From the DEPARTMENT OF CLINICAL NEUROSCIENCE
Karolinska Institutet, Stockholm, Sweden

# COGNITIVE DEFICITS IN ALCOHOL USE DISORDER

## ETIOLOGY AND TREATMENT

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Karolinska Institutet

Stockholm 2019

Published by Karolinska Institutet.

ISBN 978-91-7831-546-8
Printed by Eprint AB 2019

# Cognitive Deficits in Alcohol Use Disorder: Etiology and Treatment

THESIS FOR DOCTORAL DEGREE (Ph.D.)

Public defense in Biomedicum 1, Solnavägen 9, Karolinska Institutet
Friday 29th of November, 2019 at 09:00

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*To my family*

# ABSTRACT

Alcohol use disorder (AUD) is a psychiatric disorder characterized by a loss of control over drinking, tolerance, withdrawal and negative psychological, physical and social consequences due to excessive alcohol consumption. Even though not explicitly stated in the diagnostic criteria, it is well known that patients with AUD also exhibit impaired cognitive function, e.g., elevated impulsive behavior and deficits in executive functions such as response inhibition, attention and working memory. The aim of this thesis was twofold: First, to investigate the etiology of cognitive deficits in AUD. Second, to investigate if cognitive deficits in AUD can be a potential target for treatment.

Study I was a large-scale population-based epidemiological study of approximately 3 million unique individuals based on Swedish national registries. We investigated the effect of family history across all forms of substance use disorders (SUD), including AUD, on general cognitive ability in offspring. The exposure was defined as having a parent with SUD and the outcomes were cognitive test score at conscription and final school grades in compulsory school. At the population level, parental SUD increased the risk of lower cognitive ability in offspring, after adjusting for several covariates such as age, sex, psychiatric co-morbidity and socioeconomic status. However, when analyzing offspring to sibling-pairs discordant for SUD, the strength of this association was reduced with increasing genetic relatedness in the sibling-pairs (half siblings, full siblings, monozygotic twins). These findings suggest that the observed association between parental SUD and lower cognitive ability in offspring can partly be explained by shared genetic factors between SUD and cognitive ability.

Study II was a case-control study which further examined the association between AUD and cognitive function, by investigating whether the cognitive profile of people with family history of AUD is more similar to AUD patients than people with no such family history. The study recruited AUD patients (n = 106) and healthy controls (HC; n = 90), who were then further subdivided into AUD family history positive (FH+) and negative (FH-). All subjects underwent psychiatric evaluation and an extensive neuropsychological test battery assessing different aspects of impulsive behavior, decision making, attention, memory and emotion. FH+ and AUD patients had similar levels of elevated self-rated impulsivity, reduced future planning capability and longer emotional recognition latency compared to FH-, while no differences were found for other cognitive outcomes. These findings strengthen the notion that specific aspects of the cognitive profile associated with AUD, can be partly genetically influenced traits, elevating the risk for AUD. Other cognitive disturbances in AUD on the other hand may to a higher degree depend on non-genetic factors such as alcohol intake.

Study III and IV were based on a randomized placebo-controlled trial of a novel pharmacological agent, namely the monoamine stabilizer (-)-OSU6162 (OSU). The aims of the studies were to investigate the treatment effect and possible moderating effect of baseline impulsivity, of OSU on craving (study III) and cognitive function (study IV). Patients with

AUD (n = 56) were randomized to receive either 14 days of OSU treatment or placebo. The treatment protocol included weekly visits to the clinic and a final test day where they performed a laboratory craving experiment. The patients also underwent neuropsychological testing at baseline and on the final test day. Study III found that OSU treatment reduced alcohol-induced craving, and the greatest treatment effect was observed for patients with higher baseline levels of impulsivity. Study IV found that OSU had no short-term negative effect on any assessed cognitive domain, while improving future planning capacity, emotional recognition latency and divergent thinking. Collectively, these findings suggest that OSU may have beneficial clinical treatment effects in AUD on both craving and cognition, but larger randomized controlled trials are needed to replicate these preliminary findings.

Study V was a randomized controlled trial to investigate the effect of working memory training in AUD on drinking, working memory and transfer effects to other cognitive functions. Patients with AUD (n = 50) were randomized to 5 weeks of active computerized working memory training or control training, and came for weekly follow-up visits to the clinic to report drinking and craving. Neuropsychological testing was performed at baseline and after study completion. Active working memory training improved verbal working memory performance, but no significant effect was found for drinking, craving or any of the other assessed cognitive domains. The results did not provide support for working memory training as a sole treatment for AUD, but future studies could consider combining it with pharmacological or psychological treatments.

In summary, the current thesis demonstrated that cognitive deficits observed in AUD are in part due to shared genetic factors between AUD and cognitive function. These cognitive deficits may include impulsive behavior, capacity for future planning and emotional recognition. The treatment studies illustrate that cognitive outcomes can indeed be utilized as predictors of treatment response as well as potential treatment targets.

# LIST OF SCIENTIFIC PUBLICATIONS IN THE THESIS

I. **Khemiri L,** Larsson H, Kuja-Halkola R, D'Onofrio BM, Lichtenstein P, Jayaram-Lindström N, Latvala A. Association of Parental Substance Use Disorder with Offspring Cognition: A Population Family-based Study. Addiction (Abingdon, England) 2019, in press.

II. **Khemiri L**, Franck J, Jayaram-Lindström N: Effect of Alcohol Use Disorder Family History on Cognitive Function (Manuscript)

III. **Khemiri L**, Steensland P, Guterstam J, Beck O, Carlsson A, Franck J, Jayaram-Lindström N: The Effects of the Monoamine Stabilizer (-)-OSU6162 on Craving in Alcohol Dependent Individuals: A Human Laboratory Study. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology 2015 25;12 2240-51

IV. **Khemiri L,** Steensland P, Guterstam J, de Manzano Ö, Franck J, Jayaram-Lindström N: Effects of the Monoamine Stabilizer (-)OSU6162 on Cognitive Function in Alcohol Dependence. Psychopharmacology 2019, in press.

V. **Khemiri L**, Brynte C, Stunkel A, Klingberg T, Jayaram-Lindström N. Working Memory Training in Alcohol Use Disorder: A Randomized Controlled Trial. Alcoholism, clinical and experimental research 2019 43;1 135-146

# LIST OF ADDITIONAL PUBLICATIONS

**Khemiri L**, Jayaram-Lindström N, Hammarberg A. Psychometric evaluation of a Swedish version of the Shortened Desires for Alcohol Questionnaire (Shortened-DAQ). Journal of substance abuse treatment 2017 79; 61-66

**Khemiri L**, Kuja-Halkola R, Larsson H, Jayaram-Lindström N. Genetic overlap between impulsivity and alcohol dependence: a large-scale national twin study. Psychological medicine 2016 46;5 1091-102

**Khemiri L**, Jokinen J, Runeson B, Jayaram-Lindström N. Suicide Risk Associated with Experience of Violence and Impulsivity in Alcohol Dependent Patients. Scientific reports 2016 6; 19373-

**Khemiri L**, Guterstam J, Franck J, Jayaram-Lindström N. Alcohol dependence associated with increased utilitarian moral judgment: a case control study. PloS one 2012 7;6 e39882

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADHD | Attention Deficit Hyperactivity Disorder |
| ANOVA | Analysis of variance |
| AST | Attention Switching Task |
| AUD | Alcohol Use Disorder |
| BIS | Barratt Impulsiveness Scale |
| CANTAB® | Cambridge Neuropsychological Test Automated Battery® |
| CBT | Cognitive behavioral therapy |
| CGT | Cambridge Gambling Task |
| DA | Dopamine |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DUD | Drug Dse Disorder |
| EF | Executive functions |
| ERT | Emotion Recognition Task |
| FH+ | Alcohol use disorder family history positive |
| FH- | Alcohol use disorder family history negative |
| FTQ | Family Tree Questionnaire |
| GABA | Gamma-aminobutyric acid |
| GCP | Good Clinical Practice |
| HC | Healthy controls |
| ICD | International Classification of Diseases |
| IED | Intra-Extra Dimensional Set Shift |
| IST | Information Sampling Task |
| ITT | Intention-to-treat |
| MADRS-S | Montgomery-Åsberg Depression Self Rating Scale |
| MRI | Magnetic resonance imaging |
| MZ | Monozygotic |
| NESARC | National Epidemiological Survey on Alcohol and Related Conditions |
| OCDS | Obsessive Compulsive Drinking Scale |
| OSU | (-)-OSU6162 |

| | |
|---|---|
| $P_{correct}$ | Mean probability of correct decision |
| PET | Positron emission tomography |
| PFC | Prefrontal cortex |
| PP | Per-protocol |
| RVP | Rapid Visual Processing task |
| SCID-I | Structured Clinical Interview for DSM-IV Axis I |
| Short-DAQ | The shortened Swedish version of the Desire for Alcohol Questionnaire |
| SOC | Stockings of Cambridge |
| SRC | Substance related crime |
| SST | Stop Signal Task |
| SSRT | Stop Signal Reaction Time |
| SUD | Substance Use Disorder |
| SWM | Spatial Working Memory task |
| TLFB | Time Line Follow Back interview |
| VAS | Visual Analog Scale |
| VTA | Ventral tegmental area |
| WHO | World Health Organization |

# 1 INTRODUCTION

Individuals suffering from alcohol use disorder (AUD) exhibit loss of control over alcohol intake, coupled with negative psychological, social and physical consequences of drinking. Even though not explicitly stated in the diagnostic criteria, these individuals also exhibit cognitive symptoms, such as difficulties with impulse control, attention and memory. It is however not fully understood to what degree these cognitive symptoms are influenced by genetic factors and if they are present before onset of the disorder. In addition, it is not known whether it is possible to target and treat the cognitive symptoms in AUD patients in a clinical setting. The thesis consists of five scientific studies addressing two larger research questions:

1) What is the etiology of cognitive deficits in AUD?

2) Can cognitive deficits in AUD be treated, either by pharmacological or cognitive training interventions?

Chapter 2 will present a comprehensive background and review of previous research literature, with a focus on AUD, cognition and cognitive deficits in AUD. In chapter 3, the overall and specific aims of the thesis will be presented. Chapter 4 consists of an overview of the methods used in each study, followed by the main results in chapter 5.

Chapter 6 focuses on a discussion related to interpretation of the results and conclusions of the thesis, in relation to the original research questions. This section also aims to discuss limitations of the studies, as well as reflections in relation to the research field and ideas for future research. The thesis concludes with a summary in Swedish, acknowledgments and references, followed by the five scientific papers.

# 2 BACKGROUND

## 2.1 ALCOHOL USE DISORDER

### 2.1.1 History

AUD is fundamentally caused by a simple molecule, namely ethanol ($C_2H_5OH$), entitled alcohol throughout the thesis. It has been proposed that homo sapiens and its predecessors developed a preference for alcohol, because of the adaptive advantage to ingest ripe fermented fruits during the last 40 million years of evolution (1). Archaeological evidence suggests that human cultures have produced and consumed alcoholic beverages for thousands of years, with fermented beverages of rice, honey and fruit being consumed as early as 7000 B.C. in ancient China (2).

The American physician Benjamin Rush (1746-1813) is often credited as one of the first physicians to raise concern of the negative health consequences of alcohol, and to view habitual drunkenness as a disease rather than a sin (3). Magnus Huss (1807-1890), a Swedish physician, was however the first to systematically describe the clinical syndrome of alcoholism in his book "Alcoholismus chronicus" published in 1849 (4). A more modern clinical conceptualization was presented by Jellinek in "The Disease Concept of Alcoholism", clearly defining alcoholism as a disease within the realms of medical science, while at the same time highlighting the heterogeneity of the disorder (5). Finally, in their widely cited review article "Alcohol dependence: provisional description of a clinical syndrome" in 1976 (6), Edwards and Gross provides a review of the 'essential elements' of the disorder, many of which overlap the diagnostic criteria provided in the modern diagnostic systems used today i.e., the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the World Health Organization (WHO) International Classification of Diseases (ICD).

