al. 2009).

Alcohol and cigarettes are typically the first psychoactive substances used, and the onset of illicit substance use usually occurs some years later (Chen and Kandel 1995, Kandel and Yamaguchi 2002). There is considerable variation between countries in the use of cannabis and other illicit substances (United Nations Office on Drugs and Crime 2009), but late adolescence and young adulthood consistently emerge as typical periods of initiation and highest use (DeWit et al. 1997, Grant and Dawson 1999, Lansford et al. 2008). For example, in New Zealand where the prevalence of cannabis use is relatively high, initiation of use typically occurs around age 18, and by the age of 25 nearly 80% of young adults have used cannabis at least once (Boden et al. 2006). In Finland, 13.5% of adolescents were recently reported to have used cannabis or other illicit substances at least once by the age of 17.5 years, with early onset of smoking being the most important predictor (Korhonen et al. 2008). Quit rates for illicit drug use are high in the first few years of use (DeWit et al. 1997), but a majority of those who go on to develop substance use disorders seem to make the transition into abuse or dependence within five years from first use, the rate being faster for cannabis than alcohol (Behrendt et al. 2009).

2.2.2 Prevalence of substance use disorders

Several large-scale epidemiological surveys have been conducted in order to estimate the prevalence of psychiatric disorders, including alcohol and other substance use disorders. The National Comorbidity Survey, conducted between 1990 and 1992 on a multistage area probability sample of 8,098 Americans aged 15 to 54, reported the prevalence of any DSM-III-R substance use disorder during the lifetime to be 26.6% in that population, and a prevalence of 11.3% in the previous 12 months was found (Kessler et al. 1994). Alcohol dependence was the most prevalent diagnosis with a lifetime prevalence of 14.1%, whereas the lifetime prevalence of any illicit drug dependence was 7.5% (Kessler et al. 1994, Warner et al. 1995). A considerably larger, US-representative sample of more than 42,000 participants aged 18 years or older was interviewed in the 1992 National Longitudinal Alcohol Epidemiologic Survey (NLAES), resulting in comparable lifetime prevalence estimates of 13.3% and 4.9% for DSM-IV alcohol dependence and abuse (Grant and Dawson 1999). The lifetime prevalence of any drug abuse or dependence in the NLAES was estimated at 8.1% for men and 4.2% for women, with highest prevalence for cannabis use disorders

(Grant and Dawson 1999). In both of these early surveys, both lifetime and past year prevalence of substance use disorders were highest in young adults (Grant and Dawson 1999, Kessler et al. 1994, Warner et al. 1995).

More recently, two new surveys in the US have been conducted. The National Comorbidity Survey Replication interviewed 9,828 individuals between 2001 and 2003, and the prevalence of any DSM-IV substance use disorder during the lifetime was estimated at 14.6%, and in the previous 12 months at 3.8% (Kessler et al. 2005a, Kessler et al. 2005b). These estimates should be treated with caution, however, because the diagnostic instrument used in this study, the World Mental Health-Composite International Diagnostic Interview, was designed to skip questions on DSM-IV dependence if the respondent does not respond positively to questions on DSM-IV abuse, effectively using abuse as a screen for dependence and resulting in an underestimation of the prevalence of substance dependence (Grant et al. 2007, Kessler and Merikangas 2007). Another large-scale representative survey of more than 43,000 Americans that did not have this flaw, the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), did indeed estimate notably higher lifetime and 12-month prevalences: 30.3% and 8.5% for alcohol use disorders, and 10.3% and 2.0% for illicit drug use disorders (Compton et al. 2007, Hasin et al. 2007).

In European studies, fairly similar prevalence estimates have been found. For example, a Norwegian psychiatric epidemiological study on a random sample of 2,066 Oslo residents reported the prevalence estimates of 22.7% for lifetime alcohol and 3.4% for drug use disorders, and 12-month prevalences of 10.6% and 0.9% for alcohol and drug use disorders, respectively (Kringlen et al. 2001). Slightly lower prevalences of 18.7% and 8.9% for any DSM-III-R substance use disorder during the lifetime and in the previous 12-months were estimated in a sample of 7,076 people, representative of the Dutch population (Bijl et al. 1998). In Germany, the prevalence of any substance use disorder during the lifetime was recently estimated as low as at 9.9%, with the discrepancy in the estimates being possibly due to differences in diagnostic instruments (Jacobi et al. 2004). In Finland, the 12-month prevalence of alcohol abuse or dependence in the general adult population aged 30 or over has been estimated at 4.5% (Pirkola et al. 2005b), and that of lifetime alcohol dependence at 7.9% (Pirkola et al. 2006).

From a more global perspective, Rehm et al. (2009) recently obtained population estimates of the point prevalence of alcohol use disorders for people aged 18–64 years from 37 studies. This re-analysis estimated a global 12-month prevalence of alcohol use disorders at 3.6%, with multifold prevalence in men (6.3%) compared to women (0.9%). Variation between geographical areas was even larger, with prevalence estimates ranging from less than 0.5% in the eastern Mediterranean region to over 10% in the eastern European region (mostly Russia). However, estimates for the rest of Europe, the American region, and the western Pacific region were very close to each other (Rehm et al. 2009).

The prevalence and incidence of alcohol and other substance use disorders has in general been found to be highest among young adults. In the NESARC, the 12-month prevalence of alcohol use disorders was 16.2% among participants between 18 and 29 years, 9.7% among those between 30 and 44 years, and 5.4% among those aged 45-64 years (Hasin et al. 2007). In these same age categories, the 12-month prevalence of drug use disorders was 5.3%, 1.9%, and 0.8%, respectively (Compton et al. 2007). In a German survey of adolescents and young adults between ages 14 and 24, the lifetime and 12-month prevalence estimates for any substance use disorder were 17.7% and 11.4%, respectively (Wittchen et al. 1998). In Finland, only one study has previously estimated the prevalence of alcohol and other substance use disorders among young adults. This study used a small sample of 20–24-year-old urban young adults, and reported a one-month prevalence estimate of 6.2% for a combination of alcohol and cannabis use disorders (Aalto-Setälä et al. 2001). Thus, the lifetime prevalence of alcohol and other substance use disorders among young adults in Finland is currently unknown, motivating its estimation in the present thesis (Study I).

In summary, the lifetime risk of alcohol and other substance use disorders is currently around 10–20% in Western countries, with highest risk consistently found among men and in young adulthood. Importantly, substance use disorders are not uncommon in other parts of the world either (Rehm et al. 2009, United Nations Office on Drugs and Crime 2009, WHO 2004a, Zhou et al. 2009). Together with mood and anxiety disorders, substance use disorders are among the most common mental disorders (Bijl et al. 1998, Kessler et al. 1994, Kringlen et al. 2001, Pirkola et al. 2005b, Wittchen et al. 1998).

2.2.3 Correlates and risk factors of substance use and disorders

Substance use and the development of substance use disorders are complex phenomena. This complexity is reflected in the range of risk factors and correlates found to be associated with them (Hawkins et al. 1992). Like all human behavior, substance use and disorders—though fundamentally behavior of an individual—occur in the context of societies with their legal and cultural norms and other factors restricting or enabling behavior. Societal factors found to be related to levels of substance use and disorders include policies and laws regulating substance use, cultural norms (including religion), availability of substances, economic deprivation, lack of support structures, and lack of social cohesion and control (Babor et al. 2003, Compton et al. 2005, Galea et al. 2004, Hawkins et al. 1992, Mäkelä and Österberg 2009, Sampson et al. 2002, von Sydow et al. 2002). The importance of these societal factors is aptly reflected in the between-country variability in the prevalence of substance use disorders (Rehm et al. 2009), clearly not explained solely by the relatively small genetic differences between ethnic groups (Barbujani

and Colonna 2010, Berg et al. 2005, Chaudhry et al. 2008). However, as the focus of the present studies is on familial and individual-level factors, societal risk factors are not covered in more detail. Some of the most consistently reported familial and individual correlates and risk factors of substance use and disorders are reviewed below, although a comprehensive review of all known risk factors is beyond the scope of this thesis.

Psychiatric comorbidity

Epidemiological studies have highlighted the high levels of concurrent or comorbid psychiatric disorders among people diagnosed with substance dependence or abuse. For example, Jacobi et al. (2004) reported that of those with any 12-month substance use disorder, only 55% had a pure disorder without any comorbid conditions. First, people with substance use disorders are often dependent on or abuse more than one substance, and illicit drug use disorders without lifetime alcohol use disorders are rare (Compton et al. 2007, Grant and Dawson 1999, Hasin et al. 2007, Stinson et al. 2006). Second, both alcohol and drug use disorders occur often comorbidly with depressive and anxiety disorders (Compton et al. 2007, Conway et al. 2006, Grant and Harford 1995, Grant et al. 2004, Hasin et al. 2007, Jacobi et al. 2004, Merikangas et al. 1998a, Pirkola et al. 2005b, Schneier et al. 2010). Several longitudinal studies have investigated the temporal sequencing of this comorbidity, and there is evidence on mood and anxiety disorders preceding substance use and disorders (Flensburg-Madsen et al. 2009, Goodwin et al. 2004, Grant et al. 2009, Merikangas et al. 1998a, Sihvola et al. 2008, Swendsen et al. 2010, Zimmermann et al. 2003) as well as the other way around (Falk et al. 2008, Fergusson et al. 2009, Flensburg-Madsen et al. 2009, Schuckit 2006). Importantly, temporal precedence, although a necessary condition for causality, is not enough to prove it (Rothman and Greenland 2005), and the reasons behind the comorbidity of substance use disorders and mood or anxiety disorders are likely to be complex and heterogeneous (Edwards et al. in press, Hall et al. 2009, Merikangas et al. 1998b, Schuckit and Hesselbrock 1994, Schuckit 2006).

Education and socioeconomic correlates

Several epidemiological studies have also indicated that alcohol and other substance use disorders tend to be more prevalent among people with lower education, unemployment, or lower income (Alonso and Lepine 2007, Compton et al. 2007, Jacobi et al. 2004, Kessler et al. 2005b, Pirkola et al. 2005b, Warner et al. 1995). With regard to education, longitudinal studies have highlighted interconnections between developmental patterns of substance use and educational outcomes, suggesting both that poor school success and learning problems predict later substance use and disorders and that substance use in adolescence predicts lower education (Beitchman et al. 2001, Bingham et al. 2005, Brook et al. 2008, Cox et al. 2007, Crum et al. 1992, Crum 2006, Droomers et al. 2004, Fergusson et al. 2003a, Fothergill and Ensminger 2006, Fothergill et al. 2008, Harford et al. 2006, Hayatbakhsh et al. 2008, Horwood et al. 2010, Kessler et al. 1995, King et al. 2006, Legleye et al. 2010, Lynskey

et al. 2003, Martins and Alexandre 2009, Merline et al. 2004, Muthén and Muthén 2000, Pitkänen et al. 2008, Riala et al. 2003, Swendsen et al. 2009). Looking more closely at socioeconomic factors and drinking patterns in young adults, Casswell et al. (2003) found that lower social status was not related to frequency of drinking but was instead associated with consuming higher quantities of alcohol per drinking session, and that quantity of drinking was most strongly influenced by educational achievement. Drinking patterns may be one factor that mediates the association between lower socioeconomic status and alcohol problems (Huckle et al. 2010), and socioeconomic differences may also be associated with expectancies related to alcohol's positive effects (McCarthy et al. 2002).

More generally, socioeconomic status is known to be strongly related to a multitude of medical conditions, health behaviors, and mortality (Adler et al. 1994). In addition to this general relationship, education and other components of socioeconomic status also seem to have specific patterns of risk associated with them (Braveman et al. 2005, Geyer et al. 2006, Laaksonen et al. 2005). For example, a register-based study of Finnish men found that the social class differences in alcohol-associated suicide were mostly explained by education, whereas income had only a minor effect (Mäki and Martikainen 2008). In a similar vein, a study of nearly 50,000 Swedish men found that the association between social class and alcohol dependence was to a large degree explained by measures of school achievement in adolescence (Hemmingsson et al. 1998). Studies looking at specific factors mediating the association between socioeconomic status and high-risk alcohol consumption have indicated the involvement of both material and social resources (Droomers et al. 1999, Moos et al. 2010). In addition, partner's education seems to be related to substance use behaviors independently of own education (Monden et al. 2003).

Familial factors

It has been known for a long time that alcohol and other substance use disorders tend to run in families (Cotton 1979, Goodwin 1985, Johnson et al. 1984). Several family studies have confirmed the heightened risk of substance use and disorders in the offspring of parents with substance use disorders (Alati et al. 2005, Biederman et al. 2000, Bucholz et al. 2000, Lieb et al. 2002, Macleod et al. 2008, Merikangas et al. 1998c, Milne et al. 2009, Ohannessian and Hesselbrock 2008, Steinhausen et al. 2009, Tyrfingsson et al. 2010, Walden et al. 2007). For example, Lieb et al. (2002) found in a community sample, consistently with numerous previous studies, that offspring of alcoholic parents had an increased risk to drink more in adolescence, and that both maternal and paternal alcoholism increased the risk for children to shift into higher categories of alcohol consumption. Parental alcohol use disorders also increased the risk of alcohol abuse and dependence in the offspring (Lieb et al. 2002). Similarly, Walden et al. (2007) reported that parental substance use disorders were associated with acceleration of alcohol and other substance involvement in the offspring during adolescence. Conversely, using a population-based sample of more than 19,000 individuals and extensive genealogy information from Iceland, Tyrfingsson et al.

(2010) reported relative risk ratios in the range of 2–12 for substance dependence in parents, given that their son or daughter was dependent on the same substance. Besides substance use disorders, also other parental psychopathology increases the risk for substance use and disorders in the offspring, and there is some evidence of especially increased risk related to comorbid parental psychopathology (Ellis et al. 1997, Ohannessian et al. 2004, Ramchandani and Psychogiou 2009, Steinhausen et al. 2009). While family studies including data from parents and offspring cannot tease out the roles of biological and cultural inheritance, large numbers of studies comparing mono- and dizygotic twins have consistently provided evidence that the familiarity of substance use disorders is for the most part due to genetic factors (Dick et al. 2009), as will be reviewed in more detail in chapter 2.4.

Other familial and childhood risk factors of substance use disorders include low parental education and socioeconomic status (Caldwell et al. 2008, Hawkins et al. 1992), various childhood adversities such as economic adversity, parental divorce or death (Clark et al. 1997, Green et al. 2010b, Huurre et al. 2010, Kestilä et al. 2008, McLaughlin et al. 2010, Pirkola et al. 2005a, Schilling et al. 2008, van der Vegt et al. 2009), and poor parenting practices such as low parental monitoring (Guo et al. 2001, Latendresse et al. 2008). Importantly, an international adoption study found that severe early adversities, such as parental abuse or neglect, increase the risk of adult substance use disorders and other psychopathology even when children are taken out of their problematic environments (van der Vegt et al. 2009). A possible mechanism underlying the effects of early adversities on later substance use and disorders could be related to neurobiological effects of chronic stress, as there is compelling evidence that the stress systems of the brain are involved in the transition to substance dependence (Briand and Blendy 2010, Koob 2009, Uhart and Wand 2009). Also epigenetic changes could be involved (Launay et al. 2009).

Personality and behavioral factors

A wealth of longitudinal studies has demonstrated that personality and behavioral patterns observed in childhood and adolescence have predictive value for the risk to develop substance use disorders later in life. In perhaps one of the most striking of these studies, Caspi et al. (1996) classified 3-year-old children into groups based on observations of their behavior, and then reassessed these individuals at age 21 for DSM-III-R psychiatric disorders. A notable finding was that children who were classified as undercontrolled (i.e. impulsive, restless, or distractible) were more than two times as likely to be diagnosed with alcohol dependence (Caspi et al. 1996). In a similar vein, Cloninger et al. (1988) found that the two interrelated personality dimensions of high novelty-seeking (a tendency toward frequent exploratory activity and intense exhilaration in response to novel stimuli) and low harm-avoidance (a tendency to respond intensely to aversive stimuli and their conditioned signals) assessed at age 11 distinguished boys with a notably heightened risk for alcohol abuse at age 27. Although personality and behavioral patterns clearly are correlated, studies on their contribution to the risk for substance use disorders have

diverged into two somewhat separate lines of research, one of them focusing on various forms of childhood and adolescent psychopathology and the other more on normal variation in personality.

Several studies have reported findings related to “undercontrolled” behavior similar to those of Caspi et al. (1996), with variation between the studies in studied age periods, characterizations of undercontrol, substance use outcomes, other factors included in the analyses, and sample characteristics (Alati et al. 2005, Biederman et al. 2006, Biederman et al. 2008, Cohen et al. 2007, Dawes et al. 1997, Dierker et al. 2007, Disney et al. 1999, Elkins et al. 2007, Fergusson et al. 2005b, Fergusson et al. 2007, Grekin et al. 2006, Hayatbakhsh et al. 2008, King et al. 2004, Kirisci et al. 2006, Korhonen et al. 2010, Kuperman et al. 2001, Lynskey and Fergusson 1995, McGue and Iacono 2005, Neumark and Anthony 1997, Niemelä et al. 2006, Pardini et al. 2007, Tarter et al. 2003, Tarter et al. 2004). Taken together this bulk of evidence strongly suggests that a tendency for behavior that can be described as disinhibited, distractible, impulsive, aggressive, or externalizing, as well the psychiatric diagnoses of antisocial personality disorder, conduct disorder and attention-deficit/hyperactivity disorder (ADHD) in childhood and adolescence significantly increase the risk for all kinds of involvement with alcohol and other substances, ranging from initiation of use to substance dependence (Barman et al. 2004, de Wit 2009, Dick et al. 2010, Hawkins et al. 1992, Iacono et al. 1999, Vanyukov et al. 2003, Verdejo-Garcia et al. 2008, Weinberg and Glantz 1999). Importantly, this finding is not restricted to humans, but also animal studies have highlighted the role of impulsivity and related traits in relation to substance addiction (Belin et al. 2008, Dick et al. 2010, Oberlin and Grahame 2009, Perry and Carroll 2008, Winstanley et al. 2010). Although the neurobiology of impulsivity and related traits is complex (Depue and Collins 1999, Evenden 1999), evidence from animal and human studies suggests the involvement of dopamine transmission in important midbrain and frontal areas, also associated with the development of substance use disorders (Bardo et al. 1996, Beck et al. 2009, Crews and Boettiger 2009, Dalley et al. 2007, Forbes et al. 2009, van Gaalen et al. 2006, Zald et al. 2008).

A special question related to childhood psychopathology as a risk factor for substance use disorders concerns the relative contributions of conduct disorder-type and ADHD-type behaviors. Conduct disorder is characterized by antisocial behavior that violates the rights of others or other social norms (Loeber et al. 2009a), whereas ADHD is a disorder of attention and concentration, often including hyperactive behavior (Floet et al. 2010). Studies trying to tease out the risks related to these two intercorrelated disorders have found evidence in support of the primary role of either disorder taking into account the other, as well as of their independent effects (Biederman et al. 2006, Elkins et al. 2007, Gau et al. 2007, Kuperman et al. 2001, Lynskey and Fergusson 1995, Lynskey and Hall 2001). Several studies have also implicated a wider perspective, where different forms of antisocial and undercontrolled behavior are seen as manifestations of an underlying spectrum of

liability, strongly influenced by genetic factors (Iacono et al. 2008, Krueger et al. 2002, Vanyukov et al. 2003).

Various conceptualizations of normal variation in personality and temperament dimensions have also been studied in relation with the development of alcohol and other substance use disorders. Despite differences between these classifications, a general picture has emerged that high scores on excitatory-like personality traits, such as novelty seeking (Cloninger et al. 1988, Masse and Tremblay 1997, Mulder 2002), sensation seeking (Cyders et al. 2009, Hittner and Swickert 2006, Zuckerman and Kuhlman 2000), extraversion (Grekin et al. 2006, Sher et al. 2000), or behavioral approach (Franken et al. 2006) are associated with substance use disorders. Also low scores on their inhibitory-like counterparts, such as harm avoidance, neuroticism, or behavioral inhibition have been associated with increased risk for substance use disorders, although the findings seem less consistent (Cloninger et al. 1988, Franken et al. 2006, Grekin et al. 2006, Howard et al. 1997, Masse and Tremblay 1997, Mulder 2002).

In addition to excitatory-like traits and undercontrolled behavior (or “externalizing”), there is some evidence of an “internalizing” pathway to alcohol and other substance use disorders (Clark 2004, Sher et al. 2005, Zucker 2008). However, findings related to these temperamental traits, such as negative emotionality, depressiveness and anxiety, as predictors of substance use and disorders have in general been weaker than those of externalizing behaviors (Elkins et al. 2006, Dierker et al. 2007, King et al. 2004, Lansford et al. 2008, McGue et al. 1999, Pardini et al. 2007).

In summary, on the basis of a large number of studies, there is ample evidence that individual differences in certain temperamental and behavioral traits and especially their pathological extremities, manifested already in childhood and adolescence, are associated with increased risk for substance use and disorders. A tendency for impulsive, aggressive or otherwise undercontrolled behavior seems to indicate greatest risk.

Early initiation of substance use

Early initiation of substance use has been consistently found to increase the risk for substance use disorders. This pattern has been reported for early onset of smoking as a predictor of later alcohol and drug use and disorders (Creemers et al. 2009, Grant 1998, Hanna and Grant 1999, Huizink et al. 2010, Korhonen et al. 2008, Riala et al. 2004, Vega and Gil 2005), younger age at initiation of alcohol use as a predictor of later heavy drinking and alcohol use disorders (Buchmann et al. 2009, Dawson et al. 2008, DeWit et al. 2000, Grant and Dawson 1997, Grant et al. 2001b, Pitkänen et al. 2005, Prescott and Kendler 1999) as well as early onset of cannabis and other drug use as a predictor of later drug abuse and dependence (Behrendt et al. 2009, Chen et al. 2009, Ellickson et al. 2004, Grant and Dawson 1998, King and Chassin 2007, Lynskey et al. 2003). For example, using a Canadian community sample, DeWit et al. (2000) found that more than 30% of those who initiated drinking at ages 11–12 met

the criteria for alcohol dependence or abuse 10 years later. Among those who began to drink at ages 13–14 this rate was approximately 23%, whereas a dramatically lower rate of 3% was found among those who started drinking at 19 years or older (DeWit et al. 2000). Using a female twin cohort, Agrawal et al. (2006a) ordered psychoactive substances in ascending order of initiation (cigarettes, alcohol, cannabis, other illicit drugs) and found that women who initiated cigarette, alcohol or cannabis use at an early age in adolescence were at elevated risk for early experimentation with each subsequent drug class, and early-onset of more than one substance contributed to greater risk.

Although the risk associated with early initiation of use is well established, the meaning of this association is not clear. In addition to being causally related to the development of substance use disorders, early initiation of use may be a non-causal indicator of elevated risk, and there is evidence that these two traits are influenced by same genetic factors (Agrawal et al. 2009, Huizink et al. 2010, Prescott and Kendler 1999, Sartor et al. 2009b). On the other hand, Lynskey et al. (2003) found that individuals who used cannabis by age 17 were significantly more likely to use other drugs or be diagnosed with alcohol or drug dependence in young adulthood than their co-twins who did not use cannabis by age 17, implicating that at least associations between early cannabis use and later substance use disorders cannot solely be explained by common predisposing genetic or shared environmental factors. In contrast, the authors speculated that this association may arise from the effects of the peer and social context within which cannabis is used and obtained. However, this finding was not replicated in a recent study on another twin sample by the same authors (Grant et al. 2010).

Another risk factor that is related to initiation of substance use is the subjective response to the substance during the first times of use. For alcohol, there is evidence that lower level of response, indicated either by a low intensity of reaction to alcohol at a given alcohol concentration, or as a retrospective report of the need for more drinks to achieve the wanted effects early in life, is related to higher risk for alcohol use disorders (Schuckit and Smith 2006, Schuckit et al. 2009, Trim et al. 2009). Regarding cannabis, several studies have found that first positive reactions to cannabis (such as feeling happy and relaxed, getting high) constitute a risk factor for later cannabis dependence (Fergusson et al. 2003b, Le Strat et al. 2009, Scherrer et al. 2009). Interestingly, there is also some evidence that the risk related to first subjective responses may be independent of many other risk factors, including early initiation of use (Trim et al. 2009).

Peer groups

A consistent correlate of adolescent substance use behaviors is association with substance-using peers (Ary et al. 1993, Guo et al. 2001, Hawkins et al. 1992, Nation and Heflinger 2006, Zhang et al. 1997). While this association has been reported cross-sectionally in several studies, the long-term effects of having substance using peers may not be as strong (Poelen et al. 2007, Poelen et al. 2009). In addition, peer

group formation is an active process involving several psychological and behavioral characteristics, including attitudes towards substances as well as actual substance use behaviors, which are in part genetically influenced (Agrawal et al. 2010, Gillespie et al. 2009a, Gillespie et al. 2009b, Kendler et al. 2007, Loehlin 2010). Because of non-random association with peers, the availability of various substances—an important proximal predictor of substance use—is also in part influenced by genetic variation (Gillespie et al. 2007).

Are risk factors universal?

A vast majority of studies investigating factors that increase the risk for alcohol and other substance use disorders have been conducted in modern Western countries. The question thus arises, whether the associations between these factors and substance outcomes are specific to these cultures or whether they reflect more universal features of the development of problematic substance use. Existing cross-national studies and studies on non-Western populations have generally demonstrated relatively good consistency among the studied risk factors (Assanangkornchai et al. 2002, Beyers et al. 2004, Brook et al. 2001, Brook et al. 2006, Cheng et al. 2004, Hall and Degenhardt 2007, Rudatsikira et al. 2009, von Diemen et al. 2008). For example, paternal drinking and childhood conduct disorder were found to increase the risk for alcohol use disorders also among Buddhist Thai men (Assanangkornchai et al. 2002), and both parental and peer substance use predicted drug use among South African adolescents (Brook et al. 2006). Among adolescents in Zimbabwe, earlier smoking and alcohol use increased the risk for cannabis use, whereas parental supervision had a protective effect (Rudatsikira et al. 2009). In addition to consistency across cultures, there is evidence of consistency of risk factors across time (Brook et al. 2001, Brown et al. 2001, Merline et al. 2008).

2.2.4 Inter-correlated nature of risk factors

The wide range of factors associated with elevated risk of substance use disorders indicates multiple developmental pathways leading to problematic substance use (Clark 2004, Hawkins et al. 1992, Sher et al. 2005, Zucker 2008). Accordingly, several longitudinal studies have explored different combinations of risk factors through different developmental periods. For example, using a Finnish longitudinal sample studied from age 8 into age 42, Pitkänen et al. (2008) reported that family adversities, externalizing problem behaviors, low school success, and substance use in adolescence predicted alcohol problems in early middle age, with childhood and adolescent antecedents and drinking up to age 20 explaining 43% of males' and 31% of females' problem drinking at age 42. In a similar vein, Dubow et al. (2008) found that lower levels of behavioral inhibition and higher levels of aggression in childhood predicted adulthood alcohol use and problem drinking, whereas childhood contextual variables such as family socioeconomic status were weaker

predictors. Also highlighting the importance of individual characteristics, Merline et al. (2008) reported from a nationally representative sample that risk taking and use of cigarettes and marijuana at age 18 predicted heavy drinking at age 35, high-school theft and property damage predicted symptoms of alcohol use disorders, whereas planning to attend college predicted less frequent heavy drinking by mid-life. Similarly, longitudinal studies into developmental antecedents of illicit drug use and abuse/dependence have highlighted a range of risk factors (Coffey et al. 2000, Fergusson et al. 2008, Guxens et al. 2007, Korhonen et al. 2008, Korhonen et al. 2010, van den Bree and Pickworth 2005). In an attempt to shed light on the contribution of a range of risk factors, Fergusson et al. used a multi-stage regression approach and found that the risk of later illicit substance use and disorders was determined by a series of factors, including cannabis use, affiliation with substance-using peers, alcohol use, cigarette smoking, and novelty seeking (Fergusson et al. 2008). Also various fixed childhood factors, such as conduct disorder and parental drug use, indicated elevated risk but their effect was reduced to statistical non-significance when time-varying substance use and peer factors were taken into account (Fergusson et al. 2008).

Many familial and individual risk factors have often been found to occur concurrently, indicating correlated sources of risk. Several studies have tried to disentangle the relative roles of different kinds of risk factors, such as parental substance use and adolescent behavior problems, with many studies using informative longitudinal data or comprehensive statistical models.

First, familial and parental substance use disorders have been found to predict behavior problems and undercontrolled personality in the offspring in many independent samples (Blackson et al. 1994, Blackson et al. 1999, Chapman et al. 2007, Chassin et al. 1999, Chassin et al. 2004, Finn et al. 2000, Grucza et al. 2006, Hussong et al. 2007, Kirisci et al. 2005, Malone et al. 2002, Marmorstein et al. 2009, Ridenour et al. 2009, Tarter et al. 2004). For example, using data from the Minnesota Twin Family Study, Marmorstein et al. (2009) reported that parental alcohol or drug dependence were associated with increased risk for ADHD, oppositional defiant disorder, conduct disorder, and substance dependence in the offspring, with offspring of substance-dependent parents having 2–3 times the odds for developing a disorder by late adolescence compared to low-risk offspring. Many studies have also found support for the hypothesis that externalizing disorders or temperamental features in the offspring at least partially mediate the effects of family history on higher levels of substance use or disorders in the offspring (Chassin et al. 1999, Chassin et al. 2004, Finn et al. 2000, Ridenour et al. 2009, Tarter et al. 2004). Further, Feske et al. (2008) reported that parental substance use disorder predicted their sons' disinhibited behavior which, in turn, predicted characteristics of peer environment and, subsequently, cannabis use frequency and disorders.

Second, family history of substance use disorders also seems to predict earlier onset of substance use (Dawson 2000, Hawkins et al. 1997, Hill and Yuan 1999, Hill et al. 2000). For example, Hill et al. (2000) found that familial density of alcoholism

(number of alcoholic first- and second-degree relatives) predicted both earlier onset of regular drinking and earlier development of substance use disorders, with part of this effect mediated by the temperament trait extraversion. Highlighting early initiation as an important pathway to alcohol use disorders, Hawkins et al. (1997) in turn found that early initiation mediated the risk related not only to parental drinking but also parenting practices and peer alcohol initiation, assessed at age 10–11.

Third, externalizing behavior problems and impulsivity have been found to be related to earlier onset of alcohol and other substance use in cross-sectional and longitudinal analyses (Creemers et al. 2009, Dobkin et al. 1995, Englund et al. 2008, Kirisci et al. 2009, Sartor et al. 2007, von Diemen et al. 2008, Zernicke et al. 2010). Dobkin et al. (1995) compared the influences of individual behavioral characteristics and peer characteristics on early onset of substance abuse among adolescent boys and reported that individual characteristics were better predictors than association with deviant friends. Kirisci et al. (2009), on the other hand, reported that peer deviancy mediated the association between disinhibited personality and substance abuse at age 16. Korhonen et al. (2010), in turn, found the prospective association between externalizing behavior problems and cannabis use in adolescence to be often mediated by earlier smoking.

In summary, evidence suggests that a multitude of inter-correlated familial and individual factors are associated with elevated risk of both initiation and development of substance use and disorders. Many studies have clarified the inter-relationships between different domains of risk, and a synthesis seems to emerge where parental history of substance use and disorders predicts both behavioral-temperamental risk factors and early initiation of substance use, which are also associated with each other—and may mediate each other's effects—independently of family history of substance use disorders. Despite this wealth of research, surprisingly few studies have simultaneously looked at a wide range of risk factors in order to examine their relative contributions in the manner of Fergusson et al. (2008), discussed above. In the present thesis, the relative importance of parental factors, behavioral and affective factors, educational factors, and early initiation of substance use as correlates of substance use disorders among Finnish young adults was investigated (Study I).

2.3 Cognitive functioning in substance use disorders

Cognitive functions and abilities are among the most studied and well understood mental phenomena. They are complex and profoundly important traits which are known to have an interconnected structure, to show individual variation that is strongly influenced by genetic differences, and to have a biological basis rooted in the functioning of the brain (Deary 2001, Deary et al. 2010, Gray and Thompson 2004,

Lezak et al. 2004, Neisser et al. 1996). From the perspective of substance use and disorders, an important observation is that the acute effects of many psychoactive substances include changes in cognitive functions (Friswell et al. 2008, Heishman et al. 2010, Ramaekers et al. 2009, Volkow et al. 2008). Nearly equally robust is the finding that people with substance use disorders tend to differ from people without them on various measures of cognitive performance (Fernandez-Serrano et al. 2011, Gonzalez 2007, Gruber et al. 2007, Scheurich 2005). However, interpreting the differences has proven difficult due to many methodological challenges such as the difficulty to differentiate pre-existing differences from those induced by substance use (Clark et al. 2008, Grant et al. 2003, Rogers and Robbins 2001, Verdejo-Garcia et al. 2004, Yücel et al. 2007). Below, the literature on cognitive functioning in alcohol and other substance use disorders is reviewed, with an emphasis on verbal cognitive ability—one of the most often reported cognitive functions in which people with substance use disorders show deficits—and the possibility that cognitive differences may also predate the development of substance use disorders.

There are at least two medical syndromes characterized by impaired cognition resulting from heavy alcohol use: the foetal alcohol syndrome (FAS) and the Wernicke-Korsakoff syndrome (WKS) (Oscar-Berman and Marinkovic 2003, Tarter and Edwards 1986). FAS is a disorder that may result from prenatal alcohol exposure, and it is characterized by growth deficiencies, craniofacial anomalies, and central nervous system dysfunction that causes intellectual disabilities and behavior problems (Dalen et al. 2009, Guerri et al. 2009). WKS refers to brain damage caused by vitamin B1 (thiamine) deficiency associated with alcoholism-related malnutrition, and it is characterized by severe memory impairment arising from brain atrophy and other neuropathology (Harper 2009, Kopelman et al. 2009, Sullivan and Pfefferbaum 2009). FAS and WKS are severe neurocognitive disorders related to alcohol use, but they fall outside the scope of cognitive deficits dealt with in the present thesis, and they are not covered further in the following review.

2.3.1 Substance use disorders and deficits in specific cognitive functions

The interest in cognitive deficits related to substance use disorders has a relatively long history. Early studies include those by Tarter (1973), finding deficits in abstraction abilities but not in learning in chronic alcoholics, by Jones (1971), comparing alcoholics and controls in verbal and spatial intelligence, and by Tarquini and Masullo (1981), reporting deficits in several neuropsychological domains but especially verbal functions. This early literature was extensively reviewed by Parsons and Leber (1981) and Tarter and Edwards (1986), with both reviews drawing attention to inconsistencies in findings and discussing several possible ways to explain the observed cognitive differences, the view of cognitive deficits antedating heavy alcohol use often being as plausible as deficits caused by the

neurotoxicity of alcohol. More recent studies have continued to find deficits related to heavy alcohol and other substance use and disorders in various domains of cognition, such as learning, memory, executive functioning and problem-solving, visuospatial and verbal abilities, and speed of information processing (Fein et al. 1990, Gonzalez 2007, Gruber et al. 2007, Parsons 1998, Scheurich 2005, Verdejo-Garcia et al. 2004). A summary of findings related to specific cognitive functions is bound to be somewhat arbitrary, because different studies have targeted different and often mutually inconsistent combinations of functions, and most studies have reported some differences in a variety of cognitive tasks with no clear pattern in the combinations of statistically significant results (Fernandez-Serrano et al. 2011). Accompanying these studies, there is an extensive and growing brain imaging literature on the structural and functional correlates of substance use disorders and cognitive deficits related to them (Borne et al. 2005, London et al. 2000, Mann et al. 2001, Rojas et al. 2005).

Attention and working memory

Attention refers to the processes by which some external or internal stimuli are selectively concentrated on and processed mentally while other possible objects of thought are ignored (Eysenck and Keane 2000, Lezak et al. 2004). Working memory comprises a set of related cognitive processes by which a limited amount of information is actively manipulated and held in consciousness for a relatively short time (Eysenck and Keane 2000, Lezak et al. 2004). Several studies on alcohol and other substance use disorders have reported poorer performance on tasks assessing attention and/or working memory functioning using either visual or auditory-verbal stimuli (Duka et al. 2003, Loeber et al. 2009b, Ornstein et al. 2000, Sullivan et al. 2002, Tapert and Brown 1999, Tapert et al. 2002). Differences in attention and working memory have been found in relation to a range of substances, but they may be especially associated with alcohol use disorders (Ersche and Sahakian 2007, Fernandez-Serrano et al. 2011, Gruber et al. 2007). Neuroimaging studies in heavy substance users have reported differences in brain activation patterns and white matter quality, correlated with attention and working memory performance (Bava et al. 2010, Kanayama et al. 2004).

Executive functions

Executive functions refer to the cognitive control operations by which an individual plans and executes purposeful behavior and makes decisions, and they include abilities to flexibly and adaptively change cognitive strategies or alternate between them (Eysenck and Keane 2000, Lezak et al. 2004). Impairments in various manifestations of executive functioning and decision making have been found in several studies related alcohol and drug use disorders (Cantrell et al. 2008, Ersche et al. 2006, Giancola and Mezzich 2000, Pau et al. 2002, Rapeli et al. 2006, Severtson et al. in press, van der Plas et al. 2009, Woicik et al. 2009). Because of the substantive relevance of behavioral and cognitive control functions to addictive disorders,

as well as the well-known reliance of executive functions on frontal areas of the brain (Alvarez and Emory 2006, Badre et al. 2009, Bechara 2005), impairments in executive functions have been widely studied and their importance as potential predictors and consequences of substance use disorders has often been stressed (Clark et al. 2008, Garavan and Stout 2005, Garavan and Hester 2007, London et al. 2000, Rogers and Robbins 2001, Scheurich 2005, Schoenbaum and Shaham 2008, Yücel et al. 2007). Brain imaging studies investigating the neural correlates of impaired executive functioning in substance use disorders have found associations with neural activation in the frontal areas of the brain (Bechara et al. 2001, Bolla et al. 2005, Demir et al. 2002, Li et al. 2009, Roberts and Garavan 2010), and with the microstructure of white matter (Chanraud et al. 2009).

Learning and memory

Learning is the process of acquiring various types of new information, skills or behaviors, whereas memory refers to an organism's ability to store, retain and recall learned information (Eysenck and Keane 2000, Lezak et al. 2004). Alcohol and other substance use-related deficits in learning and memory were already indicated in early studies (Tarquini and Masullo 1981) and have since been found in many studies using either verbal or non-verbal learning tasks (Bartholomew et al. 2010, Bondi et al. 1998, Brown et al. 2000, Ferrett et al. 2010, Gonzalez et al. 2004, Grant et al. 2003, Green et al. 2010a, Hoshi et al. 2007, Medina et al. 2006, Pope et al. 2001, Rosenbloom et al. 2005, Samuelson et al. 2006, Schilt et al. 2010, Schrimsher et al. 2007, Selby and Azrin 1998). Besides the most often studied forms of declarative memory, also emotional and procedural memory are crucially involved in addiction (Robbins et al. 2008). The neural correlates of learning and memory deficits may include brain atrophy as well as widely distributed patterns of hyper- and hypoactivity (Di Sclafani et al. 1995, Roberts et al. 2009).

Visuospatial processing

Deficits in processing visual and spatial information have been found related to substance use disorders in general, but especially in alcohol use disorders (Beatty et al. 1997, Fein et al. 1990, Fernandez-Serrano et al. 2011, Gruber et al. 2007, Tapert and Brown 1999). However, as many studies have used neuropsychological tests assessing e.g. visuospatial memory or reasoning, the importance of visual information processing *per se*, independently of more general processes of memory or reasoning is not well known.

Speed of information processing

It has also been often reported that people with substance use disorders perform poorer than control participants in psychomotor tasks assessing general speed of information processing (Beatty et al. 2000, Buyske et al. 2006, de Sola Llopis et al. 2008, DeFranco et al. 1985, Robinson et al. 1999, Scheurich et al. 2004, Sher et al. 1997). Although processing speed is often studied with neuropsychological tests in

which simple cognitive and motor sequences have to be repeated, it is known to correlate positively with general intellectual ability (Finkel et al. 2005, Neisser et al. 1996).

2.3.2 Verbal and general cognitive ability in substance use disorders

Many studies have reported deficits related to substance use disorders in a variety of cognitive tasks that are assumed to measure distinct domains of cognitive functioning (Fernandez-Serrano et al. 2011). However, different subdomains of cognition are known to be intercorrelated, and performance in any of them tends to correlate with general cognitive ability (Deary et al. 2010, Neisser et al. 1996). Thus, it might be hypothesized that the observed pattern of cognitive deficits in substance use disorders could reflect differences in more general cognitive ability (Moss et al. 1994, Pope et al. 2003). Many studies have, in fact, found poorer general intelligence in people with substance use disorders compared to control participants. Further, instead of full IQ, several studies have assessed verbal cognitive ability, the cognitive domain most strongly correlated with full-scale intelligence (Lezak et al. 2004). Verbal ability refers to the ability to understand, process and produce meanings linguistically, and it is often assessed with tests of vocabulary knowledge in which meanings of words and concepts have to be explained (Lezak et al. 2004).

Table 3 gives an overview of findings from several studies comparing people with substance use disorders and control participants in verbal or general cognitive ability. It also includes studies that have assessed the predictive value of cognitive ability in relation to treatment outcomes among people with substance use disorders. Taken together, this evidence strongly suggests that people with alcohol and other substance use disorders tend to score lower than control participants in various tasks assessing verbal or general cognitive abilities. These differences are seen in adolescent, young adult and middle-aged samples, and the findings are often statistically significant even in relatively small samples, suggesting that the effect sizes are not trivially small. In addition, there is some evidence that poorer verbal or general cognitive ability has predictive value regarding the developmental course of substance use and problems among those diagnosed with substance use disorders.

TABLE 3. Verbal and general cognitive ability in substance use disorders. The table lists studies comparing people with substance use disorders and control participants in verbal or general cognitive ability, and studies assessing the predictive value of cognitive ability in relation to treatment outcomes among people with substance use disorders.

Authors	Year	Study setting	N of participants	Mean age	Cognitive measures used	Main finding related to verbal or general ability	Special
Jones	1971	Chronic alcoholics vs. controls	30 alcoholics, 30 controls	44.5 47.1	The Shipley-Hartford scale, Raven's Progressive Matrices	Alcoholics < Controls in spatial but not verbal intelligence	Groups matched on education
Tarquini & Masullo	1981	Alcoholic patients vs. controls	28 alcoholics, 83 controls	?	Word Fluency Task	Alcoholics < Controls in verbal fluency	Groups matched on education
Malloy et al.	1989	Factors related to cognitive functioning among chronic alcoholics	36 alcoholics with ASPD, 146 non-ASPD alcoholics	32.1 40.2	Halstead-Reitan and WAIS	ASPD and years of drinking correlated negatively with general intelligence	
Williams & Skinner	1990	Problem drinkers vs. controls	19 problem drinkers 19 controls	47.9 47.3	WAIS Vocabulary	Problem drinkers < Controls in vocabulary	
Moss et al.	1994	DSM-III-R AUDs vs. controls	38 with AUD, 69 controls	15.5 14.7	WISC-R / WAIS-R	AUDs < Controls in verbal and full-scale IQ	
Tarter et al.	1995	Females with DSM-III-R SUD vs. controls	106 with SUD, 74 controls	16.2 15.6	WISC-R / WAIS-R	SUDs < Controls in verbal and non-verbal IQ	
Beatty et al.	1997	Abusers of alcohol only, alcohol + marijuana, alcohol + multiple drugs and controls	45 Alc 20 Alc + MJ 29 Alc + Poly 35 controls	40.4 36.6 31.8 34.7	Shipley Vocabulary	All abuse groups < Controls in Vocabulary, no difference between abuse groups	
Sher et al.	1997	First year undergraduates with DSM-III alcohol abuse or dependence vs. no AUD	119 with AUD, 370 with no AUD	18.2	WAIS-R Vocabulary	No differences between groups in Vocabulary	College student sample
Tapert et al.	1999	Inpatients with DSM-III-R AUD only vs. AUD + other SUD	79	17.1	WISC-R	General IQ and coping strategies predicted substance use 1 year later	
Wehr & Bauer	1999	Substance abusers from residential treatment programs monitored for 6 months	122 substance abusers	35	Shipley Vocabulary	Relapsed < Abstinents in Vocabulary and full-scale IQ	
Beatty et al.	2000	DSM-III-R AUDs vs. controls	162 with AUD 165 controls	37 35	Shipley Vocabulary	AUDs < Controls in Vocabulary	
Brown et al.	2000	DSM-III-R alcohol dependence vs. controls	33 with AD, 24 controls	16.2 15.9	WISC-R	ADs < Controls in many verbal tests	Groups matched on SES and family history of alcohol dependence
Giancola & Mezzich	2000	Females with SUD-only, CD-only, SUD+CD, and controls	63 with SUD-only 58 with CD-only 239 with SUD+CD 110 controls	16	WISC-R / WAIS-R Vocabulary	Controls > All others in Vocabulary, SUD+CD < SUD-only in Vocabulary	
Grant et al.	2000	Polysubstance abusers vs. controls	30 abusers 24 controls	35.2 31.0	Shipley IQ	Abusers < Controls in IQ	

Authors	Year	Study setting	N of participants	Mean age	Cognitive measures used	Main finding related to verbal or general ability	Special
Sullivan et al.	2000	Recently detoxified alcoholic men vs. controls	71 alcoholics 74 controls	44.5 45.1	NART IQ	Alcoholics < Controls in IQ	
Tapert & Brown	2000	DSM-III-R substance-dependent adolescents vs. controls	101 with SUD 50 controls	16.0 14.8	WISC-R, Boston Naming Test, COWAT	SUD < Controls in the language domain	
Paraherakis et al.	2001	Neuropsychological study of patients admitted to treatment for substance misuse	110	39.9	Shipley, WAIS	Vocabulary score at intake predicted length of stay in treatment	
Finn et al.	2002	Young adults with early-onset alcoholism vs. controls	80 with AD only 50 with CD only 96 with AD+CD 125 controls	20.7 20.7 21.2 20.5	Shipley IQ	Alcoholics < Controls in IQ	
Sullivan et al.	2002	Women with DSM-IV AUD vs. controls	43 with AUD 47 controls	42.1 42.8	NART IQ	AUDs < Controls in IQ	
Tapert et al.	2003	8 year prospective study of adolescents with DSM-III-R AUD	139	16-24	WISC-R	Language abilities moderate the relationship between alcohol expectancies and AD symptoms	
Goldstein et al.	2004	DSM-III-R / DSM-IV alcohol or cocaine dependence vs. controls	40 with AD 42 with CoD 72 controls	41.5 35.4 40.7	WAIS-R Vocabulary	SUD groups < Controls in Vocabulary	
Scheurich et al.	2004	DSM-IV alcohol dependence vs. controls	57 with AD 59 controls	45.5 43.0	LPS IQ (a German test)	AD < Controls in IQ and verbal fluency	
Zinn et al.	2004	DSM-IV alcohol dependence vs. controls	27 with AD 18 controls	50.8 52.4	WAIS-III	AD < Controls in IQ	
Friend et al.	2005	DSM-III-R AUDs	1592	40.0	Shipley IQ	Alcohol and nicotine use correlated negatively with IQ	
Rosenbloom et al.	2005	DSM-IV AUDs vs. controls	64 with AUD 51 controls	50.6 50.1	WASI Verbal IQ	AUDs < Controls in verbal IQ	
Davies et al.	2005	Abstinent alcohol-dependent subjects vs. controls	43 with AD 58 controls	43.7 43.0	WAIS-R Vocabulary	ADs < Controls in Vocabulary	
Fein et al.	2006	DSM-III-R alcohol dependence vs. controls	48 with AD 48 controls	46.8 45.6	NART verbal fluency	No difference between the groups in verbal fluency	
Glass et al.	2006	Assessment of neurocognitive deficits related to AUDs in a community-recruited sample of men	103 with AUD 69 no AUD	43 42	WAIS-R	AUD and smoking were negatively correlated with IQ	
Wilson et al.	2006	Adolescents in a therapeutic community for drug abuse followed prospectively for 1 year	28 drug abusers	18.0	The Test of Adolescent Language-3, Vocabulary Subtest	Lower Vocabulary scores predicted attrition from treatment	
Rosenbloom et al.	2007	DSM-IV alcohol dependence vs. controls	15 with AD 26 controls	48.8 52.8	WASI	ADs < Controls in verbal and non-verbal IQ	

AD: alcohol dependence; Alc: alcohol; ASPD: antisocial personality disorder; AUD: alcohol use disorder; CD: conduct disorder; CoD: cocaine dependence; COWAT: Controlled oral word association test; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; IQ: intelligence quotient; MJ: marijuana; NART: National Adult Reading Test; Poly: polysubstance; SUD: substance use disorder; WAIS: Wechsler Adult Intelligence Scale; WAIS-R: Wechsler Adult Intelligence Scale-Revised; WASI: Wechsler Abbreviated Scale of Intelligence; WISC-R: Wechsler Intelligence Scale for Children-Revised

Neural correlates of verbal cognitive ability are not well known, but general intelligence is believed to reflect the functioning and interconnections of a widely distributed network of brain areas (Chiang et al. 2009, Choi et al. 2008, Deary et al. 2010, Gläscher et al. 2010, Gray and Thompson 2004, Song et al. 2008). Among people with substance use disorders, reduced gray and white matter volumes and changes in white matter microstructure have been reported (Bava et al. 2009, Bjork et al. 2003, Fein et al. 2009, Harper et al. 2005, Hommer et al. 2001, McQueeney et al. 2009, Pfefferbaum et al. 1992, Pfefferbaum and Sullivan 2005), but there is some evidence that lower verbal cognitive ability in alcohol dependence may not be related to brain shrinkage caused by alcohol use but may correlate more strongly with estimated pre-morbid brain size (Schottenbauer et al. 2007). Differences in the activation of language-related brain regions during an auditory language task in people with alcohol use disorders compared to healthy controls have also been found (Chanraud-Guillermo et al. 2009).