### 2.1.2 Diagnostic Criteria

AUD is conceptualized as a psychiatric disorder characterized by an inability to control alcohol intake, which results in negative social, physical and psychological consequences for the individual. The American diagnostic system, called the Diagnostic Statistical Manual (DSM) which is common practice to use in clinical psychiatry and research for diagnosing psychiatric disorders including substance related disorders, underwent an important change in its most recent version DSM-5 (7). In the previous edition of the DSM (DSM-IV), there were two separate diagnostic disorders entitled alcohol dependence (seven criteria) and alcohol abuse (four criteria). In DSM-5 however, the criteria of the two separate disorders were collapsed into one diagnosis and entitled AUD with 11 criteria. Furthermore, a novel criterion of craving was added while the criterion concerning legal problems was eliminated. Another important change in DSM-5 was that the AUD diagnosis became dimensional, i.e., the severity of the disorder now depends on number of criteria fulfilled within the last 12 months (2-3 = mild AUD; 4-5 = moderate AUD; 6-11 = severe AUD). It is important to note that the release of DSM-5 came about during the course of the current thesis work. Therefore, the

former DSM-IV diagnosis of alcohol dependence is used in the earlier studies, while AUD is used in the later publications.

The ICD, version 10 (ICD-10) is the other widely used diagnostic classification system, also utilized in the Swedish healthcare services and national patient registries. In ICD-10, the diagnosis of alcohol dependence corresponds to a high degree with the DSM-5 criteria for moderate/severe AUD, as illustrated in Table 1.

**Table 1. Diagnostic criteria for alcohol use disorder (DSM-5) and alcohol dependence (ICD-10)**

| **DSM–5 criteria for Alcohol Use Disorder** |
|---|
| 1. Alcohol is often taken in larger amounts or over a longer period than was intended. |
| 2. Persistent desire or unsuccessful efforts to cut down or control alcohol use. |
| 3. A great deal of time is spent in activities necessary to obtain, use, or recover from effects of alcohol use. |
| 4. Craving, or a strong desire or urge to use alcohol. |
| 5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home. |
| 6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by alcohol use. |
| 7. Important activities (social, occupational or recreational) activities are given up or reduced because of alcohol use. |
| 8. Recurrent alcohol use in situations in which it is physically hazardous. |
| 9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol. |
| 10. Tolerance |
| 11. Withdrawal |
| **ICD-10 criteria for Alcohol Dependence** |
| 1. A strong desire or sense of compulsion to drink |
| 2. Difficulties in controlling drinking behavior in terms of its onset, termination, or levels of use |
| 3. Withdrawal |
| 4. Tolerance |
| 5. Neglect of alternative activities because of drinking, increased amount of time necessary to obtain or drink or to recover from the effects of alcohol |
| 6. Persisting with drinking despite clear evidence of overtly harmful consequences |

### 2.1.3 Epidemiology

Alcohol use is a global health problem, causing 6% of deaths every year (3.3 million deaths) and constituting 5% of the global burden of disease (8). Consumption of alcohol is associated with more than 60 diseases, including several clinically debilitating disorders such as cancer, gastrointestinal disease, liver and pancreatic diseases, cardiovascular disease, neuropsychiatric disorders, unintentional and intentional injuries (9). Previous studies have suggested that low levels of alcohol consumption actually can exert positive effects on health e.g., reducing risk of certain cardiovascular disorders (10). However, the most recent data from the Global Burden of Disease Study 2016 found a robust association between increasing levels of alcohol and all-cause mortality, and noteworthy were the results showing that the level of alcohol consumption that minimizes overall disease (across all forms of diagnoses) was in fact zero (11).

Using surveys or national registries to estimate the prevalence of any psychiatric disorder is methodologically difficult for several reasons, such as underreporting and selection bias. To date, some of the best prevalence estimates come from the American large-scale National Epidemiological Survey on Alcohol and Related Conditions (NESARC) surveys. In these surveys, a representative sample of non-institutionalized civilian adults in the USA have been interviewed face to face by trained interviewers, in order to estimate presence of common mental disorders including alcohol and drug use disorders as defined in the DSM diagnostic system (12). The latest NESARC-III (n = 36,309) employed the DSM-5 criteria (13), and found that the 12-month and lifetime prevalence of AUD were 14 % and 29%, respectively. The mean age of onset for mild, moderate and severe AUD was 30, 26 and 24 years, respectively. Furthermore, AUD was associated with significantly increased risk of all forms of psychiatric co-morbidity, such as other types of substance use disorders (SUD), bipolar disorder, major depressive disorder and both antisocial and borderline personality disorder (13).

In Sweden, the average yearly alcohol consumption is 9 liters alcohol per capita, and this has decreased by 8% in the latest decade (14). The AUD prevalence in Sweden is approximately 6%, and is more common among men than women (15). Despite the severe health risks associated with AUD, approximately 80% of all individuals with a diagnosis of AUD have not received any form of treatment (13), making it the mental disorder with the largest treatment gap (16).

### 2.1.4 Neurobiology

The neurobiology underlying AUD is complex and involves perturbed information processing in large scale brain networks including multiple brain regions and neurotransmitter systems such as dopamine (DA), serotonin, gamma-aminobutyric acid (GABA) and glutamate (17,18). A full review of the neurobiology of AUD is outside the scope of the current thesis. The introduction thus focuses specifically on the DA system and prefrontal cortical regions, since these are particularly relevant given the topic of the thesis

and nature of the interventions evaluated in study III-V.

The mesolimbocortical DA system is the neural substrate for natural rewards, e.g. food and sex as well as drugs of abuse, consisting of dopaminergic neurons in the ventral tegmental area (VTA) projecting to nucleus accumbens (mesolimbic pathway) and the prefrontal cortex (PFC) and anterior cingulate cortex (mesocortical pathway). The acute reinforcing effects of alcohol is mediated in part by release of DA in the nucleus accumbens as shown both in rats (19,20) and humans (21). Furthermore, with the advent of positron emission tomography (PET) it has been found that AUD patients have reduced D2/D3 receptor levels and central stimulant induced DA release in the striatum (22–24). Finally, it was recently shown that AUD patients compared to healthy controls have decreased dopaminergic neurotransmission in additional brain areas including several cortical regions such as dorsolateral PFC, medial PFC and orbital frontal cortex (25). While DA is likely more important in the early phases of AUD, and perhaps especially in individuals with genetic risk, several other neurotransmitters involved in the fear/stress response are important in later stages of the development of the disorder (26).

In an influential review article, Goldstein and Volkow argue that SUD should be understood not only as a deficit in subcortical reward circuits, but also that a key neural substrate is the PFC and its regulation of both reward and higher-order cognitive functions (27). It has long been known that individuals suffering from AUD exhibit a wide range of structural abnormalities in the brain. In an early review, Mann and colleagues reported that more than half of patients have some degree of diffuse brain morphology change such as enlarged ventricles, fissures and widened cortical sulci, interpreted as a neurotoxic effect of alcohol on brain tissue (28). Several studies have found evidence of volume loss in widely different parts of the brain (e.g., cerebellum (29), hippocampus (30) and nucleus accumbens (31)), but it has been suggested that the PFC is disproportionally affected by the toxic effects of alcohol (32). In an autopsy study, Harper and colleagues found that the actual number of cortical neurons in the superior frontal cortex were significantly lower in AUD compared to healthy controls, while no such difference was found for the motor cortex (33). As reviewed by Moselhy and colleagues (32), neuroradiological studies in AUD using pneumo-encephalogram (34), computer tomography (35) and magnetic resonance imaging (MRI) (36) found evidence of widespread frontal cortex atrophy. These findings are also supported by a recent meta-analysis showing significant grey matter reductions in cortico-striatal limbic structures in AUD (37). Furthermore, in a meta-analysis of cue-induced craving activation in AUD, alcohol cues induced greater activation in limbic and prefrontal areas of the brain such as the ventral striatum, anterior cingulate cortex and ventromedial PFC (38), suggesting that these affected brain areas are also involved in the craving response and substance use in AUD. In summary, AUD is associated with functional and structural changes in the mesolimbocortical DA system and PFC, both of which are critically involved in reward and higher-order cognitive functions, as discussed later in the chapter.

### 2.1.5 Treatment

There are two main forms of treatments available for AUD: psychosocial and pharmacological treatment. Evidence based psychosocial treatments include cognitive behavioral therapy (CBT), 12-step treatment and motivational enhancement therapy (39). Pharmacological treatments approved by both the U.S. Food and Drug Administration and the European Medicines Agency are disulfiram, naltrexone and acamprosate (40). However, a majority of AUD patients do not respond to available medications (41), and there is therefore still a great need to develop effective treatment strategies for AUD. In the recent decade, it has been proposed that interventions targeting and enhancing cognitive function may be a promising treatment strategy when developing novel pharmacological and behavioral treatments for SUD (42–46).

### 2.1.6 Etiology and Endophenotypes

AUD is a multifactorial syndrome caused by an interplay of genetic and environmental factors. Early clinical studies of AUD patients and their relatives found that AUD tends to aggregate within families (47,48). In a 1979 review article of 39 published studies, it was found that relatives of AUD patients had substantially higher rates of AUD compared to control groups (49), indicative of a genetic inheritance of the disorder. These clinical observations have since been further supported by epidemiological studies utilizing adoption and family-based controlled designs in larger samples (50–55), establishing that AUD has a heritability (i.e., proportion of variance explained by genetic factors) of approximately 50 % (56). Shared environmental (10%) and unique environmental factors (40%) explained the remaining proportion of variance (56). Although there is substantial data to support the important role of genetic factors, large scale genome-wide association studies have so far only found alleles contributing to minimal increase in risk (57). The problem of "missing heritability", i.e. the large discrepancy between heritability estimates in family based studies compared to studies of risk alleles are not only an issue for AUD but also for other major psychiatric disorders such as schizophrenia, bipolar disorder and depression (58). Such a pattern suggests a simultaneous involvement of a large multitude of genes with an additive or interactive effect, all together giving rise to a risk score for developing a specific disorder.

An endophenotype is an intermediate phenotype between the genotype (genetic code, e.g., DNA) and phenotype of interest (for instance a clinical syndrome such as AUD). The concept of endophenotype has been suggested to improve the understanding of genetics underlying complex traits such as psychiatric disorders, where classic Mendelian principles of inheritance do not apply (59). The rationale is that since psychiatric disorders are extremely heterogeneous, defined by several different disparate DSM criteria, more fundamental observable characteristics may have simpler genetics and should thereby be more suitable for genetic analysis (59).

In an influential paper by Gottesman and Gould (59), several criteria for psychiatric endophenotypes were proposed. In brief, a putative endophenotype should be associated with

the illness in the population, heritable, state-independent and co-segregate with illness within families. Finally, an endophenotype should also be found at a higher rate in non-affected individuals with positive family history, compared to the general population. Suggested methods to identify such endophenotypes are neurobiological techniques (60) as well as neuropsychological tasks of cognitive function (59). Several AUD endophenotypes have been suggested (see review (61)), including a low sensitivity level of response (e.g., alcohol-induced motor impairment) to the effects of alcohol (62), a differential rate of ethanol metabolism (63) and deficits in overlapping cognitive constructs including elevated impulsivity and behavioral disinhibition (64–66).

## 2.2 COGNITION

### 2.2.1 Cognitive Science

The interdisciplinary research field of cognitive science was born in 1950-1960 in the so called "cognitive revolution", which coincided with the decreased influence of behaviorism on psychology (67). This marked an important shift in thinking, when researchers started to focus on internal mental processes, by viewing the nervous system as an information processing system that represented, processed and transformed information to complex behaviors (68). With the advancement of neuroimaging techniques, the interdisciplinary field of cognitive neuroscience emerged in the 1970-1980's. A fundamental premise of this field is that cognitive functions, such as language, memory, attention and decision-making, correlate to specific neural activity in the brain (69).

The current thesis builds on theories and constructs from different fields including psychiatry, psychopharmacology, cognitive psychology and cognitive neuroscience. Regarding cognitive functions, the thesis will focus primarily on two related and partly overlapping constructs widely referenced in the addiction research literature: executive functions (EF) and impulsivity. These two constructs will therefore be described in more detail in the following sections.

### 2.2.2 Executive Functions

The term EF is an umbrella term which refers to several different cognitive functions that allow individuals to dynamically adapt to the changing environment and select appropriate actions in accordance with their long-term goals (70–72). Although there is an ongoing discussion regarding which specific cognitive functions that constitute EF, a common feature for EFs are that they are top-down processes dependent of PFC functioning, requiring mental effort and together they build up higher-order cognitive functions such as problem solving and complex decision making involving risk (70–72).

In a review article by Bickel and colleagues, the EF most relevant for the field of addiction research are presented and include response inhibition, flexibility, attention, planning, valuing future events and working memory (73). Since these constructs to a large extent overlap with

the cognitive domains under study in the current thesis, the constructs will be reviewed in brief in the following paragraph based on the categorization by Bickel and colleagues (73). In addition, common cognitive tests utilized to assess each construct will be presented, together with hypothetical examples of how perturbance in each cognitive domain can affect an individual with AUD.

*Response inhibition* (also referred to as inhibitory control, self-control, behavioral inhibition) is the capability to override an internal or external stimulus to perform an action, and instead do what is appropriate, given the current situation (70). This construct is assessed with stop signal or go/no-go tasks, and may be involved for instance when an AUD patient declines to receive an offered drink.

*Flexibility* (also referred to as set shifting, mental flexibility) is the capacity to change perspectives spatially or interpersonally when the situation demands it, i.e. the opposite of rigidity (70). This construct is assessed with tasks such as the Wisconsin Card Sorting Task or Stroop tasks, and may be needed in AUD patients to change habits related to drinking, or to find alternative courses of actions that do not include drinking when facing a novel stressful situation.

*Attention* is the capability to focus on one specific aspect of the environment while ignoring irrelevant stimuli. It can be assessed by vigilance tasks such as the continuous performance task, and can be important for AUD patients in order to adhere to and fully acquire the skills taught for instance in different forms of psychotherapeutic treatment.

*Planning* (also referred to as future planning) is the ability to think several steps ahead in order to achieve a future goal, and can be assessed by tasks such as the Tower of London (74). This cognitive capacity is needed in order for AUD patients to structure their daily activities and avoid actions that can predictably lead to a relapse situation.

*Working memory* is defined as the ability to maintain and manipulate information during a brief period of time even when the information is not perceptually present (75). It can be further subdivided into verbal and visuospatial working memory and is often assessed by tasks such as the n-back or Digit span task. Working memory has been suggested to be important also for other EF and higher order decision making (71), and it has been hypothesized that improvement in working memory could result in improvements also in other EF (76).

*Valuing of future events* (also referred to as delay discounting) is the capacity to attribute value or importance to future potential rewards at the expense of smaller more immediate rewards, and is often assessed by different delay discounting tasks such as the Kirby Monetary Choice questionnaire (77). This cognitive process could obviously affect an AUD

patient when choosing between the value of greater positive effects of long-term abstinence compared to the smaller immediate gratification of consuming an alcoholic drink.

### 2.2.3 Impulsivity

Impulsivity is a heterogeneous construct relevant across several psychiatric disorders (78), and can be defined as "a predisposition towards rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others" (79). It is a widely held view that impulsivity is a multi-faceted construct composed of several different components such as response inhibition, delay discounting and increased risk-taking (80,81).

Impulsivity is often further deconstructed into trait and state impulsivity. Trait impulsivity is general impulsive behavior and personality across the lifespan, assessed by self-rating questionnaires such as the Barratt Impulsiveness Scale (BIS; (82)). State impulsivity, in contrast, is subject to change in different environments and susceptible to interventions such as pharmacological agents. State impulsivity can be assessed by different cognitive tests and is often divided into subconstructs such as behavioral disinhibition, impulsive choice, reflection impulsivity and attentional impulsivity (73,81). The construct of impulsivity is thus closely related to, and partly overlapping with, the construct of EF described above. In the aforementioned review article, Bickel and colleagues compares these two constructs and found that all components of state impulsivity in fact also can be conceptualized as the extreme form of deficit, or 'antipod', of different EF (73). For instance, the EF construct response inhibition directly parallels the impulsivity construct behavioral disinhibition, with inverse definitions and identical cognitive tasks (stop signal tasks, go/no-go tasks) used to assess both constructs. On the other hand, some EF, such as working memory and flexibility, do not have any direct equivalent within the construct of impulsivity (73).

In the current thesis the aim was to try to utilize the terms for the described EF above, while the term 'impulsivity' refers to the overall trait of impulsive behavior. However, in the process of manuscript writing and peer review, some inconsistencies in terminology are manifest in the different manuscripts of the thesis. For instance, the stop signal task is alternatively referred to as a 'task of response inhibition' and an 'impulsivity task'. The terms and definitions of different EF's and impulsive behavior vary between and within different research fields, which is an important general limitation in this area of research (83). This thesis does not aim to investigate the taxonomy of cognitive domains, but rather adopts the pragmatic stance to utilize well validated neuropsychological tests and questionnaires commonly used to study EF and impulsivity, thereby accepting the risk of ambiguity given the overlapping nature of these cognitive constructs.

### 2.2.4 Neurobiology

It is widely held that EF and impulse control depend on having a functional PFC. Evidence for this notion came initially from case studies, including the often-cited case of the 19$^{th}$

century railroad worker Phineas Gage, who reportedly was hit with a metal bar destroying the orbito- and medial frontal cortex, resulting in a severe personality change where he suddenly started to use profanities and became irresponsible, capricious and highly impulsive (84). Similar clinical observations were made in neuropsychological studies of patients and soldiers suffering from frontal lobe damage caused by disease or war trauma (reviewed in (85), Chapter 5).

Modern research methodologies involving neuroimaging and psychopharmacology have shed more light on the neurobiology of EF and impulsivity. Although a complete review of this literature is outside the scope of the current thesis, functional MRI studies have found that distinct parts of PFC are involved in different tasks related to EF. For instance, inhibition depends in part on the right inferior frontal cortex (86), while planning is associated with activity in the right dorsolateral PFC and left anterior PFC (87). Importantly, the PFC does not work in isolation but rather in a large cerebral network including other cortical and subcortical brain structures (88), and the activity is modulated by ascending catecholamine projections suggesting that optimal concentrations of DA and norepinephrine are needed for optimal EF performance (89). Notably, several of the aforementioned neuroanatomical areas involved in EF are affected in AUD (as reviewed above), and this common neurobiological overlap may in part explain the cognitive deficits found in AUD patients, which is also the topic of the next chapter.

## 2.3 COGNITIVE DEFICITS IN ALCOHOL USE DISORDER

An important distinction has to be made before further review of cognitive deficits in AUD. It is well known that long term severe AUD is associated with alcohol-induced dementia and Wernicke Encephalopathy (caused by thiamine deficiency), which untreated can develop to Korsakoff's syndrome (90). These forms of severe cognitive deficits, including disorientation in time, are not what the current thesis alludes to, when using the term cognitive deficits. Rather, the term is used to describe more subtle cognitive deficits related to EF and impulsivity, in treatment seeking non-institutionalized AUD patients.

### 2.3.1 Clinical Characteristics and Etiology

#### *2.3.1.1 Patient Studies*

There is a large research literature of case-control studies showing that AUD patients exhibit cognitive deficits across a wide range of cognitive domains (91). In a meta-analysis focusing on EF and impulsivity, AUD was associated with greatest impairments in inhibition and planning/problem solving (92). Specifically, AUD patients exhibit elevated trait impulsivity (93–95), impaired response inhibition (93,96–100), valuing of future events/delay discounting (93,101–103), working memory (104–106), flexibility (97,107), attention (108,109) and future planning (97,110). However, since these are case control cross-sectional studies, it is impossible to draw any conclusions regarding the etiology of cognitive deficits in AUD based on their results.

It is however widely assumed that alcohol toxicity partly explains the cognitive deficits in AUD. Studies have reported significant correlations between AUD severity and cognitive impairment (111), and different degrees of spontaneous recovery of cognitive function as well as normalization of structural brain imaging findings during abstinence (112). However, in the meta-analysis by Stavro and colleagues, impairments in cognitive function across all modalities (except attention) were evident even in patients with 12 or more months of sobriety, albeit with a reduced effect size (91). This finding of reduced effect size over time was interpreted as an indication of spontaneous recovery from the toxic effects of alcohol. An alternative interpretation however, is that the AUD patients who achieve 12+ months abstinence managed to do so because of having a more intact level of cognitive functioning. No matter the cause, it is evident that despite one year of abstinence AUD patients still exhibit significant differences across a wide range of cognitive domains compared to healthy controls. Whether this is due to long-term toxic effects of alcohol or reflect pre-morbid cognitive traits is not known. In order to address the question of etiology of these cognitive deficits, family history studies (i.e., case-control studies including family history positive negative subjects) or large scale epidemiological behavioral genetic studies are needed.

#### *2.3.1.2 Family History Studies*

Healthy individuals with positive AUD family history exhibit elevated levels of self-rated impulsivity (113), impaired response inhibition (114,115), decreased composite EF based on several tests (113) and altered neural activity in insula and inferior frontal gyrus which correlated with self-rated impulsivity (116). By employing a longitudinal design, Nigg and colleagues studied 498 children and found that poor response inhibition predicted alcohol-related problems (117). In a similar longitudinal study comprising 358 adolescents, Khurana and colleagues found that low baseline working memory capacity predicts alcohol use, and that this association was mediated by impulsivity (118). Finally, Aytaclar and colleagues showed that family history of SUD was associated with impaired EF at age 10-12, and that poor EF was a significant predictor of future drug use in adolescence (119). Taken together, these studies indicate that deficits in EF and impulsivity are to a higher degree found in individuals with positive family history of AUD, and that these cognitive deficits can precede and predict development of substance use related problems.

#### *2.3.1.3 Behavioral Genetic Studies*

Within the research field of behavioral genetics, large scale epidemiological data with information on genetic relatedness are used to draw conclusions regarding influence of genetic and environmental factors on any phenotype (120). Twin studies have found evidence of shared genetic factors between AUD and other psychiatric disorders characterized by elevated impulsivity, such as attention deficit hyperactivity disorder (ADHD) (121,122), pathological gambling (123) and conduct disorder (124). Furthermore, a bivariate twin modeling study found that the association between alcohol dependence and impulsivity was in part accounted for by shared genetic factors (125). Finally, a recent prospective twin study

of the DSM-IV personality disorder criteria found that self-harming impulsivity (borderline personality disorder criterion) and childhood conduct disorder (antisocial personality disorder criterion) predicted development of AUD, and that this association was due to shared genetic factors (126).

Taken together, there is evidence from both family history case control studies and behavioral genetic studies, that the cognitive deficits of EF and impulsivity found in AUD patients may in part be due to genetic factors. However, in order to investigate the effect of treatments for these cognitive symptoms, randomized controlled trials are needed, and these studies will be reviewed in the next section.

### 2.3.2 Interventions

#### *2.3.2.1 Cognitive Function as Predictor of Treatment Outcome*

It has been hypothesized that cognitive deficits related to impulsivity and EF can predict treatment outcome in clinical settings in AUD. For instance, Czapla and colleagues found that AUD patients with impairments in response inhibition at baseline predicted higher risk of relapse (127). Similarly, Rupp and colleagues showed that impaired response inhibition and greater delay discounting predicted poorer treatment outcome in AUD patients (128). Finally, self-rated impulsivity (129,130) and risk taking (129) also predicts relapse in AUD. In a review by Stevens and colleagues, the authors conclude that there is preliminary evidence indicating that higher levels of impulsivity/EF predict poorer treatment outcome in SUD (131), suggesting that such cognitive deficits are likely clinically important and in need of treatment.