2.3.3 Long-term effects of substance use, or cognitive functioning as a risk factor?

As discussed above, a major challenge in the interpretation of the observed cognitive deficits related to substance use disorders is the difficulty to distinguish between the two possibilities of cognitive deficits resulting from the neurotoxicity of substances and differences in cognition antedating the development of substance use disorders (Clark et al. 2008, Rogers and Robbins 2001, Tarter and Edwards 1986, Verdejo-Garcia et al. 2004, Yücel et al. 2007). To gain a better understanding of these two possibilities, evidence from other research paradigms besides comparisons of people with and without substance use disorders needs to be considered.

Studies on neurotoxicity of psychoactive substances

Neurobiological evidence from animal and human studies clearly supports the view that alcohol and other psychoactive substances have neurotoxic effects (Crews and Nixon 2009, Ward et al. 2009). Neuroradiological and neuropathological studies involving people with alcohol dependence have consistently revealed a reduction of the brain white matter volume, arising from changes in extracellular space, changes in the nerve fibers within the white matter or a combination of these mechanisms (Harper et al. 2005). Evidence suggests that alcohol-induced neurodegeneration occurs due to neuronal death during intoxication, related to increases in oxidative stress in the brain (Crews and Nixon 2009, Guerri and Pascual 2010), but also due to alcohol-induced reduction in neurogenesis (Taffe et al. 2010, Tateno and Saito 2008). Animal studies have found evidence of neurodegeneration and related deficits in memory and executive functioning even after a single binge drinking episode (Nasrallah et al. 2009, Obernier et al. 2002). However, it is also well known that regeneration of brain occurs during abstinence, resulting in brain cell genesis that

can contribute to the return of brain function and reversibility of cognitive deficits during long-term abstinence (see below) (Crews and Nixon 2009, Harper et al. 2005).

Effects of abstinence on cognitive functioning

Many neuropsychological studies of people with a history of substance use disorders have reported only minor cognitive deficits after long-term abstinence (Davies et al. 2005, Davis et al. 2002, Eckardt et al. 1995, Fein et al. 2006). Some cross-sectional studies have not found a relationship between cognitive functioning and length of abstinence or chronicity of substance use disorder (Beatty et al. 2000, Medina et al. 2004), whereas there is strong evidence from longitudinal follow-up studies of people with substance use disorders that performance in many domains of cognitive functioning improves significantly during long-term abstinence (Bates et al. 2005, Manning et al. 2008, Pitel et al. 2009, Rosenbloom et al. 2007, Sullivan et al. 2000, Zinn et al. 2004). However, abstinence may have different effects on different domains of cognition, with memory functions possibly showing greater improvement than executive functioning or general cognitive ability (Bates et al. 2005, Manning et al. 2008, Rosenbloom et al. 2007), and different profiles of improvement may be related to different substances (Di Sclafani et al. 2002). Whether impairments in the functions that show least evidence of recovery have resulted from substance use, or are individual differences independent of substance use, is not clear.

Longitudinal studies on cognitive abilities predicting substance use disorders

When considering the possibility that there might be cognitive differences between those who later develop substance use disorders and those who do not, evidence from prospective longitudinal studies is crucial. There has been a number of such studies, and they have in general offered support to the view that poorer cognitive abilities in childhood, adolescence or young adulthood are predictive of elevated risk for substance use and disorders later in life (Fergusson et al. 2005a, Gale et al. 2008, Gale et al. 2010, Jefferis et al. 2008, Mortensen et al. 2005, Osler et al. 2006, Windle and Blane 1989), although some studies have not found this association (Koenen et al. 2009, Whalley et al. 2005). In addition to general or verbal cognitive ability, also attention dysfunction and poor decision making strategies have been reported to increase the risk for later substance involvement (Schilt et al. 2009, Tapert et al. 2002). Further, in addition to these direct measures of cognitive functioning, also differences in childhood and adolescent school achievement—known to correlate with general cognitive ability (Deary et al. 2007)—has been found to predict differences in substance use and problems (Ensminger et al. 2002, Fothergill and Ensminger 2006, Poikolainen et al. 2001).

Studies of individuals at high risk for substance use disorders

Further evidence for cognitive deficits not resulting from substance use comes from studies of children and adolescents at elevated biological risk for substance

use disorders. These studies have typically used samples of individuals whose first-degree relatives have a history of substance use disorders, and have found that compared to control participants these high-risk individuals tend to show poorer performance in a range of cognitive functions including general and verbal cognitive ability (Aytaclar et al. 1999, Bates et al. 2002, Corral et al. 1999, Corral et al. 2003, Drejer et al. 1985, Fals-Stewart and Bates 2003, Faraone et al. 2007, Finn and Hall 2004, Gabrielli and Mednick 1983, Keenan et al. 1997, Knop et al. 2003, Poon et al. 2000, Sher et al. 1991, Shoal and Giancola 2001, Tarter et al. 1989, Tarter et al. 2003, Turner and Parsons 1988). While maternal history of substance use disorders may be more strongly predictive of cognitive deficits than paternal history, possibly in part due to prenatal exposure (Cottencin et al. 2009), many of these studies have excluded participants with early-onset maternal substance use disorders. In addition, some studies have found differences in the offspring of parents with only substance use disorders compared to offspring of parents with substance use disorders and comorbid antisocial personality disorders (Gillen and Hesselbrock 1992, Nigg et al. 2004). Besides cognitive deficits, also lower academic achievement among children of parents with substance use disorders has been reported (Knop et al. 1985, McGrath et al. 1999). Interestingly, a recent study reported that rats selectively bred for ethanol preference performed poorer in a working memory task than those bred for nonpreference, giving some additional evidence of cognitive impairments before onset of substance use in individuals at high biological risk for substance use disorders (Wenger and Hall 2010).

Cognitive functioning in comorbid conditions

Of relevance to the question of pre-existing cognitive differences are also studies on cognitive functioning related to behavioral and psychopathological traits that increase the risk for substance use disorders. Importantly, several studies have found associations between poorer neurocognitive functioning and childhood behavior problems, impulsivity, aggression and antisociality (Barker et al. 2007, de Wit et al. 2007, Finn et al. 2009, Plomin et al. 2002, Raine et al. 2005, Russo et al. 2008, Seguin et al. 2004, Seguin et al. 2009). Strikingly, significant negative correlations between language development already during the first two years of life and participating in criminal behavior in adolescence have been reported (Stattin and Klackenberglarsson 1993). In addition, the overlap between externalizing problems and academic underachievement in childhood and adolescence is well documented, with general cognitive ability and language deficits as possible antecedent variables (Hinshaw 1992). A further comorbidity-related finding is that also cigarette smoking is associated with a variety of cognitive functions and general intelligence (Caspers et al. 2010, Friend et al. 2005, Greenstein and Kassel 2009, Weiser et al. 2010), and a recent twin study found no evidence of a causal relationship between smoking and IQ (Wennerstad et al. 2010). Smoking has been found to be one factor associated with and possibly explaining some of the cognitive deficits in alcohol use disorders (Ceballos 2006, Durazzo et al. 2007, Glass et al. 2006, Glass et al. 2009).

In summary, a bulk of research suggests that alcohol and other substance use disorders are associated with deficits in several cognitive functions, possibly reflecting more general cognitive abilities. There is neurobiological evidence that these differences in cognition may reflect neurotoxic effects of heavy alcohol and other substance use, but strong evidence also exists from various research paradigms for pre-existing differences in general cognitive abilities. However, neuropsychological studies on substance use disorders have often used clinical samples combined with selected groups of control participants, and there is a lack of representative population-based studies. In the present thesis, the associations of alcohol and other substance use disorders with verbal cognitive ability and other cognitive functions were investigated in a population-based sample of Finnish young adults (Study II). The contribution of underlying genetic and environmental factors to the association between alcohol dependence and cognitive functioning was further investigated in an independent sample of young adult twins (Study III).

2.4 Twin studies of substance use disorders and their correlates

It has been understood for a long time that individual differences in psychological and behavioral characteristics are caused both by genetic differences and environmental influences, but their relative importance has been a matter of long-lasting and at times fierce intellectual debate (Pinker 2002). Although separating the effects of genetic and environmental factors at the level of individual organisms is biologically impossible (Meaney 2001), their relative contributions to variation in a trait at population level can be estimated by comparison of resemblance within groups of individuals who differ in the degree of their genetic relatedness (Fisher 1918, Fuller and Thompson 1960). In humans, the primary way to accomplish this is to use samples of identical (monozygotic, MZ) and fraternal (dizygotic, DZ) twin pairs (Plomin et al. 2008). The twin method, having its origins in the work of Francis Galton (1822-1911), was developed between 1900 and about 1940, with e.g. Bonnevie and Siemens among the early developers (Mayo 2009). It has been widely applied in the past three decades in its basic or more modern forms to study the origins of individual differences in human psychological and behavioral traits (Bouchard and McGue 2003, Rose 1995). Alcohol and other substance use and disorders have been an important research area in twin studies (Dick et al. 2009, Plomin et al. 2008). This section reviews the basic principles of twin studies and gives an overview of their findings related substance use and disorders. The phenomena of gene-environment correlation and interaction are also discussed in relation to substance use disorders. Finally, the two common findings of poorer cognitive ability and lower educational level in people with substance use disorders, discussed in the previous chapters, are re-introduced here from the perspective of twin studies.

2.4.1 Basic principles of twin studies

The starting point for twin research is the observation of variation in a trait of interest. Finding the origins of inter-individual variation in the behavioral trait under study is one of the main objectives of behavioral genetic research, including human twin studies (Plomin et al. 2002). Biometrical theory represents the individual phenotype (P) as a function of both total genetic (G_{tot}) and total environmental effects (E_{tot}): $P = G_{\text{tot}} + E_{\text{tot}}$, and the variance of the phenotype is thus given by $V_p = V_G + V_E + 2\text{cov}_{GE}$, where V_p represents the variance of phenotypic values, V_G and V_E the genotypic and environmental variances, and cov_{GE} the covariance between G and E (Evans et al. 2002, Posthuma et al. 2003). Basic twin methodology assumes that there is no interaction or correlation between genetic and environmental influences, but special methods for estimating them exist (Posthuma et al. 2003, Purcell 2002). Gene-environment correlation and interaction in relation to substance use disorders are discussed in more detail in section 2.4.3, below. Genetic variance is further divided into additive genetic effects (A), that represent the sum of the effects of each genetic locus, and dominant genetic effects (D), that refer to interaction effects between alleles at the same locus (Posthuma et al. 2003). In twin studies, the total effect of the environment is conceptually divided further into common environmental influences (C), which mean all environmental (i.e. non-genetic) influences that are shared by members of a twin pair and make the co-twins more similar, and unique environmental influences (E), which refer to environmental influences that are not shared by members of a twin pair and thus make the co-twins more dissimilar. Thus, assuming no correlation between genetic and environmental effects, the phenotypic variance can be decomposed into the four variance components A , D , C , and E : $V_p = V_A + V_D + V_C + V_E$ (Neale and Maes 2003, Posthuma et al. 2003).

Twin studies make use of the difference in genetic relatedness between MZ and DZ twin pairs. Members of a MZ twin pair are two individuals born together and derived from one sperm and one egg, and thus are identical at the DNA sequence level (with the exception of random mutations). DZ twins, in contrast, are two individuals born together but derived from two separate eggs fertilized by two separate sperm. Genetically DZ twins are thus comparable to ordinary siblings, and share, on average, 50% of their segregating genes (Visscher et al. 2006). Based on this difference in genetic closeness, comparing the similarity of MZ and DZ co-twins can provide evidence on the importance of genetic vs. environmental influences on variation in a trait. More specifically, greater similarity among MZ twins reared together compared to DZ twins reared together suggests the presence of genetic influences (Boomsma et al. 2002). From MZ and DZ within-pair correlations, rough estimates of proportions of total variance due to A , D , C , and E can be derived. For example, under an ACE model the proportional contribution of A to the phenotypic variance can be estimated as $2(r_{\text{MZ}} - r_{\text{DZ}})$, and that of C as $2r_{\text{DZ}} - r_{\text{MZ}}$, where r_{MZ} and r_{DZ} refer to within-pair correlations among MZ and DZ twins, respectively (Posthuma et al. 2003). The development of statistical structural equation modeling techniques

using maximum likelihood estimation methods has made it possible to produce standard errors of the estimates in order to assess their accuracy, to compare models with different combinations of variance components in order to find the factors that are necessary and sufficient for explaining variation and co-variation, as well as to use more complex modeling approaches (Neale and Maes 2003, Neale et al. 2006). For example, besides estimating the contribution of genetic and environmental factors to variation in a single variable, multivariate modeling enables investigation into the genetic and environmental influences underlying the covariance of two or more traits or disorders, and longitudinal analyses can assess genetic and environmental factors underlying the developmental trajectory of a trait (Boomsma et al. 2002, Posthuma et al. 2003).

A central concept of twin studies and genetic studies more generally is that of heritability, which refers to the proportion of total phenotypic variance that is attributable to genetic variance (Boomsma et al. 2002, Visscher et al. 2008b). Estimating heritability enables the comparison of relative importance of genes and environment to the variation in traits within and across populations, and it has an important role in the prediction of disease risk in medicine. However, it is crucial to understand that heritability is always specific to a particular population studied at a specific point in time, that high heritability does not imply genetic determination, and that heritability is not informative about the nature of between-group differences (Visscher et al. 2008b). The last point is related to the more general characteristic of the twin method, namely that it is mainly concerned with individual differences in, not mean levels of, the studied phenomena, and that the contributions of genetic and environmental influences on variation and mean levels are not necessarily identical or even closely related (Neale and Maes 2003, Visscher et al. 2008b). Thus, the heritability of height, for example, has been found to be similar in different countries despite large differences in mean height between countries (Silventoinen et al. 2003b).

The classical twin method of comparing the similarity between MZ and DZ twins makes some important assumptions. First, it is assumed that the twin pairs are correctly classified as MZ or DZ. Traditionally, zygosity has been determined on the basis of the twins' similarity in physical traits such as eye color, hair color, and hair texture, and confusability in childhood, often assessed both by the twins and their parents (Plomin et al. 2008). Using observed DNA markers, zygosity can nowadays be determined definitively, and it has been found that classification based on physical similarity is generally very accurate compared to genetic markers (Cederlöf et al. 1961, Christiansen et al. 2003, Jackson et al. 2001, Sarna et al. 1978).

A second important assumption is that findings from twins can be generalized to the general population. Twins are often born prematurely, are lighter at birth than singletons, and sharing a womb can make the intrauterine environment more adverse for twins as compared to singletons (Hall 2003, O'Brien and Hay 1987, Phillips 1993). There is also evidence of slower development of language and intellectual abilities in twins as compared to singletons (Deary et al. 2005, Record et

al. 1970, Ronalds et al. 2005), but this difference is likely to disappear by adolescence, at least in modern Western countries (Calvin et al. 2009, Christensen et al. 2006, Posthuma et al. 2000, Voracek and Haubner 2008). Further, twins do not appear to be importantly different from singletons in brain morphometry, motor development, personality, psychopathology, cancer incidence, mortality, or many other medical and behavioral traits (Andrew et al. 2001, Christensen et al. 1995, Hulshoff Pol et al. 2002, Johnson et al. 2002, Kendler et al. 1995, Ordaz et al. 2010, Verkasalo et al. 1999).

The classical twin method also assumes no assortative mating with regard to the trait under study. Assortative mating refers to non-random pairing of mates on the basis of anything other than biological relatedness. Positive phenotypic assortment—similar phenotypes mating together—is known to occur in human populations for many traits, especially education, religious affiliation, social attitudes, height, and weight, but evidence of assortative mating has also been found for personality, intelligence, substance use, psychiatric disorders, and socioeconomic status (Agrawal et al. 2006b, Eaves et al. 1999, Grant et al. 2007, Heath et al. 1985b, Heath et al. 1987, Hur 2003, Maes et al. 1998, Martin et al. 1986, Mascie-Taylor 1989, McCrae et al. 2008, Silventoinen et al. 2003a). Mates selecting partners phenotypically like themselves also choose partners that resemble themselves genetically and culturally, which results in increased genetic and environmental correlations between relatives. In the context of twin studies, assortative mating tends to increase the similarity of DZ twins relative to MZ twins. If the trait that is being selected for is genetically influenced, assortative mating will artificially inflate the estimates of common environmental influences and deflate the estimates of genetic influences in the twin models (Neale and Maes 2003). Besides phenotypic assortment, also social homogamy—similarities in the social background of spouses—can lead to assortative mating, in which case the resemblance of spouses need not reflect genetic correlation. Further, spousal correlations may arise from shared environments due to living together in the same household. With information limited to spousal correlations these different mechanisms leading to resemblance cannot be distinguished, but with data on twins and their spouses they can be teased apart (Reynolds et al. 1996, Silventoinen et al. 2003a).

Finally, an important assumption for the validity of the twin method is that the environmentally caused similarity is equal for both twin types. If the greater similarity of MZ twins was caused by experiencing more similar environments, estimates of genetic effects would clearly be inflated. The equal environments assumption has been tested in many ways, e.g. studying the effects of mislabeled zygosity by parents on the similarity of the twins, or assessing the effects of MZ twins being treated more similarly than DZ twins on the trait under study, and the assumption has been found to be valid in most cases, though not universally (Borkenau et al. 2002, Cronk et al. 2002, Derks et al. 2006, Hettema et al. 1995, Kaprio et al. 1990, Kendler and Gardner 1998, Kendler et al. 1993, Klump et al. 2000, Morris-Yates et al. 1990, Plomin et al. 2008). An important issue is that if MZ co-twins are more similar on a trait than

DZs because they evoke more similar environmental responses, and if the greater similarity of these environmental responses is due to greater similarity of MZ co-twins on another trait that is genetically influenced (e.g. physical appearance or personality), then the effect of the environmental responses on the first trait is in fact indirectly genetically influenced and does not constitute a violation of the equal environments assumption (Kendler and Baker 2007, Neale and Maes 2003, Plomin et al. 2008).

In summary, the twin method of comparing MZ and DZ twins can offer information on the origins of individual differences in psychological and behavioral traits, as well as many other human characteristics. The method makes some important, simplifying assumptions that in some cases may not completely hold, and it is thus reasonable to regard the estimates provided by twin studies as approximations. Still, in many cases twin data provide unique opportunities, testified by the large numbers of twin studies conducted in many countries around the world (Boomsma et al. 2002, Plomin et al. 2008). Findings from twin studies need to be interpreted in relation to findings from other family studies (pedigrees, nuclear families, half-sib studies and adoption studies) that are not reviewed here at length (Kim 2009, Thomas 2004).

2.4.2 Genetic and environmental factors underlying substance use disorders

Studies of substance use and disorders comprise one of the most active areas of twin research, and the extensive literature on genetic and environmental influences on substance use behaviors has been reviewed and summarized several times (Agrawal and Lynskey 2006, Agrawal and Lynskey 2008, Dick and Agrawal 2008, Goldman et al. 2005, McGue 1999, Vanyukov and Tarter 2000). Shedding light on the familial nature of substance use disorders, discussed earlier in chapter 2.2.3, early twin and adoption studies already strongly suggested that the familiarity was mostly due to genetic inheritance (Cadoret et al. 1980, Cadoret et al. 1986, Cloninger et al. 1981, Goodwin et al. 1974, Jardine and Martin 1984, Kaprio et al. 1981, Kaprio et al. 1982, Kaprio et al. 1987, Partanen et al. 1966). The bulk of subsequent twin and family studies have replicated and refined these findings, with the general picture emerging that in most populations individual variation in the risk for substance use disorders is about 50% due to genetic differences and about 50% due to unique environmental influences, with shared environmental factors having negligible importance. Recently, Dick et al. (2009) reviewed the existing large-scale community based twin studies of alcohol-related phenotypes, conducted in many different countries. Based on data from more than 18,000 twin pairs, the sample size-weighted average estimates of A, C and E effects for alcohol dependence in adult populations were 0.55, 0.08 and 0.37, respectively (Dick et al. 2009). There have been substantially less studies on illicit substances, but for cannabis—the most often studied illicit drug—

the average A, C and E estimates for abuse or dependence in adult populations were 0.42, 0.19 and 0.40, respectively, based on data from nearly 9,000 twin pairs (Dick et al. 2009). These estimates are similar to those provided by earlier reviews on alcohol and cannabis use disorders (Agrawal and Lynskey 2006, McGue et al. 1999). Studies on other illicit substance use disorders besides cannabis have been more rare, but findings have generally been consistent with those of alcohol and cannabis use disorders (Kendler and Prescott 1998, Kendler et al. 1999, Kendler et al. 2000, Kendler et al. 2006, Tsuang et al. 1996, van den Bree et al. 1998).