#### *2.3.2.2 Pharmacological Interventions*

Few studies have investigated cognitive enhancing effects of pharmacotherapy in AUD patients. In a narrative review by Butler and colleagues, there was no clear evidence of any cognitive enhancing effect by the approved AUD pharmacotherapies (disulfiram, acamprosate, naltrexone or nalmefene) in AUD patients, although very few studies have been performed on this topic (132). When evaluating novel potential pharmacological treatments in AUD, only a handful of studies have included cognitive assessment as potential outcomes. In a recent review of studies targeting SUD and impulsivity outcomes (133), three placebo controlled trials of AUD patients with impulsivity/EF outcomes were identified, investigating the effect of topiramate, modafinil and aripiprazole.

Topiramate is an anticonvulsant, facilitating GABA and blocking glutamatergic AMPA/kainate receptors, that has shown positive treatment effect on drinking outcomes in AUD (134). Rubio and colleagues found that topiramate not only reduced craving and drinking, but also improved attention (assessed by the continuous performance task) and response inhibition (assessed by the stop signal task) (135). Modafinil, acting in part as a DA transporter modulator (136), was shown to improve performance on the stop signal task of

response inhibition only in those AUD patients with low baseline level performance of the same task (137). Furthermore, in a 10 week trial of modafinil in AUD patients, it was found that modafinil decreased drinking only in subjects with low baseline level of response inhibition – while increasing drinking in subjects with better response inhibition at baseline (138). Interestingly, in a follow-up analysis of the same study it was found that the medication improved working memory function in those with lowest baseline working memory performance (139). Finally, aripiprazole, a partial D2-agonist, has been found to reduce drinking over short-term time periods (140,141), reduce cue-induced activation of the ventral striatum in a functional MRI task (140) and reduce alcohol intake in a bar laboratory experiment (141) in AUD patients. Furthermore, there was indication of the greatest treatment effect being found in AUD patients with high baseline levels of impulsivity, rated using the BIS (141,142).

Taken together, very few studies to date have investigated the potential effect of novel pharmacological agents on EF and impulsivity in AUD patients. Given the important role of DA in the neurobiology of AUD as reviewed above, it has long been a target of interest when developing pharmacological treatments. Despite some encouraging laboratory studies, neither antipsychotic DA antagonists or DA agonists have been found to improve drinking outcomes in large-scale studies (143). However, pharmacological agents targeting the dopaminergic system in other ways than pure antagonism or agonism could potentially be a more successful strategy.

The monoamine stabilizer (-)-OSU6162 (OSU) is a pharmacological compound developed by Arvid Carlsson and colleagues (144). The term ‘stabilizer’ stems from its ability to either enhance, inhibit or exert no effect on dopaminergic neurotransmission depending on the prevailing dopaminergic tone (144,145). The pharmacological mechanism of action of OSU is not fully known. It has however been suggested that the functionally opposite effects are caused by antagonism at both the postsynaptic D2 receptors as well as the presynaptic autoreceptors (144,146–148). OSU has been evaluated in both healthy individuals (149) and different patient populations such as individuals with Huntington’s disease (150) and chronic fatigue syndrome (151), and found to have a generally mild side effect profile. In a series of preclinical studies, Steensland and colleagues have shown that OSU reduces alcohol intake, withdrawal and reinstatement (152), as well as improving motor impulsivity on the five-choice serial reaction time task in rats (153). In addition, OSU has been shown to restore striatal dopaminergic deficits in alcohol-drinking rats, and was not found to have any reinforcing properties in itself (154). Taken together, based on preclinical evidence OSU shows promising results as a potential novel medication in AUD with putative effects on both drinking and impulsivity, but prior to this thesis no study had evaluated OSU in AUD patients.

#### *2.3.2.3 Working Memory Training Interventions*

Given that working memory is considered a core EF necessary for other higher-order cognitive functions, it has been suggested that improvement of working memory function through repeated training may be a feasible novel treatment strategy for SUD (42). The Cogmed® working memory training program was developed by professor Torkel Klingberg and has been shown to improve working memory function in healthy volunteers (155,156), patients with stroke (157) and in ADHD (158,159). Importantly there has been some evidence indicating that improvement in working memory via training also induces so called transfer effects, i.e. improvements in other cognitive functions such as inhibition (158–160) and attention (161). It should be noted that there is an ongoing scientific discussion regarding the degree to which working memory training can induce improvement in other cognitive domains (e.g., (162,163)), but whether such transfer effects are possible to induce in SUD patients remains an open question.

Only a handful of studies using computerized working memory training have been performed in SUD populations. Bickel and colleagues found that working memory training in stimulant dependent subjects resulted in reduced discounting rates of future rewards, but no effect on other cognitive domains (164). In a study of methadone maintenance patients, working memory training improved performance on working memory tasks similar to trained tasks and drug use remained unchanged in the treatment group while increasing in the control group (165). Houben and colleagues showed that working memory training improved working memory and reduced drinking in heavy drinking subjects recruited and tested online (166). Recently it was also shown that working memory training improved impulse control in patients with methamphetamine use disorder (167), as well as working memory and episodic future thinking delay discounting in AUD patients with poorest baseline performance (168). In contrast, recent studies have found less encouraging results. Sweeney and colleagues did not find any significant effect on clinical outcomes or transfer effects in adolescents with cannabis use disorder (169). Finally, in the largest study to date, Wanmaker and colleagues investigated the effect of working memory training in 180 SUD inpatients, finding no significant treatment effect on substance use outcomes, working memory or transfer effects to other cognitive domains (170).

In summary, previous studies of working memory training in SUD populations have shown mixed results, with some studies suggesting that this intervention actually can improve working memory, impulsive behavior and substance use outcomes while more recent larger studies have found no such effects. To the best of our knowledge however, prior to the current thesis no study had investigated the effect of working memory training on drinking, working memory and transfer effects to EF/impulsivity in a clinical sample of AUD patients.

## 2.4 SUMMARY

AUD is a multifactorial psychiatric disorder causing negative health outcomes worldwide, and is defined by diagnostic criteria such as loss of control over drinking and negative

psychological, physical and social consequences due to alcohol intake. The neurobiology of AUD is not completely known, but involves perturbances in dopaminergic neurotransmission and frontal cortex functioning, i.e., brain systems involved in both reward and higher-order cognitive functioning. AUD is heritable, but it is not known which genes or corresponding phenotypes that are inherited across generations.

Cognitive sciences offer a number of tools to understand cognition, such as standardized cognitive testing procedures, neuroimaging and psychopharmacological studies. The cognitive domains of greatest relevance for the current study are EF and the related partly overlapping construct of impulsivity, which depend on fronto-striatal circuits in the brain and are modulated by DA and norepinephrine neurotransmission.

AUD patients exhibit a wide range of cognitive deficits, especially in the domains of EF and impulsivity, some studies indicate that these cognitive deficits are in part genetically influenced. Regarding treatment, few studies have investigated the effects of pharmacological interventions or working memory training in clinical AUD patients. The current thesis will address two overall questions in need of further research. First, are the cognitive deficits in AUD caused by genetic factors? Second, can these cognitive deficits be treated and in turn improve clinical outcomes in AUD?

# 3 AIMS

## 3.1 OVERALL AIMS

The overall aims of the current thesis were to increase understanding of the etiology of cognitive deficits in AUD (study I and II) and to investigate whether cognitive deficits in AUD can be a target for treatment by pharmacological and cognitive working training interventions (study III-V).

## 3.2 SPECIFIC AIMS

Study I: Investigate the association between parental SUD and general cognitive function in offspring at the population level, and to what degree this association is independent of shared genetic factors.

Study II: Investigate to what degree family history of AUD is associated with impairments in cognition, by comparing cognitive test performance in AUD patients, and healthy individuals with positive and negative family history of AUD.

Study III: Investigate the effect of the monoamine stabilizer (-)-OSU6162 on craving in AUD, and whether baseline cognitive assessment can predict treatment outcome.

Study IV: Investigate the effect of the monoamine stabilizer (-)-OSU6162 on cognitive function in AUD.

Study V: Investigate the effect of computerized working memory training on drinking, working memory and other cognitive functions in AUD.

# 4 METHODS

In this chapter the methods for each of the scientific studies will be presented, with focus on the details most relevant to the current thesis' overall research questions. All studies were approved by the regional ethical review board in Stockholm. The pharmacological treatment study was approved by the Swedish Medical Products Agency before start of the study. In all studies involving human volunteers, each participant was informed about the study procedure both orally and in written form, and signed informed consent to participate in the study. The clinical studies were performed at the Stockholm Centre for Dependency Disorders outpatient research clinic in Stockholm, Sweden. The randomized controlled intervention studies (study III-V) were monitored by Karolinska Trial Alliance to ensure compliance with the study protocol and International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use guidelines for Good Clinical Practice (GCP). In the final section, ethical aspects of relevance for the methods used are discussed.

## 4.1 STUDY I: ASSOCIATION OF PARENTAL SUBSTANCE USE DISORDER WITH OFFSPRING COGNITION: A POPULATION FAMILY-BASED STUDY

*Aim:* To investigate the association between parental SUD and general cognitive function in offspring at the population-level, and to what degree this association is independent of shared genetic factors.

*Design:* A population family-based cohort study utilizing national Swedish registries. In Sweden, all citizens have a unique personal identity number enabling linkage at an individual level between different national registries.

*Study cohort:* Two separate population-based cohorts were created: Cohort 1 consisted of all men born in Sweden from 1951 – 1992 who had available cognitive testing data from conscription (n = 1,215,690). Cohort 2 consisted of all individuals (i.e., both girls and boys) born in Sweden 1971 – 1998 with available data for school grades when finishing compulsory school at age 15-16 (n = 2,517,030). The two cohorts were analyzed separately, which means that some individuals could be included in both cohorts – but within each cohort study there were only unique individuals. Individuals not born in Sweden, lacking information regarding parental identification or who had parents born before 1932 (and therefore not included in the Multi-Generation-Register (MGR)) were excluded.

*Exposure:* The exposure variable was parental SUD, operationalized as having any parent with a lifetime ICD alcohol or drug abuse related diagnosis (ICD 8:291, 303 and 304; ICD 9:291, 292, 303, 304, 305A, 305X; ICD 10:F10-F19, except F17) registered in the National Patient Register, which has nationwide coverage of inpatient diagnoses (since 1973) and outpatient diagnoses (since 2001). Parental SUD was also operationalized as having any parent with a criminal conviction of a substance related crime such as drunk driving. Information regarding criminal convictions were extracted from the Crime Registry including

court convictions since 1973.

*Outcome:* The current study utilized two different outcomes of cognitive function for the two separate cohort studies. In cohort 1, the outcome was total test score on the Swedish Enlistment Battery (SEB), a test of general cognitive ability, reported as standardized stanine score i.e., a nine-point scale with a mean value of 5 and standard deviation of 2. In cohort 2, the outcome was final school grades after completing compulsory education at age 15-16. The information regarding grades was extracted from the National School Register. Since there were two different grade systems during the time course of the birth cohort (1988-1997: 0-5; 1998 – 2013: 0-320), the grade data was z-standardized for each year and collapsed into one variable for the entire time period.

*Covariates:* Parents education level was extracted from the national census 1970 and the Education Register from 1985 and onward, operationalized as an ordinal variable ranging from 1 (did not complete compulsory school) to 7 (post-graduate education completed). Psychiatric history in offspring and parents was defined as any registration of a psychiatric diagnosis ((ICD8 290-315; ICD 9 290-319; ICD10 F00-F99), excluding the substance related diagnoses as described in the exposure paragraph above. Information regarding immigration status of parents were extracted from the Migration Register and recoded to a binary variable as either being born in Sweden or not. Parental income was extracted from the national census data and the Swedish Longitudinal Integrated Database for Health Insurance and Labour Market Studies. Parental divorce status and region of upbringing was extracted from the national census data for the decade during which the offspring below 10 years of age.

*Statistical analysis:* For each of the study cohorts, the following statistical analytical procedure was performed: First, the association between parental SUD and offspring cognitive outcome at the population level was investigated by fitting linear regression models, with a cluster-robust sandwich estimator allowing for adjustment of standard errors taking into account the dependence of siblings among the offspring. Model 1 adjusted for birth year (in both offspring and parents) and sex. Model 2 adjusted for parental education, parental psychiatric co-morbidity (i.e., all psychiatric diagnoses excluding SUD), parental immigration status and presence of SUD in the other co-parent. Finally, model 3 adjusted for psychiatric disorders in the offspring.

Second, children-of-siblings analyses were performed to investigate to what degree any associations between parental SUD and offspring cognitive function observed at the population level were independent of shared genetic factors. Conditional linear regression models, i.e., fixed-effects regression models (171,172), were fitted within offspring to pairs of siblings with different degree of genetic relatedness in the parental generation. The fixed-effects models adjusts for factors shared between members of extended families - and by performing separate analyses in offspring to siblings discordant for SUD this family-based design allows for gradually increasing adjustment of genetic confounding factors (173,174).

Three separate models were performed for offspring to siblings who were half-siblings (sharing on average 25% of their genes), full siblings and dizygotic twins (sharing on average 50% of their genes) and monozygotic (MZ) twins (sharing 100% of their genes). If the associations in all these models remain stable and similar to the full population irrespective of genetic relatedness within the parent siblings, this would suggest that the observed association at the population level was not influenced by genetic confounding factors. In contrast, if the associations are reduced when the parents are more genetically similar, this would suggest that the association observed in the population in fact was in part due to shared genetic factors.

Finally, several sensitivity analyses were performed using different definitions of the exposure, different subgroups (e.g., sex) and further adjustment of potential confounders. The sensitivity analysis most relevant for the current thesis, was the population-level analyses performed separately for parental AUD, drug use disorder (DUD) and substance related criminality (SRC).

## 4.2 STUDY II: EFFECT OF ALCOHOL USE DISORDER FAMILY HISTORY ON COGNITIVE FUNCTION

*Aim:* To investigate to what degree family history of AUD is associated with cognitive deficits, with focus on impulsivity and EF.

*Design:* Case-control cross-sectional study.

*Participants:* AUD patients (n = 106) and healthy controls (HC; n = 90) matched for age and sex. The HC group was further subdivided into AUD family history positive (FH+) or negative (FH-).

*Inclusion and exclusion criteria:* The inclusion and exclusion criteria for the AUD patients are described in detail in the method section for study III and V. For the HC, the main inclusion criteria were age 18-70 and willing and able to leave informed consent to participate in the study. Main exclusion criteria were current or past severe psychiatric disorder (e.g., psychotic disorder, bipolar disorder or suicidal depression) or SUD (except nicotine), current psychoactive medication, any narcotic use the past 12 months, self-reported first-degree relative with severe psychiatric disorder (schizophrenia, bipolar disorder or suicidal depression), severe somatic illness (e.g., cancer, cardiovascular disease or diabetes), history of stroke or traumatic brain injury, traces of narcotic substances in urine or positive alcohol breathalyzer test on test day.

*Clinical instruments:* Sociodemographic information was collected by a locally developed self-report questionnaire. All participants underwent psychiatric evaluation by an M.D. using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (175) for AUD patients and the Swedish DSM-5 version of the Mini-International Neuropsychiatric

Interview (176) for HC. Drinking history for the last 90 days (AUD) and 30 days (HC) were collected by the Time Line Follow Back (TLFB) interview (177). Alcohol craving and depressive symptoms were assessed by the Obsessive Compulsive Drinking Scale (OCDS; (178)) and the Montgomery-Åsberg Depression Self Rating Scale (MADRS-S; (179)), respectively. Presence of AUD family history in the HC group was assessed by a Swedish translation of the Family Tree Questionnaire (FTQ; (180)), a self-rating scale where the subject is asked to categorize each blood relative (Grandparents, parents, siblings) as 1) Never drank; 2) Social drinker; 3) Possible problem drinker (a person who you believe or were told might have had an alcohol problem); 4) Definite problem drinker (only for persons who either are known to have received treatment for an alcohol problem or who have experienced several alcohol-related consequences) or 5) Don't know/don't remember. In the main analysis, subjects were classified as FH+ if they had responded option 3 or 4 to any biological relative, and otherwise they were classified as FH-. In a sensitivity analysis, the definition of FH+ was restricted to only include subjects who responded option 4 to any biological relative.

*Cognitive assessment:* All neuropsychological tests were administered by trained research staff in a silent test room at the research clinic. Participants were told that they could drink coffee and use nicotine before, but not after the start of the test session. All cognitive tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB®) were performed on a touch screen tablet PC (MOTION model J3500-i7B) and a press pad provided by Cambridge Cognition Ltd. See www.camcog.com and the attached scientific publications for full description of the different CANTAB® tasks and outcomes.

The BIS, translated into Swedish, was used to assess self-rated overall impulsive behavior. The questionnaire consists of 30 statements describing impulsive behaviors/thoughts in different situations. The subject rates each item on a 4-point scale ranging from 1 (rarely/never) to 4 (almost always/always) and all item scores are added to a total score. The BIS can also be further subdivided into three subscales: Motor, attentional and non-planning impulsivity.

Stop Signal Task (SST) is a widely used task of response inhibition, i.e. the ability to inhibit a prepotent response (181), with the main outcomes stop signal reaction time (SSRT), proportions of successful stops and standard deviation of response time on go trials. Cambridge Gambling Task (CGT) was used to assess risk taking in decision making (182), with the main outcomes risk taking, overall proportion bet and deliberation time. Stockings of Cambridge (SOC) is a task of future planning and problem solving (74), with main outcomes being the number of problems solved in minimum moves and mean moves performed for the most difficult problems (5-move-problems). Information Sampling Task (IST) is a task of 'reflection impulsivity', i.e., the propensity to collect and evaluate information before making a decision (183), with the outcomes number of boxes opened per trial, mean probability of correct decision ($P_{correct}$) given the sampled information and total correct trials. Rapid Visual

Processing task (RVP) is a task of maintaining attention over prolonged time (184), with main outcomes probability of hit, false alarm and mean latency. Attention Switching Task (AST) assesses both attention and mental flexibility, with the main outcomes percent correct trials and reaction latency. Working memory was assessed by the Spatial Working Memory task (SWM) (74), with outcomes total errors and strategy, and the Digit span task, with outcomes total score and backward score, from the Weschler Adult Intelligence Scale-IV (Swedish version, 2010, Pearson assessment). The Emotion Recognition Task (ERT) assesses capability to recognize emotions expressed in facial expressions, with main outcomes percentage correct responses and mean response latency.

*Statistical analysis:* Sociodemographic variables, clinical outcomes and neuropsychological test outcomes were compared between AUD patients and HC using Student's t-test, Mann-Whitney U test and Chi-square goodness of fit for continuous, ordinal and categorical outcomes, respectively. In the FH analyses, one-way analysis of variance (ANOVA) analyses with group (AUD/FH+/FH-) as independent variable and the neuropsychological test outcome as dependent variable were performed. Only subjects who completed each assessment in full was included in analysis, no missing data was imputed. Effect sizes were reported as Cohen's d, i.e., mean difference between groups divided by the pooled standard deviation (185). Given the exploratory nature of the study, the alpha level was set at 0.05, two-tailed, uncorrected. The statistical analyses were performed using IBM SPSS statistics (version 24.0, SPSS Inc., Chicago, Illinois).

## 4.3 STUDY III: THE EFFECTS OF THE MONOAMINE STABILIZER (-)-OSU6162 ON CRAVING IN ALCOHOL DEPENDENT INDIVIDUALS: A HUMAN LABORATORY STUDY

*Aim:* To investigate the effect of the monoamine stabilizer OSU on craving in AUD, and to what degree baseline impulsivity can predict treatment outcome.

*Design:* Double-blind, placebo-controlled study of 14 days of treatment with OSU or matched placebo tablets in AUD patients.

*Participants:* Treatment seeking patients with AUD (n = 56) who were recruited through public advertisements in local media.

*Inclusion and exclusion criteria:* The main inclusion criteria to participate in the study were fulfillment of DSM-IV criteria for alcohol dependence, 20-55 years old, at least 45 heavy drinking days (5/4 standard drinks of 12 g alcohol for men/women) within the last 90 days as assessed by the TLFB, minimum four and maximum 14 days of sobriety before inclusion. Main exclusion criteria were fulfilment of DSM criteria of any severe psychiatric disorder, severe somatic illness, history of heart disease, clinically significant electrocardiogram abnormality, current use of any psychoactive medication, clinically significant alcohol withdrawal on inclusion day, previous withdrawal-induced seizures or delirium tremens, use

of any narcotic substance the last 30 days or traces of any such substance on day of inclusion.

*Study medication:* Medication (OSU and matched placebo tablets) was produced by Galenica AB (Malmö, Sweden). The dosing regimen was adapted from previous studies (150,186) with the aim of minimizing the risk of intolerable side effects: Day 1-5: 10 mg x 2; Day 6-10: 15 mg x 2; Day 11 – 14: 30 mg x 2. The randomization was done by Karolinska Trial Alliance and Galenica AB, without the involvement of any of the research staff, with each study participant inclusion number being allocated to either placebo or active treatment (1:1).

*Procedure:* After a telephone interview, potential participants were invited to a screening visit where they underwent physical examination, psychiatric evaluation using SCID-I, TLFB interview, blood samples, breathalyzer, urine dip test and electrocardiogram (Mortara Instrument ELI150c). This was followed by the inclusion visit, where subjects underwent cognitive testing (as described in study II) including SST, and received the first dose of allocated study medication. During the treatment period, the subject came for three follow-up visits including electrocardiogram, blood and urine sample, medication dispensing, report of drinking (TLFB), mood (MADRS-S) and report of any adverse events. On the final test day, participants arrived in the morning and received the final dose of study medication, underwent an alcohol craving experiment (see next paragraph), and were offered referral for continued AUD treatment.

*Alcohol craving experiment:* The alcohol craving experiment was adapted from Hammarberg and colleagues (187), and consisted of three sessions. The first and second sessions (randomized order and counter-balanced within treatment groups) were either alcohol cue or neutral cue sessions. In the alcohol cue session, participants were presented with a tray with different alcohol beverages (beer, wine, liquor), a two-minute movie depicting people enjoying alcohol in social situations and were asked to open and pour their preferred drink in a glass and smell the content. In the neutral cue session, the participants instead were presented with a pitcher of water, watched a two-minute video of nature footage, and were asked to pour themselves a glass of water and smell the content. Finally, in the third priming session the participant was given a fixed dose of alcohol (0.20 g ethanol/kg bodyweight) of their preferred beverage type. They were then instructed to take a "first sip" of their alcoholic beverage and then asked to finish the drink at their preferred pace (up to maximum 20 minutes).

For each session, subjective ratings of craving were collected before, immediately after cue/finishing of drink, and then at specific time points 5 min, 10 min, and only for the priming session also 25 and 40 min after finishing the alcoholic drink. Craving was assessed by two types of questionnaires at each time point. The shortened Swedish version of the Desire for Alcohol Questionnaire (Short-DAQ) (188,189), consisting of eight statements (e.g., "To drink alcohol right now would be satisfying") to which the participant rated using a seven-point Likert scale to what extend he or she agreed (1 = "Do not agree at all" and 7 =

"Fully agree"). A Visual Analog Scale (VAS) ranging from 0 to 100 asking the question "How much craving for alcohol do you experience right now?" was also administered at each time point. Finally, to capture the immediate subjective effects after the first sip of alcohol, VAS items for "liking", "anxiety" and "arousal" were also administered directly after the first sip in the priming session.