In addition to the classical twin study design, other genetically informative methodologies have been used to investigate the genetic and environmental origins of substance use disorders. For example, a recent study by Slutske et al. used a large sample of children of twins to assess the direct causal effects of being exposed to an alcoholic parent (Slutske et al. 2008). Consistently with adoption studies, no differences between children of alcoholics and children of non-alcoholics were found after genetic factors were controlled, suggesting that being exposed to an alcoholic parent has at best modest direct causal effects on the development of alcohol use disorders in young adulthood (Slutske et al. 2008).

Studies of adolescent twins have clarified the nature of factors underlying initiation of substance use. In contrast to abuse/dependence, initiation of alcohol and other substance use in adolescence appears to be more strongly influenced by environmental factors, including notable effects of the environments shared by co-twins. The weighted average estimates from large-scale studies for initiation of alcohol use, based on 8,500 twin pairs, were 0.37, 0.36 and 0.27 for genetic, shared environmental and non-shared environmental effects, respectively (Dick et al. 2009). For initiation of cannabis use in adolescence, corresponding average estimates of 0.32, 0.53 and 0.14 were found. Interestingly, besides initiation of use, also abuse/dependence in adolescence seems to be significantly influenced by shared environmental factors, but genetic differences still explain about a third of the variance in risk (Dick et al. 2009).

Both longitudinal and retrospective data have been used to estimate the contribution of genetic and environmental factors to the development of substance use. Findings from these studies have generally suggested that shared environmental factors contribute to the early stages of alcohol and other substance use in adolescence, but become less important in subsequent stages (Fowler et al. 2007, Kendler et al. 2008, Pagan et al. 2006, Rhee et al. 2003, Rose et al. 2001). However, early initiation of substance use may be an indicator of genetically influenced risk for substance use disorders, as many studies have found significant genetic influences on age at initiation of substance use, as well as overlap with the genetic influences on substance use disorders (McGue et al. 2001, Poelen et al. 2008, Prescott and Kendler 1999, Sartor et al. 2009b).

Several twin studies have utilized multivariate analysis methods to investigate factors underlying the common phenomenon of comorbid use or abuse of two or more substances. Findings from many different twin samples have strongly

suggested that this comorbidity is best explained by a single common liability factor, or alternatively, by separate highly correlated factors (Baker et al. in press, Dick et al. 2007, Kendler et al. 2003, Kendler et al. 2007, Madden and Heath 2002, Palmer et al. 2009, Rhee et al. 2006, Vanyukov et al. 2003, Young et al. 2006). In addition, there is evidence of common genetic influences on the timing of first use of different substances (Sartor et al. 2009a), and of significant genetic influences on the number of different substances used in adolescence (Derringer et al. 2008).

In addition to comorbidity of different substance use disorders, also the comorbidity of substance use disorders with various types of externalizing behavior problems and personality has been suggested to reflect a common liability that is significantly influenced by genetic factors (Button et al. 2007, Iacono et al. 2008, Krueger et al. 2002, Miles et al. 2002, Pickens et al. 1995, Rose et al. 2004, Viken et al. 2007). Some evidence has also been reported for genetic and environmental overlap between substance use disorders and internalizing disorders, such as depression and anxiety (Edwards et al. 2011, Kendler et al. 2003, Prescott et al. 2000).

2.4.3 Gene-environment correlation and interaction in substance use disorders

As was discussed above, basic twin study methodology assumes that there are no correlations or interactive effects between genetic and environmental factors. These are simplifying assumptions that are known to be invalid in many situations. Importantly, although not included in basic twin models, gene-environment correlation and interaction are increasingly investigated with special methods, and both phenomena are likely to be importantly involved in the development of substance use disorders (Dick et al. 2009, Heath et al. 2002, Sher et al. 2010).

Gene-environment correlation refers to non-random distribution of genotypes with respect to environmental variation. Scarr and McCartney (1983) described three forms of gene-environment correlations: passive, active, and evocative. First, passive gene-environment correlation refers to the situation where parents provide their children with both genetic and environmental factors that are associated with the trait under study. For example, if musical ability is heritable, musically gifted parents are likely to provide their children with both genes and environmental stimuli that are beneficial for the development of musical ability (Plomin et al. 2008). Second, active gene-environment correlation occurs when individuals create or seek out environments based on their genetically influenced characteristics. Considering musical ability again, musically gifted individuals are likely to actively select environments which enable and increase the possibilities of musical experiences. Finally, evocative gene-environment correlation refers to environmental reactions that are evoked by genetically influenced characteristics of individuals. For example, musically talented individuals might be picked out at school and given special opportunities to develop their abilities (Plomin et al. 2008). All forms of gene-

environment correlations are likely to play a role in the development of substance use and disorders. Passive, active and evocative gene-environment correlations might be observed, for example, in children of alcoholic parents (passive), in individuals whose personality risk factors create stressful life events that, in turn, provide a trigger for substance use (active), and in children whose behavioral deviance contributes to unstable rearing environments (evocative) (Dick et al. 2009). Gene-environment correlations are difficult to detect with traditional twin methods, but they may be investigated using extended samples of twins and their parents or children (Evans et al. 2002, Narusyte et al. 2008). However, these methods have rarely been applied to substance use behaviors so far (Maes et al. 2006). Addressing such issues through molecular genetic approaches is more powerful but information on robust risk genes with substantial effect sizes is needed.

Gene-environment interaction refers to variation in the importance of genetic influences as a function of variation in the environment, or, equivalently, variation in the importance of environmental influences as a function of the genotype. Evidence from several twin studies has suggested that the importance of genetic influences underlying the risk for substance use and disorders is not uniform, but in fact depends on various environmental factors (Heath et al. 2002, Sher et al. 2010, van der Zwaluw and Engels 2009). Early gene-environment interaction studies found the heritability of alcohol use to be dependent on various environmental contexts, such as marital status, religious upbringing, and urban vs. rural residency, with heritability being higher among those who were not married, who were less religious, and who lived in more urban environments (Dick et al. 2001, Heath et al. 1989, Koopmans et al. 1999, Rose et al. 2001). More recent studies have reported, for example, enhanced genetic influences on adolescent substance use in environments with lower parental monitoring and more substance-using friends (Dick et al. 2007a, Dick et al. 2007b). These findings suggest that environments can indeed exacerbate the expression of genetic predispositions or have a protective effect against genetic risk. Rather than simply assessing the relative importance of genes and environments, current twin studies of substance use disorders and other behavioral traits are increasingly focusing on the complex interplay of genetic and environmental factors (Johnson 2007, Sher et al. 2010), and special modeling approaches for gene-environment interactions have been developed (Purcell 2002).

2.4.4 Cognitive functioning and education in substance use disorders: A twin study perspective

As was discussed earlier in chapter 2.3, people with substance use disorders are often found to perform poorer than healthy controls in tasks assessing several cognitive functions and general cognitive abilities. Evidence also suggests that these observed differences might at least partly antedate the development of substance use disorders. Importantly, cognitive abilities have been studied extensively with twin

methods, and findings from these studies consistently suggest that genetic factors play an important role in the etiology of individual differences in cognitive abilities, with heritability estimates generally ranging from 40% to 80%, and increasing with age (Bouchard 1998, Deary et al. 2010, Plomin 2003, Plomin et al. 1994, Plomin et al. 2008). Further, the genetic and environmental etiology of verbal ability is known to be very similar to that of general intelligence (Deary et al. 2010).

Taken together the evidence on cognitive differences potentially predating the development of substance use disorders and the strong evidence on genetic influences on both substance use disorders and cognitive abilities, the question arises whether part of these genetic influences might be overlapping. The possibility of shared genetic influences on poorer verbal ability and the risk for alcohol dependence was suggested already more than 25 years ago by Gabrielli and Mednick (1983) in relation to the finding of poorer verbal ability in children of alcoholics. However, it has not been properly studied with genetically informative data. Instead, there is evidence of shared genetic influences between poorer cognitive capacity and ADHD, antisocial behavior, and the personality trait excitement seeking (Koenen et al. 2006, Kuntsi et al. 2004, Pincombe et al. 2007), all well-known correlates of substance use disorders.

In fact, there appears to be only two previous twin studies on alcohol problems and cognitive functioning. In a small sample of 25 pairs of MZ twins discordant for heavy drinking, Gurling et al. (1991) found that twins with high alcohol consumption performed significantly less well than their co-twins in various cognitive functions, including verbal ability, suggesting that heavy alcohol use has cognitive consequences. On the other hand, using a sample of more than 4,700 twins, Christian et al. (1995) found that cognitive scores were significantly lower in diagnosed alcoholics than in healthy participants, but co-twin-control analyses of 120 drinking-discordant MZ twin pairs found no evidence of an association between heavy long-term alcohol intake and lower cognitive scores when genetic and familial factors were controlled for.

It thus appears that the genetic and environmental etiology of poorer verbal ability in alcohol use disorders is not well understood. In the present thesis, the relative contributions of genetic and environmental influences on alcohol problems, verbal cognitive ability and their association were studied using data from a sample Finnish young adult twins (Study III).

Besides verbal ability, similar reasoning can also be applied to the common finding of low educational level among people with substance use disorders, discussed in chapter 2.2.3. Individual differences in educational outcomes are also known to be influenced by genetic differences (Baker et al. 1996, Heath et al. 1985a, Johnson et al. 2009a, Silventoinen et al. 2000, Silventoinen et al. 2004). In addition, cognitive abilities are highly predictive of the level of education to be attained (Deary et al. 2007), and genetic factors contribute to this association (Bartels et al. 2002, Johnson et al. 2006, Lichtenstein & Pedersen 1997). It is thus possible that the co-occurrence of alcohol problems and low education is also, in part, due to genetic influences common to these outcomes. This perspective can be seen to extend the prevailing

approaches to the relationship between educational level and health outcomes in general, namely the social causation, social selection, and interactionist perspectives (Conger and Donnellan 2007), which would argue that low education leads to alcohol problems, alcohol problems lead to low education, or that educational level and alcohol problems reciprocally influence each other.

Concerning the association between educational level and substance use disorders, however, another type of relationship between genetic and environmental factors also seems possible, namely gene-environment interaction. Educational level is related to many facets of an individual's environment throughout the lifespan, ranging from chemical exposures to interpersonal relations (Evans and Kantrowitz 2002, Gallo et al. 2006). Thus, educational level might also have a moderating effect on the genetic etiology of alcohol and other substance use and problems. For example, it might be posited that education-related differences in homogenizing environmental influences, such as social norms, modify the importance of genetic influences—an example of social context as a control mechanism for genetic risk (Shanahan and Hofer 2005). However, gene-environment interaction effects between education and substance use disorders have not been extensively studied.

Finland is a Nordic country whose educational system offers public schooling of uniform quality without tuition fees, rendering educational opportunities virtually independent of financial and other family background (OECD 2007). This feature, combined with the fact that only a small proportion of the population totally abstains from alcohol (Helakorpi et al. 2009), makes Finland an informative setting for a genetic study of educational level in relation to alcohol problems. In the present thesis, data from Finnish twins in early adulthood was used to examine the two non mutually exclusive scenarios of shared genetic influences and gene-environment interaction between alcohol problems and low education (Study IV).

3 AIMS OF THE STUDY

The present thesis investigated substance use disorders and their cognitive and other correlates in young adulthood in two population-based samples, one of which consisted of monozygotic and dizygotic twin pairs enabling genetically informative analyses.

The specific aims of the study were:

1. To estimate the prevalence of alcohol and other substance use disorders among Finnish young adults (Study I).
2. To examine the relative importance of behavioral and affective factors, parental factors, early initiation of substance use and educational factors as correlates of substance use disorders in young adulthood (Study I).
3. To investigate the associations of alcohol and other substance use disorders with verbal cognitive ability and other cognitive functions in young adulthood (Studies II & III).
4. To estimate the relative contributions of genetic and environmental influences on alcohol problems, verbal cognitive ability and their association in young adults (Study III).
5. To examine the possibility of shared genetic influences and gene-environment interaction between alcohol problems and educational level in young adulthood (Study IV).

4 METHODS

4.1 Participants

Two population-based samples of Finnish young adults were utilized in the present studies. The Mental Health in Early Adulthood in Finland study is a continuation of the nationwide Health 2000 Survey (Aromaa and Koskinen 2004) that was coordinated at the National Public Health Institute of Finland (since 2009: National Institute for Health and Welfare). The FinnTwin16 study is part of the Finnish Twin Cohort studies (Kaprio 2006), conducted as a collaboration of the Department of Public Health, University of Helsinki, and the Department of Psychological and Brain Sciences, Indiana University at Bloomington.

4.1.1 Studies I & II: The Mental Health in Early Adulthood in Finland study

The Mental Health in Early Adulthood in Finland (MEAF) sample was initially drawn and assessed in 2001 as part of the nationwide Health 2000 Survey (Aromaa and Koskinen 2004, Pirkola et al. 2005a, Pirkola et al. 2005b), and re-examined in 2003–2005 to investigate psychiatric disorders among young adults in Finland (Suvisaari et al. 2009). The sampling procedure of the original Health 2000 Survey was designed to obtain a nationally representative sample of subjects from the general population, aged 18 years and over. A two-stage stratified cluster sampling frame was used such that the strata were Finland's five university hospital districts, each serving approximately one million inhabitants and differing in several features such as sociodemographic characteristics of the population (Pirkola et al. 2005a, Pirkola et al. 2005b). Finland's 15 largest cities were first included with a probability of one, and 65 other areas from the five strata were then sampled using the PPS method (probability proportional to population size). Finally, random samples of individuals from these 80 areas were drawn. The resulting sample comprised 8028 persons aged 30 years or over (as of July 1st, 2000), and 1894 persons aged 18–29 years. This latter sample of young adults was re-targeted in the MEAF study (Suvisaari et al. 2009).

MEAF was a two-phase study. In the first phase, a questionnaire was sent to all 1,863 living members of the original Health 2000 young adult sample who had not refused further contact. In the second phase, respondents who were screened positive for mental health or substance use problems, and a random sample of screen-negative persons were invited to participate in a mental health interview and neuropsychological assessment.

The MEAF questionnaire included several scales assessing mental health and substance use that were used as screens for the mental health interview. Briefly, in addition to substance use disorders, symptoms of psychological distress, eating disorders, psychotic disorders, bipolar spectrum disorders and suicidality were screened for (Suvisaari et al. 2009). Two separate screens were used to assess substance use: a score of at least three in the CAGE questionnaire (Mayfield et al. 1974) for alcohol use, and self-reported use of any illicit drug at least six times. The CAGE questionnaire is a widely used screening instrument for alcohol problems, and it contains four dichotomous questions assessing problems related to drinking (Need to cut down, Annoyed by criticism, Feeling guilty, Need for an eye opener). In addition to screen-positive persons, individuals with hospital treatment due to any mental or substance use disorder (ICD Chapter V: Mental and behavioural disorders) during the lifetime according to the Finnish Hospital Discharge Register information were asked to participate.

Because of the study design, there were non-respondents in two study phases: in the questionnaire containing the screens for the interview, and in the interview (Figure 2). Of the 1863 members of the original study population who were contacted, 1,316 (70.6%) returned the questionnaire. Participation in the psychiatric interview and neuropsychological testing was 55.8% (458/821) for the screen-positive and 54.7% (88/161) for the invited screen-negative persons, yielding a total of 546 participants. Non-participation in both study phases was found to be related to age, sex, and education, but not to self-reported mental health disorders or symptoms, including the CAGE scores (Suvisaari et al. 2009). Age, sex, and attained education in 2001 were used when calibrating post-stratification weights to correct for non-response. The study protocol of the MEAF study was accepted by the ethics committees of the National Public Health Institute and the Hospital District of Helsinki and Uusimaa. Written informed consent was provided by the participants.

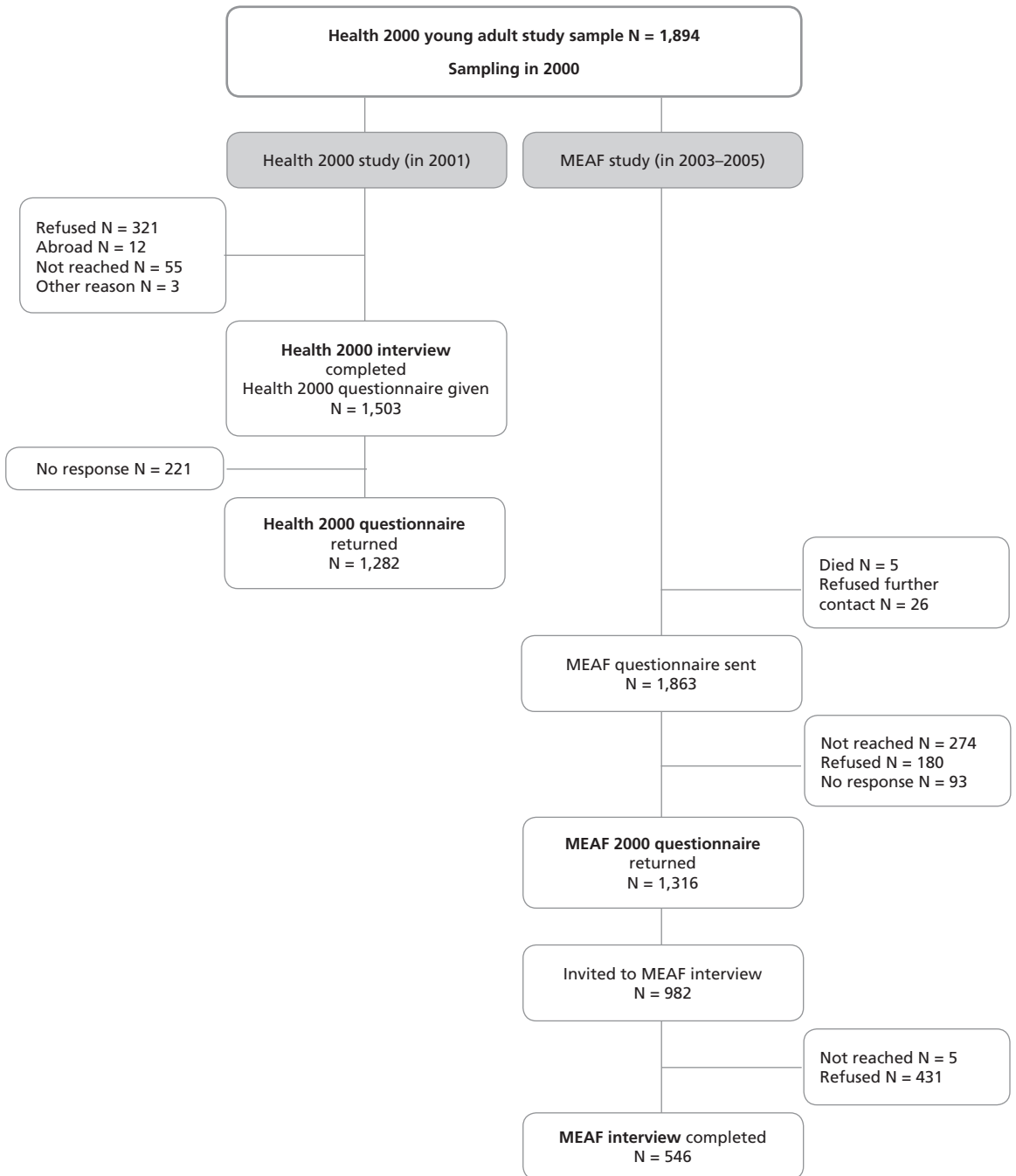


Figure 2. Sampling and data collection in the Health 2000 and Mental Health in Early Adulthood in Finland (MEAF) studies.

The sample used in Study I

In Study I, prevalence and correlates of substance use disorders were investigated. The prevalence estimation was based on diagnostic assessment that was completed in 605 individuals, of whom 546 participated in the in-person psychiatric interview and the rest were diagnosed based on case records from hospital and outpatient treatments. Of the 605 individuals used in the prevalence estimation, 328 (54.2%) were females. Data on the studied correlates of substance use disorders came from the questionnaires and interviews of both the Health 2000 Survey and MEAF, and the sample available for these analyses was thus comprised of the 546 participants of the MEAF interview. Of these participants, six individuals had missing information in three analyzed variables from the MEAF questionnaire, and were dropped from the analyses. Of the 540 participants with data available, 313 (58.0%) were females, and the mean age of the sample was 28.1 years ($sd = 3.7$ years, range: 21.3-35.4 years).

The sample used in Study II

Study II assessed cognitive functioning in substance use disorders using data from neuropsychological tests conducted on the participants of the MEAF interview. Of the 546 participants, neuropsychological test data were considered as valid for the present study in 466 individuals. Reasons for exclusion were alcohol or other substance use during the testing day (with the exception of tobacco), disturbances in the testing situation, native language other than Finnish, neurological disorders, psychotic disorders, and being a psychologist or a psychology student. Of the 466 individuals used in the analyses, 267 (57.3%) were females, and the mean age of the sample was 28.1 years ($sd = 3.7$ years, range: 21.3-35.4 years).

4.1.2 Studies III & IV: The FinnTwin16 study

FinnTwin16 (FT16) is a population-based longitudinal study of five consecutive birth cohorts (1975–1979) of Finnish twins (Kaprio et al. 2002, Rose et al. 1999). These twins, along with other birth cohorts of the Finnish Twin Cohort studies, were identified through the use of family member links existing for all persons in Finland's Central Population Registry, considering persons born on the same day to the same mother as multiples.

FT16 was initiated in 1991 when the 1975 cohort was sequentially enrolled in ten mailouts during 1–2 months following the twins' 16th birthdays. Baseline questionnaire data collection was completed in 1996 with pairwise response rates exceeding 88%, yielding baseline data from 2,733 twin pairs. Subsequent follow-up assessments were made at ages 17, 18.5, and in young adulthood. The first three waves were tightly controlled for age, in appreciation of the rapid development of alcohol use in adolescence. In young adulthood, the surveys were telescoped into a 30 month period, with each birth year assessed in a six month window during

2000–2002 (Kaprio et al. 2002). The baseline and follow-up assessments included surveys of health habits and attitudes, symptom checklists, personality scales, and social relationships. The data collection procedures were approved by the Ethical Committee of the Department of Public Health, University of Helsinki, Helsinki University Central Hospital ethical committee, and by the Institutional Review Board of Indiana University.

The sample used in Study III

In study III, verbal ability and other cognitive correlates of alcohol dependence were studied using a subsample of 602 twins from the full FT16 sample. A pairwise selection strategy was used to identify informative twin pairs for intensive laboratory study after their young adult questionnaires were received. Twin pairs extremely discordant and concordant (EDAC selection) for alcohol-related problems, using a 22-item version of the Rutgers Alcohol Problem Index (RAPI) (White and Labouvie 1989) administered at age 18.5 were identified. EDAC selection was used in order to enhance statistical power by focusing on the most informative twin pairs. A sample of 484 twin pairs was selected, with most pairs characterized by extreme discordance or extreme concordance of the co-twins for their RAPI scores. Of the 968 twin individuals yielded by this selection procedure, 151 were ineligible for participation, because one or both twins were living abroad, were not reached, had diseases or were using medications affecting the test protocols, or were deceased. Of the 817 eligible twins contacted and invited to participate, 602 (73.7%) did so, yielding 300 complete twin pairs plus individual co-twins from two additional pairs. Non-participants did not differ from participants in their RAPI scores, age, zygosity, or gender, whereas they had lower educational level as compared to the participants ($p < .001$).