*Statistical analysis:* For the alcohol cue and priming-induced craving experiment outcomes, mixed ANOVA with treatment as between-subject factor and condition (active, neutral) and time (pre, immediately after, post cue/drink) as within-subject factor was performed. Based on previous studies which had found a moderating effect of baseline performance on the SST, we repeated the main analysis but with participants classified as high or low impulsive based on the median split of the SSRT outcome at baseline. Independent Student's t-tests were used to evaluate VAS items post sip, and to evaluate change scores (change from baseline to test day) in alcohol consumption, self-reported craving and mood. Given the exploratory nature of this first study to evaluate a novel pharmacological compound in AUD patients, the alpha level was set to 0.05, two-tailed, uncorrected. No missing data was imputed, and the data was analyzed using IBM SPSS statistics (version 21.0, SPSS Inc., Chicago, Illinois)

## 4.4 STUDY IV: EFFECTS OF THE MONOAMINE STABILIZER (-)OSU6162 ON COGNITIVE FUNCTION IN ALCOHOL DEPENDENCE

Study IV was a second publication from the same clinical trial described in study III. For design, participants, inclusion/exclusion criteria and study medication see previous paragraph.

*Aim:* To investigate the effect of the monoamine stabilizer OSU on cognitive function in AUD.

*Cognitive assessment:* At the inclusion visit, prior to receiving the first dose of study medication, all participants underwent the cognitive assessment previously described in the methods section of study II.

At test day after 14 days treatment, the subjects returned to the clinic and repeated the cognitive test battery, and also performed two additional cognitive tests: The Intra-Extra Dimensional Set Shift (IED) is a task of cognitive flexibility involving rule acquisition and adaptation of behavior. Main IED outcomes were numbers of extra-dimensional stage errors, pre-extra dimensional errors, stages completed and total response latency. In addition, based on previous studies suggesting an association between D2 receptors and divergent thinking (190), the Berliner Intelligenz Struktur Test (191) was administered on the test day only. It consists of one figural and verbal test. In the verbal test, the participant is presented with an object (e.g., 'brick') and asked to write down different uses of that object, while in the figural test the participant is asked to complete a simple line drawing to create pictures of as many different real objects as possible. The test was corrected by a research colleague (blinded to

treatment allocation), using the test instructions which provided predefined categories for a wide range of responses. The final outcome used is the number of different categories written/drawn by the participant. Given the short treatment period and risk of practice effects, both of these tests were only administered on the final test day.

*Statistical analysis:* The cognitive test outcomes were analyzed using mixed ANOVA with treatment (OSU and placebo) as between-subject factor and time (baseline and test day) as within-subject factor. One-way ANOVA was used for the cognitive tests only administered one time at the final test day. Effect sizes were reported as Cohen's d (185). Given the exploratory nature of the study, and the importance to detect both potential improvements and negative effects on cognitive function, the alpha level was set to 0.05, two-tailed, uncorrected. All statistical analyses were performed using IBM SPSS statistics (version 21.0, SPSS Inc., Chicago, Illinois).

## 4.5 STUDY V: WORKING MEMORY TRAINING IN ALCOHOL USE DISORDER: A RANDOMIZED CONTROLLED TRIAL

*Aim:* To investigate the effect of computerized working memory training on drinking, working memory and transfer effects to other cognitive functions in AUD.

*Design:* Double-blind randomized controlled trial of five weeks treatment with computerized working memory training or control training in AUD patients.

*Participants:* Treatment seeking patients with AUD (n = 50) who were recruited through public advertisements in local media.

*Inclusion and exclusion criteria:* The main inclusion criteria were: 18 – 60 years old, minimum 9 years of education, fulfilling DSM-IV criteria for alcohol dependence, minimum 4 and maximum 14 days of sobriety before study inclusion and having full access to a home computer with internet connection. Main exclusion criteria were presence of any other DSM-IV dependence or abuse diagnosis besides alcohol (except nicotine) or any other severe major psychiatric disorder (e.g., psychotic disorders, bipolar disorder), severe somatic illness, history of stroke, intracranial hemorrhage or head trauma, current regular intake of psychotropic medication the last three months (with the exception of on-going stable treatment with serotonin reuptake inhibitors for depression or anxiety in remission), alcohol withdrawal in need of pharmacological treatment, previous withdrawal-induced delirium tremens or seizures, use of any narcotic substance within the last 30 days or positive urine sample for any narcotic substance on inclusion or during the course of the study.

*Cognitive working memory training intervention:* The study intervention was the computerized working memory training software Cogmed® research version, which has been utilized in several previous studies of different patient populations (158,165). The program consists of 12 different exercises of visuospatial and verbal working memory, and for each

training session the participant performs eight of these exercises, which in different ways ask the participant to perform working memory tasks (e.g., remember sequences of numbers or letters). In the active treatment group, the training was adaptive, meaning that the tasks became progressively more difficult as the participant completed the tasks. In contrast, in the control condition, the same exercises were performed but they were non-adaptive i.e., the tasks did not increase in difficulty and asked the subject to only remember maximally two to three items.

*Procedure:* After an initial telephone interview, participants were invited to a screening visit with a study physician for psychiatric and somatic assessment to ensure fulfillment of inclusion criteria. At inclusion, each participant was randomized (1:1 allocation) to a unique login number and password associated with either active training or control training, but neither the research staff or participant knew which treatment they had been allocated to. The randomization list was prepared by Karolinska Trial Alliance together with Cogmed® without the involvement of the research staff. The participants were asked to perform five training sessions per week (each session takes approximately 30-40 minutes) during the five-week study. They were also informed that they would receive 50 Swedish crowns (5.75 USD) for each completed training session as an incentive to perform the training. At inclusion, each participant underwent cognitive assessment (See Study II), and returned weekly to the clinic to report drinking, craving and mood and after five weeks the study ended with a final test-day where the cognitive assessment was repeated. After study completion, all participants were offered referral to continued treatment within Stockholm Centre for Dependency Disorders.

*Outcomes:* Drinking outcomes was quantified by the TLFB interview at every visit. OCDS was used to assess craving at baseline, while short-DAQ was used as a craving outcome during the weekly visits. Mood was assessed by the MADRS-S. The cognitive test battery and outcomes are described in detail in the Study II methods section. In the current study, participants also performed the Kirby Monetary Choice Questionnaire (77,192) which consists of 27 items consisting of offers of either a smaller immediate or a larger delayed money sum – and the participant is asked to choose which option he or she would choose given such an offer. Based on the responses on the different items, a discount rate (k value; range 0.00016 – 0.25) is calculated for each subject in total and for different types of rewards (small, medium, large). The k value represents the rate at which future rewards are deemed less valuable – with a high k indicating a greater tendency toward smaller immediate rewards.

*Statistical analysis:* Similar statistical analyses were performed as described in study III and IV. In brief, for the main outcomes of working memory, drinking and cognitive function mixed ANOVA with treatment (active or control training) as between-subject factor and time (pre and post treatment) as within-subject factor was utilized. In the per-protocol (PP) analysis only participants who completed the study (i.e., performed >20 training sessions and completed the test day) were included. In the intention-to-treat (ITT) analysis all participants,

including drop-outs, were included. Since both analyses yielded similar results, only the PP analysis is reported.

## 4.6 ETHICAL ASPECTS

There are several potential ethical issues related to the studies included in the current thesis in need of discussion. The overall ethical issue is the potential conflict between the risks and rights of the individual participant on the one hand, and the putative value of the potential knowledge that may be gained by the research study results. Four specific examples of this conflict will be discussed more in detail:

First, study participation, for both patients and healthy volunteers, involves activities that are time-consuming (cognitive testing, filling out questionnaires), potentially painful/stressful (blood sampling, urine sample) and intrusive (reporting sensitive personal information). However, the best way to minimize such discomfort in study participants is to perform research in accordance with GCP and the Helsinki Declaration (193), which clearly emphasizes the individual research participant's right to make an informed decision regarding study participating, and that the welfare of the research participant always takes precedence over other higher-order values such as the scientific knowledge gained by the study.

To minimize risks of harming study participants, the clinical studies were externally monitored by Karolinska Trial Alliance who assured that the study was indeed performed in accordance with GCP, such as correct documentation, data collecting and informed consent procedure. Furthermore, all healthcare research staff involved in the studies had undergone GCP education, and a research physician provided both orally and written detailed information to each participant before collecting the informed consent to participate in the research studies.

Second, when evaluating pharmacological agents, especially off-label therapeutics not yet approved by regulatory authorities, the participants are exposed to the additional risks of experiencing unexpected potentially dangerous side effects. In order to minimize the risk of such unintended harms, the study dosage used (60 mg) was well below the maximally tolerated dose of 150 mg found in healthy volunteer dosing studies (149). Furthermore, careful systematic evaluation of any adverse events at every visit, and electrocardiogram and blood samples for safety were performed during and at the end of the study.

Third, AUD patients in study III underwent an alcohol cue- and priming-induced craving experiment in which they were exposed to alcoholic cues and beverages, and asked to consume a standardized drink of alcohol while rating their subjective experience. The potential risk here was that participants would be exposed to the actual negative outcome, i.e., alcoholic drinks, which could be thought of as directly harming the participant and may cause stress or discomfort or lead to relapse. However, previous studies have found that taking part in craving experiments do not increase subsequent substance use (194). This is also in line

with the experience from previous similar research studies in our own research group (187) suggesting that the craving reaction subsidies completely after the experiment session. Several steps were also taken to minimize the risk of any adverse events for the AUD patients in the study: Each participant was clearly informed about this procedure before study inclusion and reminded again on the day of testing. Furthermore, the patients were explicitly instructed that they could abort the experiment whenever they wanted to if they for any reason did not want to complete the procedure. In addition, each participant stayed in the clinic until complete sobriety was confirmed by breathalyzer test, and received a clinical evaluation by a research physician to ensure that he or she was mentally stable before leaving. Finally, the participants came back within a few days for an additional follow-up visit to minimize risk of relapse.

Fourth, all patients that participated in the clinical treatment studies were treatment-seeking and wanted to reduce or quit drinking. By participating in research studies, including potential allocation to control treatment conditions, the participants did not receive evidence based psychopharmacological and/or psychosocial treatment. This was however clearly stated to each participant prior to study inclusion. Furthermore, it is well known that participants in treatment studies reduce their drinking, even when being allocated to placebo (195), and this was evident also in our two treatment studies where a significant main effect of time was found for drinking outcomes, irrespective of treatment allocation. Finally, many of the participants had never ever been in AUD treatment before, and the study participation rather became a way of entry to evidence-based treatment since all participants were offered referral to continued evidence-based treatment within the Stockholm Centre for Dependency Disorders after study completion.

In summary, we identified several ethical issues related to the scientific studies in the current thesis. By adherence to GCP and the declaration of Helsinki, with specific focus on the informed consent procedure and the well-being of the individual participant, several of the potential risks of participation were minimized. Furthermore, the benefits of study participation (e.g., reduced drinking, referral to continued treatment) likely outweighed the risks for each of the included participants.

# 5 RESULTS

The results section comprises a summary of the most important results in each of the studies.

## 5.1 STUDY I

The total study cohort consisted of 3,004,401 individuals born between 1951 and 1998. There were 418,831 individuals who had a father with SUD (of which 45% had AUD) and 129,374 had a mother with SUD (of which 60% had AUD). In the full population analysis, a robust negative association between parental SUD and cognitive function was found for both conscription test score (-0.54 [-0.55 - -0.53]) ) and school grades (-0.48 [-0.48 - -0.47]). Similar effects were found specifically for parental AUD, as illustrated in Table 2. These estimates were reduced, but remained negative and statistically significant, when adjusting for additional covariates. As shown in Figure 1, having two parents with SUD was associated with even lower cognitive outcome compared to only having one parent with SUD, suggestive of a dose-response relationship.