Concordance was defined as a maximum RAPI intrapair difference of 5 points, whereas discordant pairs had a minimum intrapair difference of 10 points (theoretical maximum: 66). These limits approximated the bottom 65% and top 17% (or 1/6) of the distribution of RAPI intrapair differences in the full FinnTwin16 sample. In addition to the discordant ($n = 202$) and concordant participants ($n = 147$), the dataset included a representative non-EDAC sample of twins residing in the greater Helsinki area ($n = 253$). Zygosity was determined for all same-sex twin pairs in this subsample using multiple highly polymorphic genetic markers assayed at the Paternity testing unit of the National Public Health Institute (since 2009: National Institute for Health and Welfare) in Helsinki. Of the 602 individuals in the sample, neuropsychological data were considered invalid for eight participants with a neurological or developmental disorder (e.g. severe epilepsy). Of the 594 participants with valid neuropsychological data, 295 (49.7%) were females, and the mean age of the sample was 26.2 years ($sd = 1.3$ years, range: 23.3–30.1 years). The sample contained 211 MZ and 383 DZ individuals, including 294 complete pairs (104 MZ pairs, 190 DZ pairs) and six twin individuals.

The sample used in Study IV

In study IV, genetic correlation and gene-environment interaction between alcohol problems and educational level were assessed using data from the wave IV young adult questionnaire survey of FT16. Wave IV data of the outcomes of interest were available for a total of 4,974 individuals from 2,671 twin pairs (from 838 MZ, 879 same-sex DZ, and 954 opposite-sex DZ pairs). Of the sample, 2,724 (54.8%) were females, and the mean age was 24.5 years (sd = 0.9 years, range: 22.8-28.6 years). The data included 116 individuals (2.3% of the sample) who could be classified as probable lifetime abstainers based on their responses throughout the data collection. These individuals were excluded from all analyses to avoid the assumption that a single unidimensional distribution encompasses both initiation of alcohol use and problem drinking. Thus, the final sample contained 4,858 twin individuals (2,414 complete pairs and 30 individual twins). Zygosity was determined on the basis of a well-validated questionnaire, containing items on the twins' similarity and confusability, completed by both co-twins and their parents at the baseline (Kaprio et al. 2002).

4.2 Measures

4.2.1 Substance use disorders and alcohol problems

Studies I and II

Alcohol and other substance use disorder diagnoses in the MEAF sample were based on a psychiatric interview and case notes from hospital and outpatient treatments during the lifetime, obtained from the Finnish Hospital Discharge Register excluding individuals who had refused any participation in the Health 2000 study. The psychiatric interview was conducted by experienced psychiatric research nurses or psychologists using the Research Version of the Structured Clinical Interview for DSM-IV-TR (First et al. 2001). All interviews were reviewed jointly by a psychiatrist and the interviewer. Two psychiatrists and two residents in psychiatry made the final best-estimate diagnoses based on all available information from the interview and case records. All DSM-IV substance use disorders except for nicotine dependence were assessed. Reliability of the diagnoses was tested on 40 cases rated by all four clinicians. For alcohol disorders, the unweighted pairwise kappa values ranged from 0.94 to 1.

Studies III and IV

In the subsample of the FT16 data, used in Study III, a psychiatric interview, the Semi-Structured Assessment for Genetics of Alcoholism (SSAGA) (Bucholz et al. 1994), was conducted to diagnose lifetime DSM-III-R alcohol use disorders (APA 1987). In addition to the categorical alcohol dependence diagnosis, the number of

alcohol dependence symptoms met (range 0–9) was analyzed. Besides DSM-III-R diagnoses, two indicators of alcohol problems were assessed in Study III: a self-reported estimate of maximum number of alcoholic drinks consumed in a 24-hour period during the lifetime (Maxdrinks), also derived from the SSAGA interview, and the RAPI scores (White and Labouvie 1989) from questionnaires at age 18.5. RAPI is a self-report measure of alcohol-related problems experienced during the previous 12 months (White and Labouvie 1989). The original RAPI has 23 items, but in the FT16 young adult data collection, the item on whether alcohol use interfered with school work or exam preparation was omitted, creating a 22-item Finnish adaptation of RAPI with four response options. The internal consistency of this adapted version in the FT16 sample was as good (coefficient alpha = .90) as that of the original RAPI (coefficient alpha = .92) (White and Labouvie 1989). Maxdrinks has been used in genetic studies as a quantitative phenotype closely related to diagnosis of alcohol dependence (Saccone et al. 2005).

In Study IV, data from the young adult questionnaire of the full FT16 sample was used, and diagnoses of alcohol use disorders were not available. As in Study III, RAPI and Maxdrinks were used as alcohol problem variables. In Study IV, both RAPI and Maxdrinks were derived from the young adult questionnaire, completed at an average age of 24.5 years.

4.2.2 Correlates and confounding factors

Studies I and II

The variables for correlates of substance use disorders, used in studies I–IV are listed in Table 4. Studies I and II included a range of correlates, selected on the basis of earlier studies on risk factors for substance use disorders and categorized as representing the four domains of behavioral and affective factors, parental factors, early initiation of substance use, and educational factors. In Study I, the relative contributions of these factors as correlates of substance use disorders were studied, whereas they were included as covariates in the analyses of cognitive functioning in Study II. In addition, comorbid psychiatric diagnoses based on the best-estimate diagnostic procedure were used as covariates in Study II.

TABLE 4. Correlates of substance use disorders included in studies I–IV.

Domain	Studies I & II		Study III		Study IV	
	Variable	Data source	Variable	Data source	Variable	Data source
Education & learning	Basic education (dichotomous)	MEAF Interview	Basic education (dichotomous)	FT16 Young Adult Questionnaire	Years of education	FT16 Young Adult Questionnaire
	Learning difficulties at school	Health 2000 Interview				
Age at substance use initiation	Initiation of daily smoking	MEAF Questionnaire	Initiation of daily smoking	FT16 Interview (SSAGA)		
	Initiation of drinking to intoxication	MEAF Questionnaire	Initiation of drinking to intoxication	FT16 Interview (SSAGA)		
Comorbid disorders	Comorbid DSM-IV Axis-I disorder	MEAF Interview (SCID-I) + Case records	Comorbid DSM-III-R Axis-I disorder	FT16 Interview (SSAGA)		
Behavioral & affective factors	Behavior problems at school	Health 2000 Interview				
	Aggression	MEAF Questionnaire				
	Anxiousness	MEAF Questionnaire				
Parental factors	Parental alcohol problems	Health 2000 Questionnaire				
	Parental basic education	Health 2000 Interview				

MEAF: the Mental Health in Early Adulthood in Finland study; FT16: the FinnTwin16 study; SSAGA: the Semi-Structured Assessment for Genetics of Alcoholism; DSM-IV: The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; SCID-I: the Research Version of the Structured Clinical Interview for DSM-IV; DSM-III-R: The Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised

Behavioral and affective factors included the following variables. Attention or behavior problems at school were derived from a set of questions on difficulties during school time, lasting longer than one semester (four to five months). A positive response to either of the items on attention or behavior problems was used as an indicator of attention or behavior problems at school. Aggression was assessed with a short measure of trait aggressiveness, constructed based on selected items from the Buss-Perry Aggression Questionnaire (Buss and Perry 1992). Two items from each of the four aggression subscales were translated into Finnish, creating an eight-item scale. A summary scale of the eight items, responded to on a five-point Likert scale, was constructed (theoretical range 8-40, coefficient alpha = .82). Aggression scores were further classified as low (<11), moderate (11–17), and high (>17), approximating the observed 25th and 75th percentiles. Anxiousness was assessed with a single item that has been used as an indicator of trait anxiousness

in previous studies in Finland (Fröjd et al. 2007). The question asked was “Are you usually tense or distressed?”. The five-point scale was: 1 “I have good control over my feelings and do not become tense or distressed easily”, 2 “I do not feel tense or distressed”, 3 “I become distressed quite easily”, 4 “I become anxious, tense or distressed very easily”, and 5 “I feel anxious or tense all the time as if I had lost my nerves”. A three-class variable was created by classifying anxiousness scores 1 and 2 as low, score 3 as moderate, and scores 4 and 5 as high.

Parental factors included parental alcohol problems, derived from a series of questions concerning various childhood adversities, experienced before age 16. Items “Did your father have alcohol problems” and “Did your mother have alcohol problems” were combined so that a positive response to either item was considered as an indicator of parental alcohol problems. Parental basic education was also included, such that a binary variable of having at least some academic secondary (high school) studies vs. not was created on the basis of the highest secondary education of either parent.

Factors related to substance use initiation were age at initiation of daily smoking and age at initiation of drinking to intoxication. Lifetime never-smokers were classified as a separate category, while for smokers the age at daily smoking initiation was categorized into three classes: 18 years or older, 15–17 years, and younger than 15 years. Concerning drinking to intoxication, the question “At which age were you for the first time so drunk that you felt sick afterwards?” was asked. Three classes were created: those responding “Never” or at age 18 or older, at age 15–17, and at age younger than 15 years.

Educational factors included learning difficulties at school and basic education. Having had learning difficulties at school was determined as a positive response to any of the four learning related difficulties items (Reading, Writing, Mathematics, Languages) in a set of questions related to school time problems. For basic education, a binary variable was created coding academic secondary education (high school degree) and less than academic secondary education as separate categories. Basic education was included instead of highest attained education because a large part of the sample were still students.

Study III

Comorbid psychiatric diagnoses were available from the SSAGA interview. Other covariates included in Study III were basic education, using the same dichotomous classification as in Studies I and II, and age at initiation of daily smoking and drinking to intoxication, also categorized identically to Studies I and II.

Study IV

In Study IV, the focus was on the relationship between alcohol problems and educational level. Information on the attained level of education was available as categorical classifications of each participant’s completed and ongoing studies. Using this information, a variable representing the estimated total years of education was

created. This was done on the basis of the standard duration of each type of education. In the Finnish educational system, compulsory education continues through grade nine (age 16). Secondary education is divided into vocational (non-academic) and academic secondary education (high-school), which typically take two and three years to complete, respectively. Tertiary education is provided by polytechnics and universities, lasting typically three and a half and five years, respectively. Polytechnics train professionals in various fields in response to labor market needs, whereas universities conduct scientific research and provide the highest levels of education. In order to enter tertiary education, academic secondary education is generally required, although some exceptions exist. For the participants who still had their studies underway when completing the young adult questionnaire, ongoing studies were taken into account by using half of the standard duration of the type of education in question as an average estimate of years studied. For example, individuals who reported having completed academic secondary education and currently studying in the university were thus given the value 14.5 (9 + 3 + 2.5) for years of education.

4.2.3 Cognitive measures

In both MEAF and FT16, neuropsychological tests were administered by experienced and well-trained psychologists, psychology students or research nurses as part of the intensive data collection that also included the psychiatric interviews. Scoring of all tests was done by psychologists. As shown in Table 5, the neuropsychological test batteries used in Studies II and III were nearly identical, containing validated measures of verbal ability, psychomotor processing speed, working memory, executive functioning, and verbal learning.

TABLE 5. Cognitive test measures used in Studies II and III.

	Study II	Study III
Verbal cognitive ability	WAIS-R: Vocabulary	WAIS-R: Vocabulary
Psychomotor processing speed	WAIS-R: Digit Symbol	WAIS-R: Digit Symbol
Verbal working memory	WMS-R: Digit Span Forward WMS-R: Digit Span Backward WAIS-III: Letter-Number Sequencing	WMS-R: Digit Span Forward WMS-R: Digit Span Backward WAIS-III: Letter-Number Sequencing
Visual working memory	WMS-R: Visual Span Forward WMS-R: Visual Span Backward	
Executive functioning	Trail Making Test	Trail Making Test California Stroop Test
Verbal learning	California Verbal Learning Test	California Verbal Learning Test

WAIS-R: the Wechsler Adult Intelligence Scale-Revised (Wechsler 1981); WMS-R: the Wechsler Memory Scale-Revised (Wechsler 1987); WAIS-III: the Wechsler Adult Intelligence Scale, 3rd Edition (Wechsler 1997).

Verbal cognitive ability was assessed with the Vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler 1981). Vocabulary is a highly reliable and valid test, and it is considered to be one of the best single indicators of general intelligence (Lezak et al. 2004). In the test, the subject is asked to explain the meaning of a list of words, increasing in abstractness. The sum score of correct answers (1 or 2 points each) was included in the analyses. Another subtest of WAIS-R, Digit Symbol, was used to examine psychomotor processing speed. In this test, the subject's task is to fill in blank spaces with abstract symbols that are paired to numbers corresponding to a key sequence printed in the top part of a test sheet. The subject is urged to perform as quickly as possible. The number of items correctly filled in 90 seconds was used in the analyses.

Scores of the Digit Span Forward and Backward subtests of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler 1987) and the Letter-Number Sequencing subtest of WAIS-III (Wechsler 1997) were used as variables for verbal working memory in both studies. The Digit Span and Letter-Number Sequencing tests are auditory tasks in which the examiner reads out numbers and letters to be processed and repeated by the subject. More specifically, in Digit Span Forward, the participant's task is to repeat verbatim the number sequences read out by the examiner, whereas in Digit Span Backward, the number sequences have to be repeated in reverse order. In the Letter-Number Sequencing test, the examiner reads out sequences of numbers and letters ordered randomly, and the subject is required to repeat them ordering first the numbers in ascending order, followed by the letters in alphabetical order. For example, the sequence M-4-E-7-R-2 would thus be reproduced as 2-4-7-E-M-R. In both the Digit Span and Letter-Number Sequencing tests, the length of the test sequence is increased by one item until the participant fails two consecutive trials of a given length.

Study II also investigated visual working memory, assessed with the Visual Span Forward and Backward subtests of WMS-R (Wechsler 1987). In these tests, the examiner sequentially points at squares printed in a geometrical array on the test sheet, and the subject's task is to repeat the sequence in the same order in Visual Span Forward, and in reverse order in Visual Span Backward. Similar to the verbal span tests, the length of the sequence is increased until the participant fails two trials of a certain length.

The Trail Making Test (TMT) (Reitan and Wolfson 1993) was administered to assess executive functioning in both studies. TMT contains two parts. In Part A, consecutively numbered circles on a test sheet must be connected by lines to obtain the correct sequence (1-2-3-...). In Part B, the same number of consecutively numbered and lettered circles must be connected by alternating between the two sequences (1-A-2-B-3-C-...). In both parts, the participant is urged to perform as fast as possible. Time to complete parts A and B, and the difference score B-A were analyzed. As another measure of executive functioning, the California Stroop Test (Delis et al. 2001) was included in Study IV. The standard Stroop procedure has three parts, in which the participant's task is, first, to name the colors of colored rectangles

printed on the test sheet, second, to read out a list of color names, and, finally, to name the colors in which a list of color words are printed. In this third part of the test, the color names and the actual colors of the words are incongruent, and the task thus requires active cognitive control processes compared to the more automatic tasks of color naming and reading. In addition to these tasks of the standard Stroop, the California Stroop adds a fourth part, in which the subjects' task is either to name the color in which a color word is (incongruently) printed (similar to part three) or to read out the word if it appears in a rectangle. This part requires set-shifting between the two rules. Time to complete parts 1-4 was analyzed from the California Stroop Test.

In both studies, verbal learning was assessed with the California Verbal Learning Test (CVLT) (Delis et al. 1987). In this test, the participant is presented with a list of 16 words representing four semantic categories. The examiner reads out the list five times, and after each reading the subject is asked to repeat as many words as possible in free order. A new, interfering word list is then presented, after which the subject is asked to recall the words from the original list. Finally, after an interval of 20 to 30 minutes, during which other tests are administered, the subject is again asked to recall as many words as possible from the original list. These measures of total recall from trials 1–5 (learning performance), short-delay recall and long-delay recall were included in the analyses.

4.3 Statistical methods

In Studies I and II, the initial cluster sampling design of the Health 2000 Survey (Aromaa and Koskinen 2004) was taken into account in the analyses, and post-stratification weights calibrated by Statistics Finland were used to adjust for non-response. These weights were applied to correct the survey distributions to correspond to the population distributions. In addition, the two-phase screening for the MEAF interview and neuropsychological testing was taken into account using expansion weights calculated for the screen-positives (M) by dividing their total by the number interviewed ($M1$), i.e. $M/M1$, and for the screen-negatives in the same way, $N/N1$ (Dunn et al. 1999, Pickles et al. 1995). These weights were calculated separately for men and women. The final weights used in statistical analyses were obtained by multiplying the expansion weights by the post-stratification weights (Suvisaari et al. 2009).

In Studies III and IV, the non-independence of observations in twin data, clustered in pairs, was taken into account in the analyses using robust variance estimation (Williams 2000).

All statistical analyses in Studies I–IV were performed using Stata 9 (StataCorp 2005), with the exception of biometrical twin modeling in Studies III and IV. Twin models were fitted to raw data using Mx, a statistical modeling software for

genetically informative data (Neale et al. 2006). In all studies, the probability level of $p < 0.05$ was taken to indicate statistical significance.

4.3.1 Principles of quantitative genetic modeling

In quantitative genetics, standard univariate biometrical twin approaches model the total variance of a single trait as a sum of additive genetic (A), dominant genetic (D), common environmental (C), and unique environmental (E) variance components (Neale and Maes 2003). Biometrical twin models are structural equation models in which the variance components are represented as latent factors that influence the observed variables, and maximum likelihood estimation is used to derive values for the parameters of the model (Kline 2005, Neale et al. 2006). As described earlier in chapter 2.4.1, A effects represent the sum of the individual effects of each gene on the phenotype. The effects of A thus correlate perfectly in the twin models in MZ co-twins, who are genetically identical, but the correlation is set to 0.5 for DZ co-twins, who share on average 50% of their segregating genes. The effects of D represent interaction effects between alleles at the same locus, and thus also correlate perfectly in MZ co-twins, whereas their correlation is set to 0.25 in DZ co-twins, because that is the probability of DZ co-twins having received the same alleles at a given locus from both the father and the mother (Posthuma et al. 2003). C effects denote all the environmental influences shared by co-twins, and they are set to correlate perfectly in both twin types. E effects, in contrast, are environmental influences that affect only one member of the twin pair and as such only contribute to trait variance but not to the covariance between co-twins. E effects also include measurement error.

In the classical twin design, information on the different variance components comes from three observed statistics: the phenotypic trait variance, the covariance between MZ twins and the covariance between DZ twins. With data from twins alone, C and D effects cannot be estimated simultaneously, as they are confounded: C influences increase the DZ correlation relative to the MZ correlation, whereas D influences decrease the DZ correlation relative to the MZ correlation (Evans et al. 2002). Because models that contain dominant genetic influences in the absence of additive genetic influences are biologically implausible (Posthuma et al. 2003), and because E effects include measurement error and as such have to be included in the model, a choice between ACE and ADE models has to be made. This choice is generally based on the comparison of MZ and DZ within-pair correlations, such that a DZ correlation greater than a half of the MZ correlation suggests an ACE model, whereas a DZ correlation less than a half of the MZ correlation leads to selecting an ADE model (Evans et al. 2002).

The basic twin model can be extended to investigate gene-environment interaction effects. The univariate moderation models are extensions of the standard univariate model, modified to include a moderation component (Purcell 2002). As shown in Figure 3, in addition to the standard paths a, c, and e, which indicate additive

genetic influences, common environmental influences, and unique environmental influences, a moderation effect β is included on each of these influences. In the moderation model, the additive genetic value is a linear function of the moderator variable M , represented by the equation $a + \beta_x M$, where β_x , an unknown parameter to be estimated, represents the magnitude of the moderating effect. A β_x that is significantly different from zero is taken as evidence for a moderation effect on additive genetic influences. Moderation effects on common and unique environmental influences, β_y and β_z , are estimated similarly. The pathway $\mu + \beta_M M$ models the main effects of the moderator variable on the outcome. Importantly, this pathway also includes any covariance between the moderator and the outcome, including genetic correlation. Moderation effects are thus not confounded by possible common genetic influences on the moderator and outcome variables.

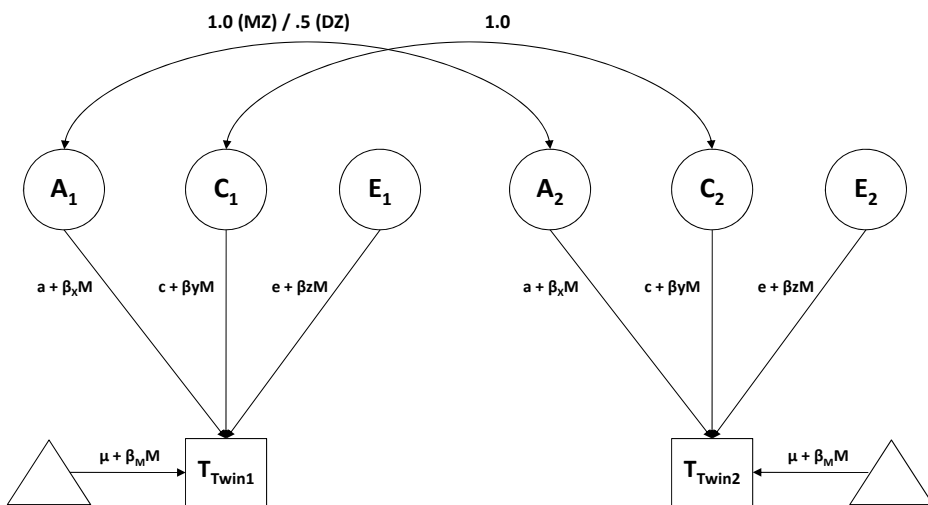


FIGURE 3. Univariate twin model including moderation effects. Depicted as circles, the latent variables A, C and E indicate additive genetic, common environmental, and unique environmental influences on the trait (T) of interest for both co-twins of a twin pair. The triangle indicates the mean of T. The paths a , c , and e indicate the magnitude of each latent variance component's effect on the trait. Each path also includes a β term, which indicates the moderation coefficient for the moderator variable M . When the moderation coefficients equal zero, the model is reduced to the standard univariate model.

The relationship between two or more variables can be modeled in multivariate Cholesky decomposition models which are mathematically similar to principal components analysis (Figure 4). Here, the phenotypic covariance of the variables is decomposed into proportions accounted for by A, C (or D), and E effects. The degree of association of the genetic factors influencing the two variables can then be estimated as the genetic correlation (r_A) between the latent genetic factors for the two variables. Common and unique environmental correlations (r_C , r_E) are estimated in

a similar fashion. For example, a genetic correlation of 1.0 would indicate identical genetic influences on the two studied traits, whereas a genetic correlation of 0 would indicate that two completely different sets of genes influence the traits.

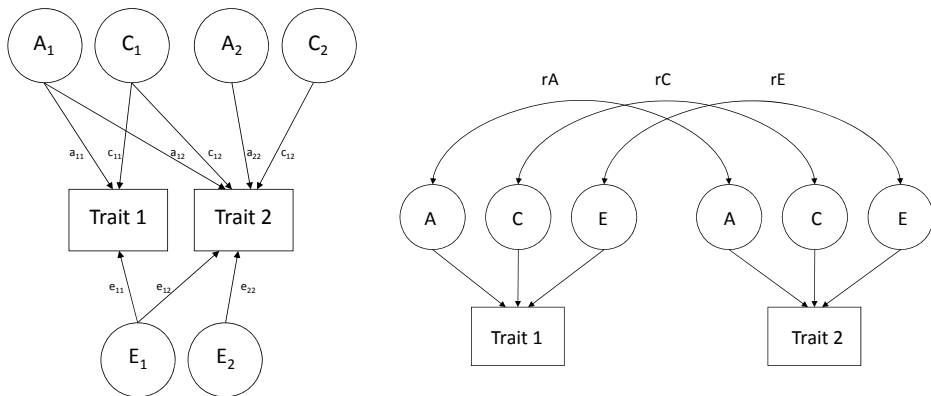


FIGURE 4. Bivariate Cholesky decomposition model. The left panel depicts the Cholesky model as it is actually fitted, including additive genetic (A), common environmental (C), and unique environmental (E) variance components common to traits 1 and 2, and specific to trait 2. The right panel shows an alternative representation of the model (the correlated factors solution), that includes correlations between the genetic (rA) and environmental variance components (rC , rE) for traits 1 and 2. For simplicity, the model is shown for one twin of the pair only.

In all twin modeling, the fit of the full model including the variance components A, C or D, and E can be compared to the nested submodels AE, CE, and E. The significance of each parameter in the model is tested by dropping the parameter and evaluating the change in $-2 \log$ likelihood between the initial model and the nested submodel. This difference is asymptotically distributed as chi-square. Model comparisons are made with a likelihood ratio chi-square test, and a significant change in chi-square indicates that dropping the parameter significantly decreases model fit, suggesting that the parameter should be retained in the model (Neale and Maes 2003). General assumptions of twin models, such as equality of variances between co-twins and between twin types, are tested with so called saturated models that do not make these assumptions.

4.3.2 Statistical analyses in Study I

In Study I, the lifetime prevalence of substance-specific abuse and dependence diagnoses and any substance abuse or dependence were estimated separately for men and women. Associations between the selected correlates and lifetime any substance abuse or dependence were then studied, first using t-tests and chi-square tests, and

then with a series of logistic regression models designed to provide information on whether behavioral and affective factors and correlates from other domains associate with substance use disorders independently of each other. More specifically, unadjusted associations between each correlate variable and substance use disorder diagnosis were first assessed, after which the associations between behavioral and affective factors and substance use disorders were investigated sequentially adjusting for correlates from other domains.

Data from four distinct sources were used in the logistic regression models (Table 4, Figure 2). As described above, six individuals had missing values in three correlate variables from the MEAF questionnaire, and were dropped from the logistic regression analyses. In addition, there were five individuals who had responded to seven out of the eight items of the aggression scale in the MEAF questionnaire. For these individuals the mean of the seven existing responses for each individual was substituted for the missing value. Finally, in order to use all available information, individuals who had participated in the MEAF interview but had missing values in any of the four variables from the Health 2000 study (Table 4) were also included in the logistic regression analyses by coding missingness as a separate category of these categorical variables (Schafer and Graham 2002).

4.3.3 Statistical analyses in Study II

In Study II, associations between lifetime any substance use disorder diagnosis, cognitive measures and confounding factors were studied with t-tests, chi-square tests, and linear regression models. Assumptions of linear regression were tested by conducting Shapiro-Wilk tests for the normality of the residuals, and by making plots of residuals versus fitted values to check the homoscedasticity of the residuals. Logarithmic, square, and 1/square root transformations were used for the cognitive measures to approximate normality, when needed. Standardized cognitive variables were used in the regression models to enable comparisons of predictor variable effects for different cognitive outcomes. In Visual Span Forward, Visual Span Backward, CVLT Short Delay Recall and CVLT Long Delay Recall, modest ceiling effects were detected (5–12% of the observations). Therefore, Tobit regression was used in addition to linear regression to study the associations between substance use disorder diagnosis and these measures, but no significant changes in the results were detected.

4.3.4 Statistical analyses in Study III

In Study III, three phases of analyses were performed. First, in multiple regression models, twins were studied as individuals to investigate the associations of alcohol dependence diagnosis and symptoms, maximum number of drinks, and RAPI score

with cognitive measures. Effects of the covariates on these associations were also studied. Next, in intrapair analyses, correlations of intrapair differences in alcohol dependence symptoms, maximum number of drinks, and RAPI scores with intrapair differences in verbal ability were analyzed. Comparing these correlations in MZ and DZ twin pairs yields a first estimate of the presence of genetic and environmental influences on the covariation of alcohol problems and verbal ability. In order to infer a causal environmental association between these traits, a significant correlation between intrapair differences in alcohol problems and intrapair differences in verbal ability should be observed in both twin types. As intrapair analyses in MZ twins control for all genetic influences, an association observed in DZ but not MZ pairs argues against an environmental association and suggests, in contrast, shared genetic factors influencing both verbal ability and alcohol problems (cf. Kujala et al. 2002). Further, the cognitive performance of co-twins discordant for alcohol dependence was also compared.

Based on the individual-level and intrapair analyses, biometrical genetic modeling was conducted. To estimate the relative magnitudes of genetic and environmental influences underlying Vocabulary scores, alcohol problems, and their covariation, bivariate ACE Cholesky models were fitted separately for Vocabulary with each of the continuous alcohol problem measures: RAPI scores, maximum number of drinks, and alcohol dependence symptoms. Because RAPI scores were also available from questionnaires in the full epidemiological FT16 sample, effects of the EDAC sample selection in Study III on model estimates could be tested by comparing modeling results for RAPI obtained with data from the full sample.

4.3.5 Statistical analyses in Study IV

In Study IV, the association of educational level with RAPI and Maxdrinks was first studied with linear regression models treating twins as individuals. Due to strong positive skewness, Box-Cox transformations of mean RAPI and Maxdrinks scores were used in the analyses. For a first estimation of the presence of genetic influences on these traits and their covariation, twin and cross-twin cross-trait correlations were compared in different zygosity groups.

Twin modeling in Study IV was initiated with standard univariate analysis for each of the outcomes using the full sample including opposite-sex DZ pairs. Besides estimates of additive genetic, common environmental and unique environmental influences on the outcomes, these models also enabled testing the presence of quantitative and qualitative sex differences in genetic influences. Next, trivariate Cholesky decomposition models for education and the alcohol variables (RAPI and Maxdrinks) were estimated separately for the sexes. Finally, gene-environment interaction effects between educational level and the alcohol problem variables were investigated with univariate moderation models where a standardized variable of years of education served as a moderator for RAPI and Maxdrinks.

5 RESULTS

5.1 Prevalence and correlates of substance use disorders and alcohol problems in early adulthood

5.1.1 Lifetime prevalence of alcohol and other substance use disorders in Study I

The prevalence of any substance abuse or dependence during the lifetime was estimated at 14.2% (95% CI: 11.6–17.4%). In general, substance use disorders were more prevalent in men than in women (for any substance abuse or dependence 20.9% [95% CI: 16.5–26.1%] vs. 7.4% [95% CI: 4.9–10.9%], respectively). Alcohol diagnoses were most prevalent (13.1%), followed by cannabis (1.7%) and amphetamine (1.5%) (Study I, Table 2, page 6/14). Of those with a substance use disorder, 24% had an abuse or dependence diagnosis of two or more classes of substances. The prevalence of any illicit substance diagnosis without a comorbid alcohol diagnosis was 1.1%. In 53% of the cases with a substance use disorder, the diagnosis was dated at age 18 or younger.

5.1.2 Correlates of substance use disorders in Study I

Unadjusted associations. Individually, all correlates from the four domains of behavioral and affective factors, parental factors, early initiation of substance use, and educational factors were significantly associated substance use disorders (odds ratios 2.4–11.6, $p < .001$ for all variables). Individuals with a substance use disorder diagnosis were also slightly older than those with no diagnosis [$t(538) = -2.9, p < .01$], and the male:female ratio was higher in the diagnosis group [$\chi^2(1) = 27.9, p < .001$].

Adjusted associations. A series of logistic regression models was conducted to assess the associations between behavioral and affective factors and substance use disorders adjusting for the correlates from other domains. The results of these analyses are shown in detail in Table 4 of Study I (pages 8–9/14). In *Model I*, behavioral and affective factors and the covariates age and gender were included as predictor variables. When assessed simultaneously, all three variables (attention or behavior problems at school, aggression, and anxiousness) were still significantly associated with substance use disorders [adjusted odds ratios (AORs) 2.2–6.8].

Model I established the baseline for the effect of behavioral and affective factors, with which the subsequent models could be compared. In *Model II*, parental

factors were added. The AORs of attention or behavior problems at school and aggression were not significantly different from those of *Model I*, and the effect of high anxiousness was also close to statistical significance ($p = .053$). Among parental factors, only missing information of parental alcohol problems was significantly associated with substance use disorders. In *Model III*, the effect of early initiation of substance use was assessed. Adjusting for behavioral and affective factors, age at initiation of drinking to intoxication was not independently associated with substance use disorders, whereas daily smoking was associated with elevated risk. Initiation of daily smoking before age 15 showed a large effect (AOR = 8.5). Behavioral and affective measures remained significant predictors of a substance use disorder diagnosis, but the AOR of attention or behavior problems at school was reduced compared to *Model I* (5.0 vs. 6.8; adjusted Wald test, $p = .042$). In *Model IV*, a similar analysis was conducted with measures of learning and education. Learning difficulties at school showed no risk independently of behavioral and affective factors, but not having a high school degree was still significantly associated with substance use disorders (AOR = 3.1). Also the effects of attention or behavior problems at school, high aggression, and anxiousness were still significant, but the AOR of high aggression was reduced compared to *Model I* (3.0 vs. 4.3; adjusted Wald test, $p = .020$).

Finally, in *Model V*, the correlates from all four domains were assessed simultaneously. Adjusting for all the correlates, attention or behavior problems at school (AOR = 3.4) and anxiousness (Moderate anxiousness, AOR = 3.0; High anxiousness, AOR = 4.0) remained significantly associated with substance use disorders, whereas high aggression was bordering on significance ($p = .065$). Of the other domains, only age at initiation of daily smoking emerged as a statistically significant correlate in this analysis. Compared to non-smokers, smokers regardless of the age at initiation were at elevated risk. Having initiated daily smoking before age 15 had a strong association with a substance use disorder diagnosis (AOR = 7.5).

Although the AORs for many variables were nonsignificant in Models II–V, these additional domains of correlates clearly improved the statistical prediction of substance use disorders over behavioral and affective factors only, as is evident from the statistically significantly higher maximum likelihood of these models compared to *Model I* (Study I, Table 4, page 8–9/14). These comparisons take account of the number of additional variables in the models.

5.1.3 Alcohol problems and education in Study IV

Low education as a correlate of two indicators of alcohol problems was investigated in the full FT16 sample in Study IV. In both sexes, lower educational level was significantly associated with higher RAPI scores and maximum number of drinks, assessed in young adulthood (Study IV, Table 2, page 214). As an example of

education-related differences in alcohol problems, the mean of RAPI was 11.4 (95% CI: 9.3–13.5) among men with compulsory education only, compared to 6.4 (95% CI: 5.9–6.8) in those with tertiary education, and the numbers of reported maximum drinks in these educational categories were 25.0 (95% CI: 22.7–27.3) and 20.4 (95% CI: 19.9–21.0), respectively.

5.2 Cognitive functioning in alcohol and other substance use disorders

Cognitive functioning in alcohol and other substance use disorders was assessed in Studies II and III. Table 6 gives the means of all cognitive variables in participants with and without substance use disorders in Study II, and with and without alcohol dependence in Study III. In addition to raw mean comparisons, associations adjusted for gender and age are given for both samples. In both studies, lower Vocabulary scores among people with substance use disorders were found, and the standardized beta coefficients (corresponding to effect sizes) were relatively similar in both samples (-0.32 and -0.20). In addition, poorer Digit Symbol performance related to substance use disorders was observed in Study II (Beta = -0.65), but not in Study III. Overall, the distributions of cognitive measures were fairly similar in these two different samples of Finnish young adults, although higher means were observed in some cognitive variables in FT16.

5.2.1 Cognitive functioning in substance use disorders in Study II

In unadjusted analyses of Study II, young adults with a lifetime substance use disorder were found to perform poorer than those without a substance use disorder in six cognitive measures: Vocabulary, Digit Symbol, Letter-Number Sequencing, CVLT Total Learning and CVLT Short Delay Recall. Adjusting for age and gender, differences in Vocabulary and Digit Symbol remained statistically significant, whereas differences in Digit Span Forward, Letter-Number Sequencing, TMT Part A, and CVLT Total Learning were bordering on being significant ($p < 0.10$) (Table 6).

Based on these results, Vocabulary, Digit Symbol, Digit Span Forward, Letter-Number Sequencing, TMT Part A, and CVLT Total Learning were selected for the next phase of analyses. Associations of substance use disorder risk factors from Study I with these cognitive measures were studied in separate linear regression models, adjusting for age and gender. Both parental and own low basic education was strongly associated with all cognitive measures. Other risk factors had associations with some of the cognitive measures, with the exception of the Axis I disorder diagnosis,

TABLE 6. Cognitive functioning in substance use disorders (SUD) and alcohol dependence (AD) in Studies II and III.

	MEAF sample (Study II)							FT16 sample (Study III)						
	No SUD (n = 408)		SUD (n = 58)		P	Beta	Adj. P	No AD (n = 326)		AD (n = 268)		P	Beta	Adj. P
	Mean	(95% CI)	Mean	(95% CI)				Mean	(95% CI)	Mean	(95% CI)			
Verbal cognitive ability														
WAIS-R: Vocabulary	45.1	(44.0–46.2)	41.3	(39.0–43.6)	0.035	-0.32	0.022	49.4	(48.2–50.6)	47.2	(45.9–48.6)	0.013	-0.20	0.023
Psychomotor processing speed														
WAIS-R: Digit Symbol	63.9	(62.5–65.3)	54.8	(52.0–57.7)	<0.001	-0.65	<0.001	62.6	(61.2–64.1)	61.1	(59.7–62.5)	0.106	-0.10	0.232
Working memory														
WMS-R: Digit Span Forward	7.6	(7.4–7.9)	7.1	(6.6–7.6)	0.075	-0.29	0.071	7.7	(7.5–7.9)	7.5	(7.2–7.7)	0.144	-0.16	0.056
WMS-R: Digit Span Backward	6.8	(6.6–7.0)	6.5	(6.1–6.8)	0.114	-0.20	0.149	7.0	(6.8–7.2)	7.0	(6.8–7.3)	0.619	0.00	0.999
WAIS-III: Letter-Number	10.9	(10.5–11.2)	10.1	(9.4–10.8)	0.043	-0.32	0.078	11.1	(10.8–11.4)	10.8	(10.5–11.1)	0.170	-0.15	0.084
WMS-R: Visual Span Forward	9.4	(9.1–9.6)	9.1	(8.6–9.6)	0.401	-0.12	0.455							
WMS-R: Visual Span Backward	9.0	(8.8–9.2)	8.9	(8.4–9.4)	0.896	-0.08	0.681							
Executive functioning														
TMT: Part A	24.8	(23.8–25.8)	28.3	(24.9–31.7)	0.056	0.37	0.081	29.0	(27.8–30.3)	28.5	(27.3–29.8)	0.530	-0.01	0.886
TMT: Part B	59.6	(56.4–62.8)	65.1	(59.3–71.0)	0.111	-0.24	0.139	63.3	(60.6–65.9)	64.1	(60.7–67.4)	0.689	0.04	0.660
TMT: Part B-Part A	35.0	(32.3–37.7)	36.2	(32.3–40.1)	0.637	0.02	0.887	34.3	(32.0–36.5)	35.5	(32.7–38.4)	0.444	0.06	0.471
California Stroop: Part 1								28.7	(28.0–29.4)	28.9	(28.2–29.5)	0.725	-0.02	0.812
California Stroop: Part 2								22.4	(22.0–22.9)	22.4	(21.9–22.8)	0.781	0.03	0.739
California Stroop: Part 3								45.9	(44.7–47.2)	47.6	(46.2–49.0)	0.063	-0.16	0.064
California Stroop: Part 4								52.2	(50.8–53.5)	51.7	(50.3–53.1)	0.634	0.03	0.701
Verbal learning														
CVLT: Total Learning	54.9	(53.8–55.9)	50.7	(48.0–53.3)	0.004	-0.29	0.058	57.2	(56.2–58.2)	56.9	(55.8–58.0)	0.695	0.00	0.961
CVLT: Free Recall, Short Delay	12.3	(12.0–12.6)	11.5	(10.9–12.2)	0.025	-0.23	0.122	12.3	(12.0–12.7)	12.3	(12.0–12.6)	0.799	0.00	0.973
CVLT: Free Recall, Long Delay	12.7	(12.4–13.1)	12.0	(11.4–12.8)	0.075	-0.17	0.295	12.9	(12.6–13.2)	12.7	(12.4–13.0)	0.317	-0.06	0.496

CI: Confidence interval; Adj.: Adjusted

Means and 95% CIs are estimated without covariates. Beta is the regression coefficient of standardized cognitive variables regressed on SUD/AD diagnosis, adjusting for age and gender, and Adj. P is the corresponding adjusted p value. Lower means indicate worse performance, except for the TMT and California Stroop measures for which they indicate better performance. To correct for non-normality in the regression analyses, the following variables were transformed in Study II: TMT Part A and Part B-Part A (logarithmic transformation), TMT Part B (1/square root transformation), CVLT measures (square transformation), and in Study III: Digit Span Backward (square root transformation), TMT variables (logarithmic transformation), California Stroop variables (1/square root transformation).

anxiousness, and age at initiation of drinking (Study II, Table 4, page 1564); these variables were not carried over to the next phase of analysis.

Multiple regression models were then used to study the association of substance use disorders with the cognitive measures, adjusting for selected risk factors and covariates (Study II, Table 5, page 1656). Substance use disorders had an independent association with poorer performance on Digit Symbol, but not on Vocabulary, Digit Span Forward, Letter-Number Sequencing, TMT Part A, and CVLT Total Learning. Statistically significant predictors of lower Vocabulary score were male gender, and both parental and own low basic education, whereas older age at testing was related to better Vocabulary score. Besides substance use disorder diagnosis, poorer performance on Digit Symbol was related to male gender, learning difficulties at school, and both parental and own low basic education. Low education also predicted poorer performance on all the other cognitive measures, whereas low parental education and learning difficulties at school predicted poorer performance on Letter-Number Sequencing. Besides Vocabulary and Digit Symbol, male gender was related to poorer performance on CVLT Total Learning (Study II, Table 5, page 1656).

Restricting analyses to participants with substance use disorders ($n = 58$), the effects of diagnosis type (abuse vs. dependence), current disorder (current vs. in remission), early onset of substance use disorders (≤ 18 years vs. ≥ 19 years), number of lifetime diagnoses (1 vs. at least 2), and comorbid Axis I disorder, and personality disorder on Vocabulary and Digit Symbol performance were assessed. In Vocabulary, participants with a substance abuse diagnosis performed poorer than those with a substance dependence diagnosis (38.8 vs. 45.0, $t = -2.49$, $df = 56$, $p < 0.05$), whereas current phase of the disorder, age at onset, number of lifetime diagnoses, comorbid Axis I disorder, or personality disorder were not related to Vocabulary score. None of the characteristics of substance use disorders or comorbid disorders were related to performance on Digit Symbol. Of the covariates, comorbid psychiatric diagnoses and risk factors, abuse and dependence groups differed only in aggression, with the dependence group having higher aggression scores (15.7 vs. 19.7, $t = -2.54$, $df = 56$, $p < 0.05$). Adjusting for aggression did not affect the results on cognitive functioning. Compared to persons with substance abuse, those with substance dependence also had lower scores on the Social and Occupational Functioning Assessment Scale (SOFAS) (77.2 vs. 68.1, $t = 2.46$, $df = 56$, $p < 0.05$) and almost statistically significantly lower scores on the Global Assessment of Functioning (GAF) scale (73.2 vs. 65.9, $t = 1.95$, $df = 56$, $p = 0.056$). Adjusting for these measures did not affect the cognition results.

5.2.2 Cognitive functioning related to alcohol problems in Study III

The analyses of Study III were focused on Vocabulary, which was significantly associated with alcohol dependence in that sample (Table 6). Associations of Vocabulary with RAPI score, maximum number of drinks, alcohol dependence symptoms and diagnosis were studied in separate linear regression models with Vocabulary as the dependent variable. Adjusted for gender and age, a significant negative association was found between all four alcohol measures and Vocabulary (Study III, Table 2, page 646). Adjusting for antisocial personality disorder and comorbid Axis I disorders did not affect these associations. In contrast, the associations between Vocabulary and alcohol dependence symptoms and diagnosis were weakened and became statistically non-significant when adjusted for age at onset of daily smoking and drinking to intoxication, and low education. The associations of Vocabulary with RAPI score and maximum number of drinks were reduced in size but remained statistically significant, when adjusting for these covariates individually. Adjusting for all covariates simultaneously, RAPI scores remained statistically significantly associated with Vocabulary, and the association with maximum number of drinks approached statistical significance ($p < 0.08$) (Study III, Table 2, page 646).

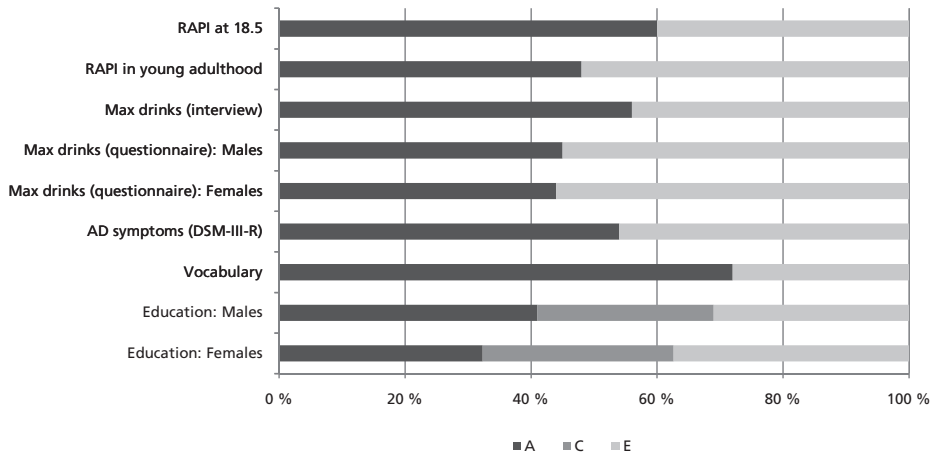
Of the covariates, low basic education was strongly associated with lower Vocabulary score (Beta in the range of -0.93 to -0.98, $p < 0.001$). In addition, early onset of daily smoking, but not that of drinking to intoxication, was associated with poorer Vocabulary score (smoking onset before age 15: Beta in the range of -0.67 to -0.80, $p < 0.001$; smoking onset between ages 15 and 17: Beta in the range of -0.52 to -0.61, $p < 0.001$).

5.3 Genetic and environmental influences on verbal ability, educational level and alcohol problems

5.3.1 Heritability of alcohol problems, verbal ability and education

In Studies III and IV, intrapair correlations of alcohol problem variables, Vocabulary, and educational level were systematically larger in MZ than in DZ pairs, suggesting genetic influences. For example, in Study IV, the intrapair correlation of educational level was 0.68 in MZ male twins, 0.47 in male twins from same-sex DZ pairs, and 0.31 in opposite-sex DZ twins (Study IV, Table 3, page 214).