In the children-of-siblings analyses, the overall trend was that the association between parental SUD and cognitive ability was gradually reduced in the models with increasing adjustment of genetic confounding factors (Table 3 presents the results for grades). Even though the overall pattern was similar for maternal and paternal SUD, it is notable that in the offspring of MZ-twins, all coefficients were not significantly different from zero, with the sole exception of maternal SUD and cognitive test score at conscription where a negative association was observed (Population: -0.54 [-0.56 - -0.52]; Sons of MZ-twins: -0.95 [-1.76 - -0.13]). The sensitivity analyses however did not find any evidence of any sex difference in the grade data (similar negative regression coefficients in both boys and girls for maternal and paternal SUD), and were otherwise in line with the overall results from the main analyses.

**Table 2.** Population regression analyses: Parental alcohol use disorder (AUD) as a predictor of cognitive test score at conscription (A) and primary school grades (B). Values presented are unstandardized regression coefficients and 95% confidence intervals within the brackets. Standard errors were adjusted for the clustering of siblings.

| **A. Cognitive test score** | | | | |
|---|---|---|---|---|
| Full sample (n) | AUD in any parent | AUD in father | AUD in mother | Number of parents with AUD |
| Model 1[a] (n = 1,215,690) | -0.54 [-0.55 ; -0.53] | -0.54 [-0.55 ; -0.52] | -0.55 [-0.57 ; -0.53] | 1. -0.52 [-0.53 ; -0.50]<br>2. -0.93 [-0.98 ; -0.88] |
| Model 2[b] (n = 1,202,017) | -0.32 [-0.33 ; -0.31] | -0.31 [-0.32 ; -0.29] | -0.24 [-0.27 ; -0.22] | 1. -0.31 [-0.32 ; -0.29]<br>2. -0.50 [-0.55 ; -0.45] |
| Model 3[c] (n = 1,202,017) | -0.31 [-0.32 ; -0.29] | -0.29 [-0.31 ; -0.28] | -0.23 [-0.26 ; -0.21] | 1. -0.30 [-0.31 ; -0.28]<br>2. -0.47 [-0.52 ; -0.43] |
| **B. Grades** | | | | |
| Full sample (n) | AUD in any parent | AUD in father | AUD in mother | Number of parents with AUD |
| Model 1[a] (n = 2,517,030) | -0.48 [-0.49 ; -0.47] | -0.47 [-0.47 ; -0.46] | -0.53 [-0.54 ; -0.52] | 1. -0.46 [-0.47 ; -0.45]<br>2. -0.82 [-0.85 ; -0.80] |
| Model 2[b] (n = 2,499,592) | -0.28 [-0.28 ; -0.27] | -0.25 [-0.26 ; -0.25] | -0.23 [-0.24 ; -0.22] | 1. -0.27 [-0.27 ; -0.26]<br>2. -0.44 [-0.46 ; -0.42] |
| Model 3[c] (n = 2,499,592) | -0.27 [-0.28 ; -0.27] | -0.25 [-0.25 ; -0.24] | -0.22 [-0.23 ; -0.21] | 1. -0.26 [-0.27 ; -0.26]<br>2. -0.42 [-0.45 ; -0.40] |

**Figure 1**. Cognitive test score at conscription (A) and final primary school grades (B) in individuals grouped by number of parents with substance use disorder (SUD). Values are presented as mean ± 95% confidence intervals. ***p<0.001.

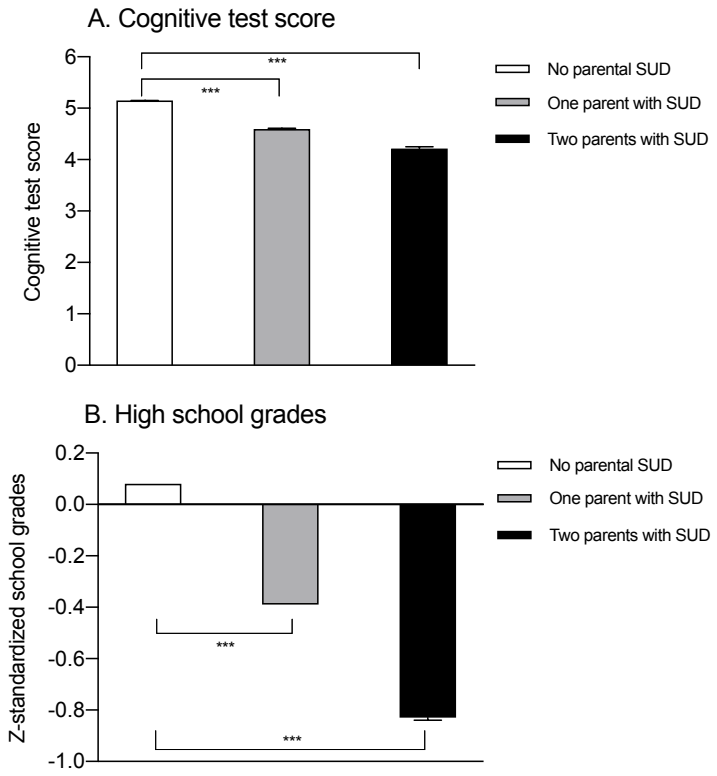



**Table 3.** Children-of-siblings analysis: Maternal (A) and paternal (B) substance use disorder (SUD) as a predictor of offspring's final primary school grade in the full population (linear regression) and the within-family-models with increasing genetic similarity in offspring (fixed-effects regression).

| A. Maternal SUD | | Within-Family-models | | |
|---|---|---|---|---|
| | Full population<br>N = 2,517,030 | Children of half siblings<br>N = 60,816 | Children of full siblings<br>N = 387,988 | Children of MZ-twins<br>N = 2,736 |
| Model 1[a] | -0.55 [-0.56 ; -0.54] | -0.35 [-0.40 ; -0.31] | -0.31 [-0.33 ; -0.28] | -0.16 [-0.52 ; 0.21] |
| Model 2[b] | -0.27 [-0.27 ; -0.26] | -0.17 [-0.22 ; -0.13] | -0.19 [-0.21 ; -0.16] | -0.11 [-0.49 ; 0.27] |
| Model 3[c] | -0.26 [-0.27 ; -0.25] | -0.17 [-0.21 ; -0.12] | -0.18 [-0.20 ; -0.16] | -0.14 [-0.51 ; 0.24] |
| B. Paternal SUD | | Within-Family Models | | |
| | Full population<br>N = 2,517,030 | Children of half siblings<br>N = 52,670 | Children of full siblings<br>N = 384,604 | Children of MZ-twins<br>N = 1,956 |
| Model 1[a] | -0.47 [-0.47 ; -0.46] | -0.36 [-0.39 ; -0.33] | -0.27 [-0.28 ; -0.25] | -0.06 [-0.28 ; 0.16] |
| Model 2[b] | -0.28 [-0.28 ; -0.28] | -0.23 [-0.26 ; -0.20] | -0.19 [-0.21 ; -0.18] | 0.02 [-0.19 ; 0.23] |
| Model 3[c] | -0.27 [-0.28 ; -0.27] | -0.22 [-0.25 ; -0.19] | -0.19 [-0.20 ; -0.17] | 0.02 [-0.19 ; 0.24] |

## 5.2 STUDY II

The AUD patients and HC were well matched and did not differ in sociodemographic variables such as age, sex or education. In fact, the HC group had a significantly lower income level than the AUD patients, and as expected had lower levels of drinking, craving, nicotine use and depressive symptoms (Table 4).

**Table 4.** Sociodemographic and clinical background variables in patients with alcohol use disorder (AUD) and healthy controls. Values are presented as percentages or mean (standard deviation).
Abbreviations: MADRS-S - Montgomery-Åsberg Depression Self Rating Scale; TLFB – Time Line Follow Back; OCDS – Obsessive Compulsive Drinking Scale; N.S. – not statistically significant (p>0.05).

| | AUD patients (n = 106) | Healthy controls (n = 90) | Statistical significance |
|---|---|---|---|
| Males | 51.9 % | 43.3 % | N.S. |
| Age | 47.9 (7.5) | 48.1 (11.8) | N.S. |
| Education level | | | N.S. |
| - Did not finish primary school | 0.0 % | 1.1 % | |
| - Primary | 17.0 % | 4.5 % | |
| - Secondary | 34.0 % | 46.1 % | |
| - University | 49.1 % | 48.3 % | |
| Income | | | p = 0.004 |
| - Low | 18.1 % | 33.7 % | |
| - Medium | 48.6 % | 43.8 % | |
| - High | 33.3 % | 22.5 % | |
| DSM-IV criteria for alcohol dependence | 5.1 (1.2) | 0 (0) | p < 0.001 |
| Age when alcohol use became a problem | 34.1 (10.6) | - | - |
| Number of years with current levels of drinking | 7.7 (6.6) | - | - |
| TLFB % drinking days | 72 % (20.7) | 13.6 % (12.4) | p < 0.001 |
| TLFB % heavy drinking days | 62 % (26.8) | 0.9 (3.0) | p < 0.001 |
| TLFB drinks per drinking day | 7.3 (3.4) | 2.4 (1.6) | p < 0.001 |
| OCDS score | 23.8 (6.5) | 2.1 (2.5) | p < 0.001 |
| Daily nicotine use | 58.1 % | 11.2 % | p < 0.001 |
| MADRS-S score | 7.5 (6.4) | 3.0 (3.3) | p < 0.001 |

In the comparison between AUD patients and HC irrespective of family history status, AUD patients exhibited higher levels of self-rated impulsivity on the BIS total score ($t(178)=4.1$; $p<0.001$) including all the subscales of attention ($t(178)=4.7$; $p<0.001$), motor ($t(178)=2.9$; $p=0.005$) and non-planning ($t(178)=2.8$; $p=0.005$). In the SST task of response inhibition, the AUD patients had greater SSRT ($t(191)=3.4$; $p=0.001$) and response time standard deviation ($t(191)=2.4$; $p=0.016$) compared to HC. Finally, AUD patients performed worse on the RVP attention task with lower probability of hit ($t(185)=-2.3$; $p=0.021$), and a trend was observed suggesting less information gathering in the IST task manifested as lower correct responses ($t(171)=-1.8$; $p=0.073$) and less opened boxes ($F(1,171)=3.4$; $p=0.065$).

In the family history analysis, four subjects in the HC group were excluded because of missing data on FTQ (n=2) or responding '5' (Don't know/don't remember') on all relatives (n=2). Of the remaining 86 HC, 39 and 47 subjects were classified as FH- and FH+, respectively. There was a statistically significant main effect of group on BIS total score ($F(2,177)=10.5$; $p<0.001$), with lowest scores in FH- (53.6±6.7) followed by FH+ (57.3±9.2) and AUD patients (62.0±11.0). Post hoc tests of the total score found that AUD patients scored significantly higher than both FH groups ($p<0.01$) while a trend was observed suggesting higher scores in FH+ compared to FH- ($p=0.096$). Figure 2A and 2B illustrate the BIS score including all subscales. On the SST SSRT there was also a statistically significant main effect of group ($F(2,188)=5.8$; $p=0.003$), but the post hoc comparisons suggested no difference between FH+ and FH- ($p=0.727$), while AUD patients had significantly greater SSRT than both FH groups (Figure 2C). In addition, a statistically significant main effect of group was also found for the SOC task of future planning for both mean moves ($F(2,181)=7.7$; $p=0.001$) and number of problems solved in minimum moves ($F(2,181)=3.7$; $p=0.027$) for the most difficult problems (i.e., 5-move-problems), where the FH+ and AUD patients performed similarly and significantly worse than the FH- group (Figure 3). Similar effects of FH were found for ERT response latency, but not for percentage correct responses (Figure 4).