Heritability estimates for the alcohol problem variables, Vocabulary, and educational level are summarized in Figure 5. Heritability of alcohol problems ranged from 44% to 60%, and besides genetic influences, only unique environmental factors contributed significantly to variation in alcohol problem variables. The heritability of Vocabulary scores was estimated at 72%, and that of educational level at 41% in males and 32% in females. For educational level, significant common environmental influences were also detected, explaining 28% of the variation in males and 30% in females.



RAPI: Rutgers Alcohol Problem Index; Max drinks: maximum number of drinks consumed in a 24-h period; AD: alcohol dependence; DSM-III-R: The Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised.

Variables from Study III (n = 594): RAPI at 18.5, Max drinks (interview), AD symptoms, Vocabulary.

Variables from Study IV (n = 4,858): RAPI in young adulthood, Max drinks (questionnaire), Education.

FIGURE 5. Estimates of additive genetic (A), common environmental (C) and unique environmental (E) influences on alcohol problems, verbal ability and education from Studies III and IV.

5.3.2 Genetic influences on the covariation of alcohol problems with verbal ability and education

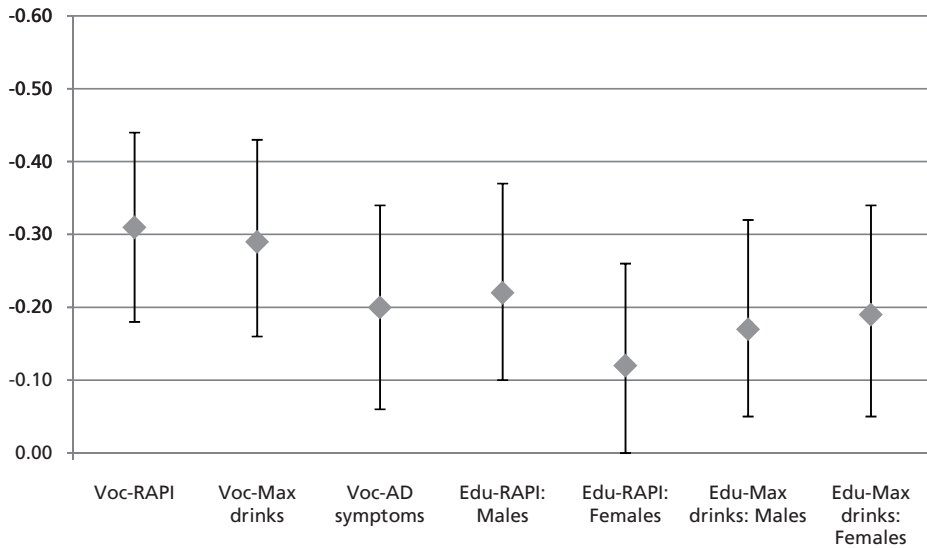
Studies III and IV assessed shared genetic and environmental influences underlying the covariance between alcohol problems and Vocabulary scores, and between alcohol problems and educational level, respectively. In both studies, only genetic covariance was required to explain the phenotypic associations, and the estimated genetic correlations are summarized in Figure 6.

In Study III, bivariate ACE Cholesky models (Figure 4) were fitted separately for Vocabulary with each of the continuous alcohol problem measures: RAPI scores, maximum number of drinks, and alcohol dependence symptoms. In each model,

the common environmental component (C) was found to be non-significant and could be dropped from the model. An AE model provided the best fit in each case, and the unique environmental (E) correlation was non-significant in all models. For Vocabulary and alcohol dependence symptoms, an AE model without genetic correlation was also marginally acceptable ($p = 0.06$), but an AE model without environmental correlation provided better fit. Details of the model comparisons are presented in Table 3 of Study III (page 647), and the parameter estimates from the best fitting models in Table 4 of Study III (page 647). The genetic correlations of Vocabulary and the alcohol problem variables ranged from -0.20 to -0.31 (Figure 6).

Effects of the EDAC sample selection in Study III on the model estimates could be tested in the case of RAPI scores, which were available for 4,892 participants (from 838 MZ pairs and 1,810 DZ pairs) from the full FT16 sample at age 18.5. A bivariate AE Cholesky model for Vocabulary and RAPI scores was fitted such that all available information for RAPI ($n = 4,892$) was utilized, whereas Vocabulary had a missing value for those who were not part of the intensively studied subsample ($n = 594$). Estimates from this model were very similar to the estimates from the selected sample, and the differences were not statistically significant as assessed with 95% confidence intervals [heritability of RAPI: 0.63 (95% CI: 0.59–0.66) in the full sample vs. 0.60 (95% CI: 0.46–0.71) in the selected sample; genetic correlation between RAPI and Vocabulary -0.27 (95% CI: -0.39--0.15) in the full sample vs. -.31 (95% CI: -0.44--0.18) in the selected sample].

In Study IV, the significance of additive genetic, common environmental and unique environmental correlation between years of education and alcohol problems was tested in trivariate models separately by sex. For both alcohol problem variables and education, covariance due to correlated genetic influences was significant in both sexes (Figure 6) (Females: $p < 0.05$ for Education and RAPI, $p < 0.01$ for Education and Maxdrinks; Males: $p < 0.01$ for Education and RAPI, $p < 0.05$ for Education and Maxdrinks), whereas covariance due to correlated environmental influences could be removed from the models without statistically significant decrease in model fit. In contrast, both additive genetic and unique environmental sources of covariance contributed significantly to the association between RAPI and Maxdrinks in both sexes (Females: $p < 0.001$ for r_A and r_E , Males: $p < 0.001$ for r_A , $p < 0.01$ for r_E).



Voc: WAIS-R Vocabulary; RAPI: Rutgers Alcohol Problem Index; Max drinks: maximum number of drinks consumed in a 24-h period; AD: alcohol dependence; Edu: Educational level.

Correlations with Vocabulary are from Study III ($n = 594$), in which RAPI from age 18.5 and Max drinks from the in-person interview were used. Correlations with education are from Study IV ($n = 4,858$), in which RAPI and Max drinks from the young adult questionnaire were used. To reduce skewness, RAPI and AD symptoms were Box-Cox transformed and Max drinks square root transformed in Study III. The estimates are from multivariate models with only genetic covariance in the model.

FIGURE 6. Genetic correlations (with 95% confidence intervals) between Vocabulary and alcohol problems, and between education and alcohol problems from Studies III and IV.

5.3.3 Gene-environment interaction between alcohol problems and education

Univariate moderation models (Figure 3), conducted separately for the sexes, were used in Study IV to test whether educational level served as a moderator of genetic and environmental influences on RAPI and Maxdrinks. Effects of education were retained in the model for means in all models, in order to adjust for the significant covariance between education and alcohol problems.

Statistically significant moderation effects were present for both alcohol problem variables in both sexes. For RAPI, educational level moderated unique environmental influences such that higher education was related to decreased unique environmental variance (Females: $p < 0.05$, Males: $p < 0.01$), whereas moderation effects on A and C influences were not statistically significant. For Maxdrinks, significant moderation effects on both common and unique environmental paths were detected (Females: $p < 0.001$ for both effects, Males: $p < 0.01$ for moderation on C, $p < 0.001$ for moderation on E). Higher education was related to decreased

unique environmental variance also in Maxdrinks, whereas the effect on common environmental influences was more complex. An increase in C variance was found related to both low and high levels of education whereas C variance was reduced close to zero at the mean of the education distribution. This non-linear change in variance was due to the fact that the moderating effect changed the direction of the C effect on Maxdrinks from negative at low education to positive at high educational level. As shown in Figure 7, as a result of these moderating effects, additive genetic influences explained a larger proportion of variance in both alcohol problem variables in those with higher education, whereas common and unique environmental influences were more important in twins with lower education. For example, the heritability of RAPI in men increased from 0.29 at low education (1.5 standard deviations below the mean) to 0.56 at high education (1.5 standard deviations above the mean).

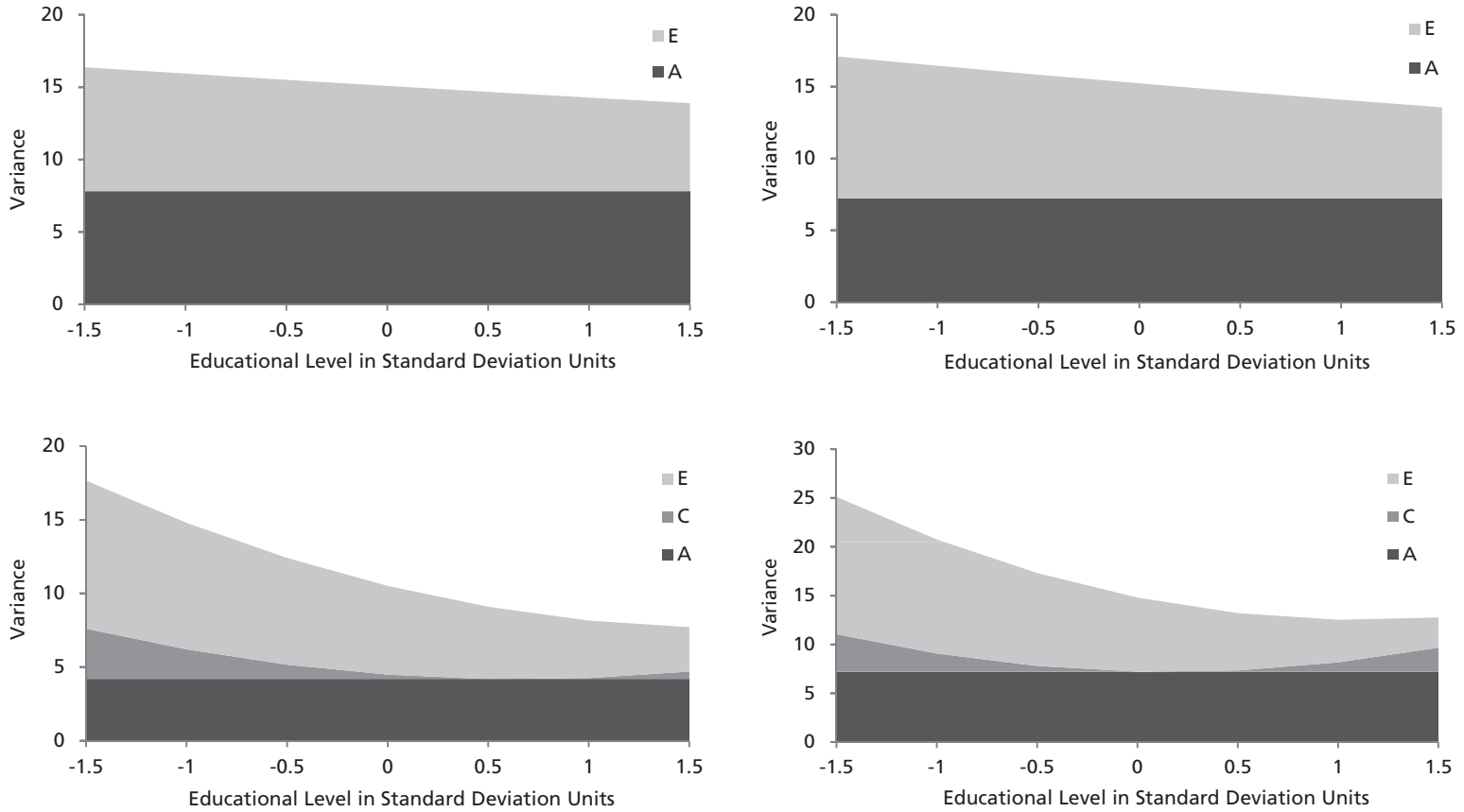


FIGURE 7. Additive genetic (A), common environmental (C) and unique environmental (E) variance components of the Rutgers Alcohol Problem Index scores (top panel) and maximum number of drinks in a 24-h period (bottom panel) in females (left) and males (right) as a function of educational level in standard deviation units from Study IV.

6 DISCUSSION

The present thesis investigated alcohol and other substance use disorders and their correlates in young adulthood using two Finnish population-based samples, one of which contained MZ and DZ twin pairs enabling genetically informative analyses. A special focus of the thesis was on cognitive functioning in substance use disorders, assessed with similar neuropsychological methods in both samples. The influence of genetic and non-genetic factors on alcohol problems, verbal cognitive ability, educational level, and their covariation was estimated using standard biometrical twin models.

6.1 Summary of main results

Substance use disorders were found to be common in Finnish young adults, with approximately 14% of persons aged 21-35 years having met the criteria for any substance dependence or abuse during the lifetime (with the exception of nicotine dependence which was not assessed). As expected, substance use disorders were more common among men than women, and a vast majority of diagnoses were alcohol use disorders, with the prevalence of illicit substance use disorders without a comorbid alcohol disorder being approximately 1%. All studied correlates, representing the domains of behavioral and affective factors, parental factors, early initiation of substance use, and educational factors were individually associated with substance use disorders. The associations between behavioral and affective factors (attention or behavior problems at school, aggression, anxiousness) and substance use disorders were found to be largely independent of correlates from other domains, whereas daily smoking and low education were the only correlates associated with substance use disorders after adjustment for behavioral and affective factors. In addition to diagnoses of substance use disorders, lower educational level in young adulthood was associated with reporting significantly more problems related to alcohol use and having drunk larger amounts of alcohol in one go.

Using a wide array of neuropsychological tests in two relatively large population-based samples, consistent evidence of slightly but significantly poorer verbal cognitive ability related to alcohol and other substance use disorders was found. In addition, participants with substance use disorders performed worse than those without disorders in a task assessing psychomotor processing speed in one of the two samples, whereas no evidence of more specific cognitive deficits was found in either sample. Further, twin modeling suggested that the association between alcohol dependence symptoms and verbal ability could be explained by shared genetic factors influencing these phenomena with no environmental sources of covariance

contributing to the correlation. Finally, the relationship between educational level and alcohol problems in young adulthood was found to be complex, reflecting both genetic correlation and gene-environment interaction. The co-occurrence of low education and alcohol problems was influenced by overlapping genetic factors, but independently of this co-occurrence, higher educational level was associated with increased relative importance of genetic influences on alcohol problems, whereas common and unique environmental influences played a more important role in young adults with lower education.

6.2 Prevalence of substance use disorders

The estimated lifetime prevalence of 14.2% for any substance use disorder in Study I is fairly similar to estimates from elsewhere in Europe and the United States. In Europe, Wittchen et al. (1998) reported a lifetime prevalence of any substance disorder of 17.7% among adolescents and young adults, and a prevalence of 18.7% for any DSM-III-R substance use disorder during the lifetime in the Dutch population has been estimated (Bijl et al. 1998). In the US, the National Comorbidity Survey Replication reported a lifetime prevalence of 16.7% for any substance dependence/abuse in the age group 18–29 years (Kessler et al. 2005a), but as discussed in Chapter 2.2.2 the diagnostic methodology in that study lead to an underestimation of substance dependence (Grant et al. 2007). Compared to the present estimates, substantially higher lifetime prevalence of both alcohol (30.1%) and drug disorders (14.2%) in this age group were reported from The National Epidemiologic Survey on Alcohol and Related Conditions (Compton et al. 2007, Hasin et al. 2007). In addition to true population differences, discrepancies in prevalence estimates between studies arise due to differences in diagnostic methods. In the MEAF study, structured clinical interview (SCID-I) was complemented with medical record data over the participants' lifetime (Suvisaari et al. 2009). This method was chosen to improve the assessment of clinical significance of the symptoms of mental disorders, which has been deemed a potential problem in psychiatric epidemiological studies (Regier et al. 1998).

Estimates of the lifetime prevalence of alcohol and other substance use disorders among young adults in Finland have not been previously available. Pirkola et al. reported the lifetime prevalence of alcohol dependence of 7.9% in the Health 2000 adult sample aged 30 years and over (Pirkola et al. 2006), whereas in the present sample of young adults the lifetime prevalence of alcohol dependence was 5.6%. In an urban sample of 20–24-year-old Finns, Aalto-Setälä et al. (2001) estimated the one-month prevalence of any substance use disorder to be 6.2%, but that sample only included alcohol and cannabis disorders. The present prevalence estimates for alcohol and other substance use disorders in young adults fit well with the general profile of substance use in the Nordic countries, characterized by a high level of drinking to intoxication and a fairly low level of use of illicit substances, especially

cannabis (EMCDDA 2008, Halme et al. 2008, Kringlen et al. 2001, WHO 2004a). For example, in Study I, 75% of young adults reported having been drunk during the last 12 months, while only 8% reported having used cannabis more than five times during the lifetime, which is in line with earlier findings on the relatively low prevalence of cannabis use among Finnish adolescents and young adults (Korhonen et al. 2008). Finally, consistently with findings from other countries, substance use disorders are among the most common psychiatric disorders in Finnish young adults, with depressive disorders having a slightly higher estimated prevalence during the lifetime (17.7%) (Suvisaari et al. 2009).

6.3 Correlates of substance use disorders

Study I replicated several previous findings on a wide range of risk factors associated with substance use disorders in a cross-sectional setting. As majority of previous studies have been conducted in Anglo-Saxon societies, and because the availability of substances and the prevailing general culture of substance use potentially influence the associations, it is of importance that these correlates were also associated with substance use disorders among Finnish young adults. Disinhibitory behavioral traits as well as affective traits such as depressiveness and anxiety have been extensively studied as risk factors of substance use disorders (Elkins et al. 2007, Fergusson et al. 2007, Zimmermann et al. 2003). The association between parental alcohol problems and offspring substance use disorders was also expected due to the strong familial transmission of substance use problems (Lieb et al. 2002, Merikangas et al. 1998c, Walden et al. 2007). The effect of parental education is less well studied, but in line with some previous findings (Caldwell et al. 2008), the results of Study I suggest elevated risk related to low parental education. The role of early initiation of drinking to intoxication as a strong correlate of substance use disorders was anticipated on the basis of earlier studies (DeWit et al. 2000), but the even stronger association between early onset of smoking and substance use disorders was notable, although the importance of early onset of smoking as a risk factor for substance use and disorders has also been highlighted previously (Grant 1998, Hanna and Grant 1999, Huizink et al. 2010, Korhonen et al. 2010, Vega and Gil 2005). Finally, the observed association between own low education and substance use disorders was not surprising on the grounds of previous epidemiological studies (Compton et al. 2007, Hasin et al. 2007, Kessler et al. 2005a), but the predictive value of learning difficulties has not been widely studied.

Beyond these individual associations, Study I aimed to investigate the relative importance of behavioral and affective factors, parental factors, early initiation of substance use, and educational factors as correlates of substance use disorders. Results suggested that the association between behavioral and affective factors and a lifetime substance use disorder diagnosis is largely independent of factors related to parents, early initiation of tobacco and alcohol use, and education and

learning. These results emphasize the importance of disinhibitory and affective factors associated with substance use disorders, and are consistent with some previous similar findings. For example, in a longitudinal study in New Zealand, Fergusson et al. assessed the effect of childhood and adolescence conduct and attentional problems on later substance use, abuse and dependence, controlling for various social, family and individual covariates (Fergusson et al. 2007). They found that conduct problems in adolescence were significantly related to use, abuse and dependence of various substances even when the wide array of covariates was included in the model. Another recent longitudinal study also found various self-reported problem behaviors in adolescence to predict substance use disorders in early adulthood even when maternal education and alcohol use among other factors were controlled for (Hayatbakhsh et al. 2008). However, focusing on illicit substance use and disorders only, Fergusson et al. reported that the effects of fixed childhood factors, such as conduct disorder, were non-significant when time-varying substance use and peer factors were taken into account (Fergusson et al. 2008). In Study I, only cross-sectional analyses were possible, and the small number of illicit substance use disorders did not allow their separate analyses.

Study I also suggested that the association between parental alcohol problems and substance use disorders in the offspring is at least partly mediated by the offspring's attention or behavior problems, aggression and anxiousness. This is compatible with several previous studies reporting that the effect of parental substance use problems on substance use disorders in the offspring is partly explained by the offspring's disinhibitory traits (Chassin et al. 1999, Chassin et al. 2004, Finn et al. 2000, Ridenour et al. 2009, Tarter et al. 2004). Further, a twin study utilizing the children-of-twins design found evidence for a partly shared genetic background of paternal substance use disorders and disinhibitory traits in the offspring (Haber et al. 2005).

Smoking increased the odds for substance use disorders irrespective of the age at initiation in Study I, but the risk related to daily smoking initiation before age 15 was remarkably elevated. It is well known that cigarette smoking often predates alcohol and drug use, but the meaning of this observation is debated. The present results extend previous findings that age at smoking initiation increases the risk for substance use disorders independently of family history of alcoholism (Grant 1998, Vega and Gil 2005) by providing cross-sectional evidence that the association between early smoking initiation and substance use disorders may not be accounted for by various behavioral and affective factors, parental factors, age at initiation of alcohol use, learning difficulties and low education. In contrast, the association between early initiation of drinking to intoxication and substance use disorders may be accounted for by comorbid early smoking initiation.

In Study I, the association between low educational level and substance use disorders was only partly accounted for by behavioral and affective factors. Because attention and behavior problems at school are bound to be associated with achieving a lower level of education (Polderman et al. 2010), this finding suggests that the common observation of lower educational level among people with alcohol and

other substance use disorders may not be an artifact of related confounding factors but may, in contrast, reflect a genuine relationship between these two behavioral outcomes. The temporal nature of this relationship could not be determined in Study I, but in more than half of the cases the age at first abuse or dependence diagnosis was younger than 19, suggesting that problematic substance use predated or took place simultaneously with the processes leading to lower education. Study IV further investigated the genetic and environmental contributions to this association.

6.4 Cognitive functioning in substance use disorders

In Study II, using a representative sample of Finnish young adults and a comprehensive diagnostic and neuropsychological assessment, poorer verbal ability and less efficient psychomotor processing were found to be associated with a lifetime diagnosis of substance use disorder. Of the other cognitive domains under study, only borderline associations ($p < 0.10$) with executive functioning, verbal working memory and verbal learning processes were observed. Study III replicated the results on poorer verbal ability in an independent sample of young adult twins, finding negative associations between verbal ability and alcohol dependence diagnosis, symptoms and two indicators of alcohol problems, whereas no consistent associations with other cognitive domains were observed.

Further analyses in Study II suggested that the association with verbal ability was accounted for and possibly mediated by parental and own low basic education, and adjusting for education weakened the associations between alcohol problems and verbal ability also in Study III. In contrast, the association with psychomotor processing speed in Study II remained statistically significant after adjusting for low basic education and other studied risk factors. It is well known that education contributes strongly to performance in tests assessing verbal cognitive ability (Lezak et al. 2004), and previous studies have found education to also correlate with verbal measures such as vocabulary and abstraction in substance use disorders (Beatty et al. 2000). Genetically informative studies have suggested that genetic factors explain a significant proportion of the variance in both intellectual ability and educational achievement, and there are also shared genetic factors influencing both phenomena (Bartels et al. 2002). Both parental and own low basic education associated with poorer verbal ability and with substance use disorders in Study I. Both genetic and environmental factors are likely to contribute to the association between parental education and verbal ability in the offspring (Asbury et al. 2005, Neiss and Rowe 2000), but the relationships between these phenomena and substance use and disorders are not well known.

It should be noted that, although statistically significant in both samples, the magnitude of the association between substance use disorders and verbal ability

is relatively modest. Expressed as sex- and age-adjusted standardized regression coefficients, the sizes of the effect of substance use disorders in Study II and of alcohol dependence in Study III on Vocabulary were -0.32 and -0.20, respectively. As a comparison, similarly adjusted coefficients for low vs. high education (having only compulsory education or vocational secondary education vs. academic secondary or tertiary education) in Studies II and III were -0.89 and -0.99, respectively. Thus, the magnitude of the association between substance use disorders and verbal ability seems to be about 20–35% of the consistently found strong association between education and verbal ability.

Among participants with DSM-IV substance use disorders, substance abuse rather than dependence was somewhat unexpectedly found to be associated with lower verbal ability in Study II. In contrast, type of diagnosis and other characteristics of substance use disorders were not related to psychomotor processing speed. The findings of poorer verbal intellectual ability, but not processing speed, in substance abuse compared to dependence may be seen as lending support to substance abuse and dependence as separate diagnostic categories. These findings also suggest that less efficient psychomotor processing in young adults with substance use disorders may not be related to severity of the disorder. Previously, less efficient psychomotor processing has been reported to correlate with greater estimated lifetime alcohol consumption but not with years of lifetime alcohol dependence or length of sobriety (Beatty et al. 2000, Sassoon et al. 2007). However, performance on the Digit Symbol task is related to the volume and microstructure of white matter pathways (Turken et al. 2008), and white matter atrophy in alcohol dependence has been found to correlate with differences in exposure to alcohol (Bjork et al. 2003).

Study II suggested no association between cognitive functioning and lifetime Axis I disorders besides substance use disorders, indicating that the observed poorer verbal ability and slower psychomotor processing in substance use disorders were not due to comorbid disorders. In addition, among persons with substance use disorders, neither comorbid Axis I disorders nor personality disorders were associated with verbal ability or psychomotor processing speed. In Study III, the associations between verbal ability and alcohol problems were not affected when comorbid Axis I disorders and antisocial personality were adjusted for either, also suggesting that these associations were not confounded by comorbid conditions. These findings are consistent with previous studies that have used subsamples of the MEAF data and have generally not found evidence of cognitive dysfunction in depressive or anxiety disorders among young adults, although severe forms of these disorders may be associated with some cognitive impairment (Castaneda et al. 2008, Castaneda et al. in press). On the other hand there is evidence that lower cognitive abilities in childhood and adolescence are associated with an increased risk for a variety of psychiatric disorders in addition to substance use disorders (Koenen et al. 2009, Weiser et al. 2004). It should be noted that participants with psychotic disorders were excluded from the cognition analyses in Studies II and III.

While the etiology of poorer verbal ability in substance use disorders could not be clarified in Study II, the relative importance of genetic and environmental influences on this association was investigated in Study III in a genetically informative twin sample. Twin intrapair differences in verbal ability and in alcohol problems were significantly correlated for DZ but not for MZ twin pairs, suggesting that this association might not have environmental origins but might, in contrast, reflect shared genetic factors influencing alcohol problems and verbal ability. Bivariate genetic models strongly supported this view, as the negative associations of verbal ability with alcohol dependence symptoms, maximum number of drinks, and drinking problems in adolescence could in each case be completely explained by correlated genetic influences with no environmental sources of covariation in the models, suggesting that poorer verbal ability and alcohol problems share part of their genetic etiology. While genetic and environmental contributions to associations between alcohol problems and measures of cognitive performance have not been widely studied, a wealth of twin studies has reported moderate to large genetic influences on alcohol problems and cognitive abilities separately (Agrawal and Lynskey 2008, Bouchard 1998, Dick et al. 2009, Plomin 2003). In the present study, the heritability estimates for verbal ability and alcohol problems were highly consistent with the bulk of this earlier research.

Two recent studies on population-based samples of Swedish male twins have investigated the association between smoking behavior and cognitive ability finding a similar pattern of results as in Study III. First, Wennerstad et al. (2010) reported an inverse association between smoking status and IQ, and found no support for a causal relationship between these traits. A follow-up study modeled the relatively weak phenotypic association between nicotine dependence and IQ, and found that this association was mainly due to shared genetic factors (Modig et al. in press). Interestingly, the genetic correlation between nicotine dependence and IQ was -0.24 in that study, which is very similar to the genetic correlations between alcohol problems and verbal ability in Study III (Figure 6).

The finding that the negative association of verbal ability with alcohol dependence symptoms, maximum number of consumed drinks, and adolescent drinking problems could be explained by correlated genetic influences argues against the view that poorer verbal ability is consequential to drinking problems. Instead, this result is compatible with the alternative view that poorer verbal ability predates or co-evolves with alcohol problems – an alternative supported by several separate lines of evidence. First, lower verbal ability has been observed already in adolescents with substance use disorders (Brown et al. 2000, Giancola and Mezzich 2000, Moss et al. 1994, Tarter et al. 1995). Second, children of parents with alcohol dependence also show poorer verbal ability compared to controls, even though they have not yet started to consume alcohol (Gabrielli and Mednick 1983, Tarter et al. 1989). These findings are particularly interesting in relation to the present results, as they also suggest that part of the genetic influences on alcohol problems and verbal cognition overlap. Third, prospective longitudinal studies suggest that poorer cognitive ability

in adolescence predicts alcohol use problems later in life (Jefferis et al. 2008, Windle and Blane 1989). In addition, a recent brain imaging study in alcohol dependent patients found that verbal ability correlated with the estimated total brain volume, but not with decrease in brain volume related to ageing and alcohol use (Schottenbauer et al. 2007). Finally, in treatment populations, lower verbal ability at treatment intake has been found to predict relapse to alcohol and drug use (Wehr and Bauer 1999). It should be noted, however, that the absence of environmental correlation in the present results can be interpreted only as suggestive of poor verbal ability predating alcohol problems. Without prospective longitudinal assessments of alcohol use and cognitive developmental trajectories, it is impossible to definitively rule out other alternatives, such as alcohol dependence contributing to decline in verbal ability via genetic mechanisms.

As discussed earlier in Chapter 2.3.2, many studies reporting lower verbal ability in substance use disorders have found similar differences in general intellectual ability, as well (Moss et al. 1994, Rosenbloom et al. 2007, Tarter et al. 1995). Verbal and full-scale intelligence are highly correlated, and the Vocabulary subtest is the best single indicator of full-scale intelligence in the WAIS (Wechsler 1997). The results of Study II related to poorer performance also on the Digit Symbol test—assessing one component of non-verbal cognitive ability—can be interpreted to provide tentative support for the possibility that the present findings represent general intelligence rather than verbal intellectual ability specifically.

Cognitive abilities are predictive of many real-life outcomes, such as educational attainment, job performance, economic preferences, health behaviors, and mortality (Batty et al. 2008a, Batty et al. 2008b, Batty et al. 2009, Burks et al. 2009, Gottfredson 1997, Jokela et al. 2009). It has been argued that this predictive utility stems from the inherent complexity of everyday life, as intelligence can be seen as ability to deal with various forms of cognitive complexity (Gottfredson 1997). A tendency to make decisions that are unfavorable in the long run is observed often in substance use disorders and other disinhibitory psychopathology, and this tendency may reflect insensitivity to future negative consequences (Cantrell et al. 2008). Similarly, substance use disorders are also associated with higher delay discounting, i.e. preferring smaller proximal rewards to larger distal ones (Bobova et al. 2009). Importantly, a meta-analysis found a robust negative association between intelligence and performance in delay discounting tasks, with tests of verbal ability alone producing equally large effect sizes as those that also measured nonverbal abilities (Shamosh and Gray 2008). Interestingly, a recent twin study found that poorer language skills in childhood were predictive of low self-control both cross-sectionally and longitudinally, and that their covariation was due to both genetic and environmental factors (Beaver et al. 2008). Taken together, these findings suggest some ways in which the negative association of verbal ability and substance use disorders might be manifested.

Although genetic and environmental contributions to the association between verbal ability and substance use disorders have not been widely studied, poorer

intellectual abilities have been observed among those exhibiting ADHD, antisocial behavior, and the personality trait of excitement seeking, and in each case, there is evidence that shared genetic factors influence this covariation (Koenen et al. 2006, Kuntsi et al. 2004, Pincombe et al. 2007). As discussed earlier in Chapter 2.4.2, each of these phenomena often co-occurs with substance use disorders, and there are shared genetic influences between these components of the so-called externalizing spectrum behaviors and substance use disorders, as well (Button et al. 2007, Iacono et al. 2008, Krueger et al. 2002, Miles et al. 2002). However, the joint developmental pathways of cognitive abilities, externalizing traits, and substance use are not well known, and future studies should longitudinally assess genetic and environmental contributions to their development.

The negative findings of Studies II and III on other cognitive domains besides verbal ability and psychomotor processing speed may be due to the young age of the samples, as compared to many studies on middle-aged or ageing individuals, but also limited power to detect more modest effects. On the other hand, as discussed earlier, findings on cognitive deficits related to substance use disorders have been inconsistent, with many studies also failing to show differences in specific cognitive functions (Beatty et al. 2000, Fein et al. 2006, Smith and Fein 2010, Wood et al. 2002).

6.5 Education and the etiology of alcohol problems

Using data from a population-based sample of Finnish twins in early adulthood, evidence of genetic correlation and gene-environment interaction between educational level and two indicators of alcohol problems were found in Study IV. Biometrical twin modeling suggested that genetic factors influence the co-occurrence of alcohol problems and low education, with a proportion of the genetic variation that increases the risk for alcohol problems also predisposing to attaining lower education. Consistently with earlier studies (Agrawal and Lynskey 2008, Baker et al. 1996, Dick et al. 2009, Johnson et al. 2009a, Silventoinen et al. 2004), heritability estimates of educational level and alcohol problems in Study IV were moderate, ranging from 32% to 48%. In addition, independently of this genetically influenced co-occurrence, educational level also moderated the genetic and environmental influences specific to alcohol problems. For both indicators of alcohol problems, the relative importance of genetic influences was greater among those with higher level of education.

These results extend the scarce existent genetically informed research on the relationship between alcohol use behaviors and education. Two recent studies reported on genetic correlation and gene-environment interaction between these phenomena, respectively, but neither study assessed both with the same sample. In their multivariate analysis of young adult data from the Minnesota Twin Family

Study, Johnson et al. (2009b) reported overlapping genetic influences on education and an alcohol use composite, including symptoms of alcohol abuse/dependence and maximum number of drinks. Their multivariate model also included IQ, assessed in adolescence, and most of the shared genetic variance with alcohol use in fact reflected both IQ and education. A large proportion of the covariance of IQ, education, and alcohol use also seemed to be due to overlapping common environmental influences, but the authors concluded that their sample of 626 twin pairs lacked sufficient statistical power to distinguish between genetic and common environmental influences in the multivariate setting. Timberlake et al. (2007), on the other hand, investigated the effects of college attendance on drinking behaviors, and because their sample included twins and siblings, they could model gene-environment interaction. Results suggested that college students exhibited greater genetic influence on quantity of alcohol consumed per drinking episode—a finding parallel to the present gene-environment interaction results. However, as discussed by the authors, the experiences and drinking promoting influences related to college attendance in the US may be quite specific to that environmental context, e.g. participation in fraternities/sororities and various athletic programs. Thus, the present findings in Finnish young adults are likely to reflect at least partly different mechanisms of gene-environment interaction.

Genetically informed studies on education and substance use other than alcohol are equally few in number. McCaffery et al. (2008) reported smoking initiation to have a negative correlation with educational attainment in male twins, and this correlation was explained by overlap in both genetic and environmental influences. Educational attainment also significantly moderated the variance in smoking initiation, with higher education being associated with reduced variance also in that study, but whether this interaction occurred with genetic or environmental components could not be resolved. In Study IV, smoking correlated with alcohol problems and also had an inverse association with education, suggesting that the present findings might be at least partly replicated with smoking. Further, genetic influences on adolescent antisocial behavior have been found to be more important in socioeconomically more advantaged environments, whereas the shared environment had a stronger influence in socioeconomically less advantaged neighborhoods (Tuvblad et al. 2006).

Study IV suggested that, at least in Finland where educational opportunities are relatively equal, genetic factors contribute to the association between alcohol problems and low education. Although the present modeling results with cross-sectional data cannot rule out possible causal relations between these outcomes, they do indicate that genetically influenced individual differences should be considered as one possible mechanism underlying the associations between components of socioeconomic status and health behaviors (Conger and Donnellan 2007). General cognitive ability has been suggested as one such factor underlying socioeconomic inequalities in health (Der et al. 2009, Gottfredson 2004). Importantly, the bivariate modeling results from Study IV mirrored the results on the negative association between verbal cognitive ability and alcohol problems from Study III, suggesting

that the genetic correlation between education and alcohol problems might also encompass cognitive abilities, as was the case in the study by Johnson et al. (2009b), discussed above. However, despite their strong correlation, intelligence and education also seem to have independent associations with health outcomes (Batty et al. 2009, Lager et al. 2009).

The present GxE interaction analyses indicated that higher education was associated with reduced unique environmental variance in alcohol problems, whereas there was no direct moderation on additive genetic variance. Educational level also moderated the common environmental variance component in Maxdrinks. These moderation effects were similar in men and women, and they resulted in increased relative importance of genetic influences on alcohol problems in those with higher education. This finding may seem contradictory, as higher education was related to lower level of alcohol problems. However, the moderation models adjusted for education, so that the genetic and environmental influences estimated, as well as their moderation effects, concern only variation in alcohol problems that is independent of educational level. This feature of the model also makes sure that the moderation effect is not an artifact produced by genetic correlation (Purcell 2002), which was found to explain the co-occurrence of low education and alcohol problems in Study IV.

The observed higher heritability of alcohol problems among more highly educated young adults may reflect various environmental factors associated with educational level. In Finland as elsewhere, education is related to generally better prospects in life, including less unemployment, better working conditions, higher salaries, better neighborhood quality, and better health (Evans and Kantrowitz 2002, Havén 1999). One especially important environmental correlate of higher education in Finland is urban residency (Havén 1999). Previous studies in Finnish twins have reported increased heritability of drinking behaviors and behavior problems in adolescence in urban environments, whereas common environmental factors seem to be more important in rural environments (Dick et al. 2001, Dick et al. 2009, Rose et al. 2001). These findings have been interpreted as reflecting higher levels of social control and structural constraints placed on people in more rural environments, whereas urban environments are presumed to allow individual, genetically influenced behavioral characteristics to be more freely expressed (Shanahan and Hofer 2005). In Study IV, education was strongly related to urban residency: 86% of those with at least academic secondary education reported urban residency, whereas the proportion was 58% for those with lower education. There were other notable “environmental” differences, as well. Those young adults with less than academic secondary education were more often married or co-habiting (68% vs. 50%), were more likely to have children (24% vs. 6%), and were more likely to be working (and not e.g. studying) (60% vs. 35%) at the time of the current assessment as young adults. All these differences in the personal environment and life situation may have contributed to the increased importance of genetic influences and reduced environmental influences in those with higher education. For example, besides

urban residency, being married has also been associated with less genetic influence on alcohol consumption (Heath et al. 1989). All these features seem compatible with the scenario of less social control related to higher level of education in young adults, resulting in increased heritability of alcohol problems.

6.6 Methodological considerations

Two independent population-based samples of Finnish young adults were utilized in the present thesis. The MEAF sample, used in Studies I and II, was based on the nationally representative Health 2000 Survey (Aromaa and Koskinen 2004). Due to the two-phase study design of MEAF, it was possible to conduct the in-person SCID-I psychiatric interviews in this representative sample (Suvisaari et al. 2009). Complementing the interviews by case records from mental health treatment contacts is exceptional in population-based studies and clearly strengthened the diagnostic assessment. On the other hand, two-phase designs generally result in increased uncertainty in prevalence estimation, seen as wider confidence intervals, and in higher levels of non-response (Eurostat 2008). Also in MEAF, there were non-respondents in both of the study phases. However, non-response was not related to self-reported mental health or alcohol use problems (Suvisaari et al. 2009), and post-stratification and expansion weights were used in Studies I and II to statistically correct for non-response.

Using information from Finland's Central Population Registry, practically all twin pairs born in Finland between 1975 and 1979 were identified as the FT16 sample (Kaprio et al. 2002), utilized in Studies III and IV. In Study IV, all participants with known zygosity and available information on education and alcohol problems from the young adult questionnaire were used, resulting in a representative sample of nearly 5,000 twins. In contrast, the sample used in Study III was a subsample that was partly selected on the basis of pairwise discordance and concordance of co-twins for adolescent drinking problems, in order to intensively study twin pairs maximally informative about the associations between alcohol problems and cognitive performance. The selection strategy clearly had an effect on the representativeness of this sample, as is evident from the fact that 45% of the sample was diagnosed with alcohol dependence, compared to the estimated lifetime prevalence from Study I of approximately 13% for alcohol use disorders in the general young adult population in Finland. However, despite this influence on the prevalence of alcohol dependence, the EDAC selection had no significant effects on the biometrical twin model estimates when tested on RAPI scores. This result is not surprising on the basis of missing data theory by Little and Rubin (2002), and has been shown earlier with simulated twin data (Derks et al. 2007). The simulation study by Derks et al., however, suggested that although model estimates are not distorted, the EDAC selection may have a detrimental effect on the statistical power to detect significant C effects in ACE models. This seems unlikely in Study III, as the C component

for RAPI score was found to be equally negligible in the entire population-based FT16 sample as in the selected sample. Additionally, the design of Study III resulted in a moderate level of non-participation. However, the combination of finding no differences in alcohol problems but lower education (which correlates with verbal ability) in non-participants suggests that non-participation was not likely to cause exaggerated associations between alcohol problems and verbal ability, which could, in contrast, have been suspected e.g. if the non-participants were found to have more alcohol problems but higher education than the participants.

A notable strength of the present studies was the use of a nearly identical battery of neuropsychological tests in both samples. Further, well-known and validated test methods were used in the neuropsychological assessment that was extensive, covering the domains of verbal cognitive ability, psychomotor processing speed, verbal and visual working memory, executive functioning, and verbal learning and memory. However, the fact that besides the Digit Symbol test, other tests assessing non-verbal general cognitive ability were not included in either MEAF or FT16 can be seen as a limitation.

A general limitation of the present studies was their cross-sectional design. Studying the associations of potential risk factors, cognitive functioning and educational attainment with substance use disorders would clearly be more informative with longitudinal data. Optimally, prospective longitudinal assessments of substance use, various risk factors, and cognitive developmental trajectories, starting in childhood, would help to shed light on temporal and causal relations between these phenomena. It should be noted that FT16 is a longitudinal study containing rich information on the development of alcohol use, among other things (Kaprio et al. 2002, Pagan et al. 2006, Viken et al. 1999). However, cognitive assessments in FT16 were only made in young adulthood.

A further limitation of Studies I and II was that the studied correlates of substance use disorders were self-reported, and the possibility that those reporting more problematic substance use would be prone to report higher (or lower) levels of other negative factors cannot be excluded. However, several of these measures came from a general health survey, conducted at least two years before the psychiatric assessment and not profiled as focusing specifically on substance use disorders, which should serve to reduce reporting bias. In addition, the assessment of the four domains of correlates of substance use disorders can in no case be considered comprehensive. For example, the single item used to assess anxiousness arguably provides a very limited assessment of affective factors.

A special limitation of Study IV was that only a relatively crude estimate of years of education was available. However, the analyses were conducted also using an ordinal variable created from the original categorical classifications of completed and ongoing studies and a similar pattern of results was found in both multivariate and moderation analyses. Second, a large proportion of the sample still had their studies underway when completing the young adult questionnaire, but this information was taken into account in the variable for years of education. A further limitation was

that gene-environment interaction effects and genetic correlation were not modeled simultaneously using the moderated Cholesky approach (Purcell 2002). The more simple univariate moderation approach was chosen because of limited statistical power to reliably detect specific moderation effects on shared and non-shared genetic and environmental influences on education and alcohol problems when the phenotypic associations between these traits were weak. The moderated Cholesky model has also been criticized for potentially producing spurious interaction effects (Rathouz et al. 2008). Importantly, simulations by Purcell (2002) suggested that the presence of genetic correlation between the moderator and outcome variables does not lead to artificial interaction effects when the main effect of the moderator is included in the univariate moderation model, as was done in the present analyses. A final limitation was that diagnoses of alcohol use disorders were not available. In the subsample used in Study III, the alcohol problem indicators used in Study IV, RAPI and Maxdrinks, had moderate positive correlations with the number of alcohol dependence criteria met ($r = 0.55$ and $r = 0.50$, respectively). RAPI scores in late adolescence robustly predicted alcohol diagnoses in early adulthood, with the odds ratio of outcome alcohol diagnosis per unit increase in adolescent RAPI exceeding 10 (Dick et al. in press). In Study IV, RAPI and Maxdrinks were moderately correlated, and shared genes explained approximately 80% of this correlation in men and 70% in women.

Finally, the limitations of statistical power need to be taken into consideration when interpreting the present findings. With regard to associations between cognitive functioning and SUD diagnoses, power calculations indicated that in Study II there was good power (80%) only to detect effect sizes of approximately 0.4 standard deviations and larger, whereas effects larger than 0.2 were detectable in Study III. In biometrical twin models the power to detect C effects is often a concern. Accordingly, the sample used in Study III only yielded sufficient power to detect C variance components explaining approximately 30% of the variance or more, assuming an ACE model with an A effect of 50% (Visscher 2004, Visscher et al. 2008a). Further, power calculations in Mx indicated that there was insufficient power in the Cholesky models to detect the relatively weak E correlations between alcohol problems and Vocabulary in Study III and between alcohol problems and education in Study IV. For example, a sample of nearly 6,000 twin pairs would have been needed to reach 80% power to detect the small E correlation between RAPI and Vocabulary, which explained 7% of the phenotypic association between these traits in Study III. Also the moderation models in Study IV were likely to be underpowered for the detection of very small moderating effects.

6.7 Conclusions and implications

Substance use disorders, especially alcohol abuse and dependence, are common psychiatric disorders among young adults, and their prevalence in Finland is

comparable to that in many other Western countries. Behavior problems in childhood, and general aggressiveness and anxiousness are robustly related to substance use disorders independently of the risk related to many other factors, such as parental alcohol problems and early initiation of alcohol use. In addition, early initiation of cigarette smoking and low education are significantly associated with alcohol and other substance use disorders. Compared to healthy peers, young adults who have had alcohol or other substance use disorders or problems during their life exhibit significantly poorer verbal cognitive ability, and possibly less efficient psychomotor processing, although these differences are not large in magnitude. Genetic differences between individuals explain a notable proportion of individual differences in the risk of alcohol dependence, verbal ability, and educational level in young adults. In addition, the co-occurrence of alcohol problems with poorer verbal cognition and low education is influenced by same genetic factors having an effect on these phenomena. Finally, the importance of genetic influences on alcohol problems is different across educational levels, such that environmental influences are more important among young adults with lower education.

The findings of this thesis may be of some utility in the efforts to prevent the development of alcohol and other substance problems. However, because the relationships between substance use disorders and their correlates studied here may not be causal in nature, the potential for prevention and intervention is more likely to lie in furthering the understanding of the origins of substance use disorders and factors that are associated with them, rather than in trying to prevent substance use disorders directly by intervening with these correlates. More specifically, the present findings underscore the importance of behavioral and affective factors as indicators of increased risk. In addition, early onset of smoking in adolescence should be recognized as a robust indicator of risk for developing substance use disorders, whatever the nature of this association may be. Besides these factors, the present findings highlight lower verbal ability and educational performance as indicative of heightened risk to develop problems with alcohol and other psychoactive substances. These cognitive and behavioral traits may be useful indicators to consider when designing strategies for prevention and intervention to combat the development of substance use disorders in adolescents and young adults.

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