In the sensitivity analysis a stricter definition of FH+ was employed (at least one blood relative rated as 4 on the FTQ, i.e., definite problem drinker), resulting in 28 FH+ and 58 FH- subjects. The sensitivity analysis found similar effect of family history status for BIS, SSRT and SOC task outcomes, while the main effect of group on ERT response latency disappeared and was no longer statistically significant.

**Figure 2.** Barratt Impulsiveness Scale (BIS) total score (A), BIS subscales (B) and Stop Signal Reaction Time (C) in patients with alcohol use disorder (AUD), healthy volunteers with AUD family history (FH+) and without family history (FH-). Error bars indicate standard error of the mean.

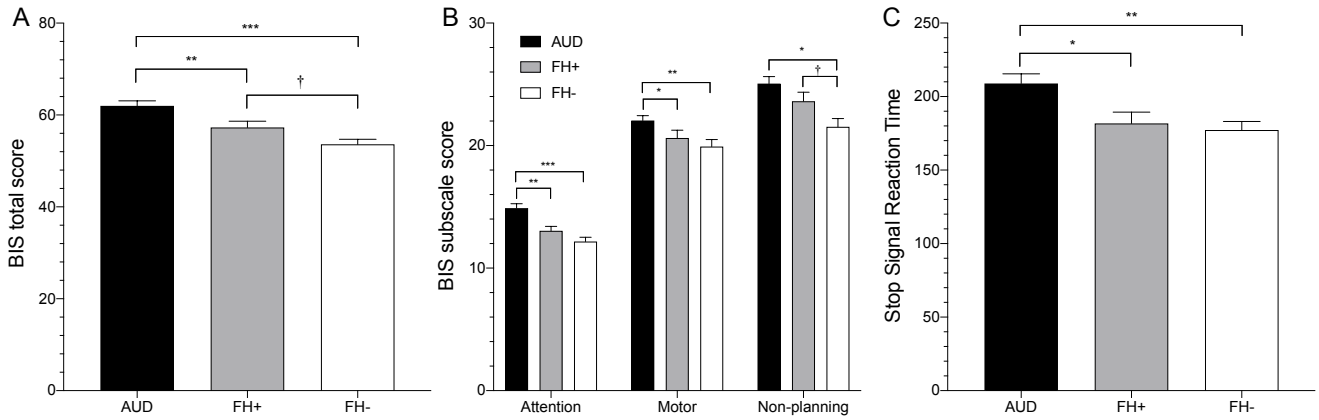


**Figure 3.** Stocking of Cambridge (SOC) mean moves (A) and number of problems solved (B) for the most difficult five-move-problems in patients with alcohol use disorder (AUD), healthy volunteers with AUD family history (FH+) and without family history (FH-). Error bars indicate standard error of the mean.

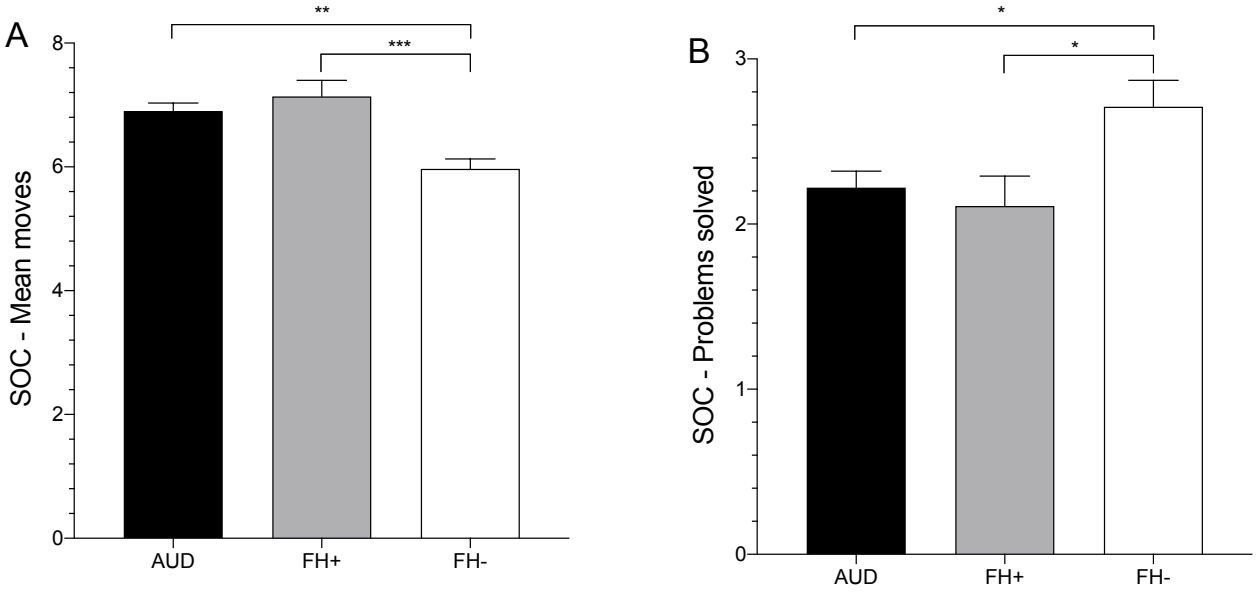
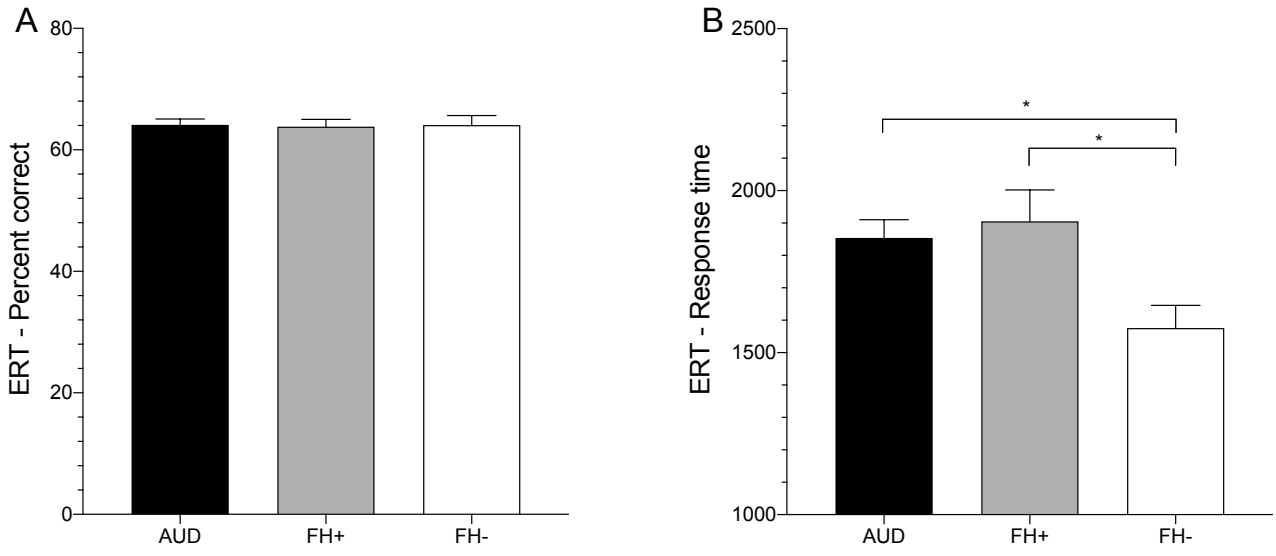



**Figure 4.** Emotional Recognition task percent correct (A) and mean response time (B) in patients with alcohol use disorder (AUD), healthy volunteers with AUD family history (FH+) and without family history (FH-). Error bars indicate standard error of the mean.



## 5.3 STUDY III

There were no statistically significant differences between the OSU and placebo group regarding sociodemographic or clinical baseline variables (Table 5).

In the cue-induced craving experiment, there were no statistically significant difference between treatment groups for the short-DAQ craving outcome, neither as a main effect of treatment ($F(1,45)=2.1$; $p=0.154$)) or treatment*condition interaction ($F(1,45)=1.3$; $p=0.262$). In the priming-induced craving session, the participants took on average 9 minutes to finish their standardized drink (range 3 – 18 minutes), but no statistically significant difference between treatment groups ($t(42)=-0.09$; $p=0.927$). There was a significant main effect of time ($F(1.5, 63.6)=13.7$; $p<0.001$) and treatment ($F(1,43)=4.1$; $p=0.050$) but no significant time*treatment interaction ($F(1.5, 63.6)=1.4$; $p=0.255$). Post hoc analyses found that the OSU group reported lower craving immediately after finishing the drink but no difference before or post drink (Figure 5). After the first sip of alcohol, the OSU group reported significantly lower liking ($t(31)=-2.27$; $p=0.031$) and a trend toward significance was seen for craving ($t(46)=-1.88$; $p=0.066$) but no significant effect regarding anxiety ($t(46)=-0.24$; $p=0.814$) or arousal ($t(46)=-1.29$; $p=0.205$; Figure 5C). Both treatment groups had a significant decrease in heavy drinking days (OSU: -55%; Placebo: -58%) but there were was no statistically significant difference between treatment group ($t(46.4)=-0.45$; $p=0.658$). Similarly, no statistically significant effect of treatment was observed for self-reported craving or mood during the trial.

In a subgroup analysis, the effect of baseline impulsivity operationalized as performance on the SST task of response inhibition (median split of SSRT at baseline) on OSU treatment response was investigated. In patients with high impulsivity, there was a significant main effect of treatment ($F(1,20)=9.8$; $p=0.005$) and time ($F(1.3, 26.0)=8.8$; $p=0.004$), but no significant treatment*time interaction ($F(1.3, 26.0)=2.5$; $p=0.116$) in the priming induced craving session. Post hoc analyses found that the high impulsive OSU group reported significantly lower craving than the placebo group at all measured time points, including the VAS craving item after the first sip of alcohol (Figure 6A). In contrast, the AUD patients with low baseline impulsivity (lower SSRT score) exhibited no main effect of treatment ($F(1,21)=0.12$; $p=0.731$) or treatment*time interaction ($F(2,42)=0.428$; $p=0.639$), and no difference in the VAS craving item post first sip of alcohol (Figure 6B).

**Table 5**. Participant characteristics at inclusion. There were no significant differences between the OSU6162- or placebo-treated groups for any of the outcomes. Continuous variables are presented as mean (standard deviation). Abbreviations: MADRS-S - Montgomery-Åsberg Depression Self Rating Scale; PACS - Penn Alcohol Craving Scale. N.S. – not statistically significant (p>0.05).

| | OSU6162 (n=28) | PLACEBO (n=28) | Significance |
|---|---|---|---|
| Males / Females | 14 / 14 | 16/12 | N.S. |
| Age | 47.3 (6.5) | 45.3 (7.7) | N.S. |
| Education years | 13.3 (2.5) | 14.1 (2.8) | N.S. |
| Married / Partner | 54 % | 54 % | N.S. |
| Full time employment | 78.6 % | 71.4 % | N.S. |
| Part time employment | 7.1 % | 17.9 % | N.S. |
| Unemployed | 14.3 % | 7.1 % | N.S. |
| Sick leave/retired | 0 % | 3.6 % | N.S. |
| Daily nicotine use (%) | 68 % | 64 % | N.S. |
| DSM-IV criteria for alcohol dependence | 5.2 (1.1) | 5.1 (1.4) | N.S. |
| Heavy drinking last 90 days (%) | 73 % | 68 % | N.S. |
| Drinks per day last 90 days | 5.8 (2.2) | 5.7 (2.4) | N.S. |
| MADRS-S score | 9.2 (6.8) | 7.9 (6.7) | N.S. |
| PACS craving score | 11.1 (6.5) | 10.4 (6.0) | N.S. |

**Figure 5.** Mean total scores on (A) the shortened version of the Desire for Alcohol Questionnaire (Short-DAQ) and (B) VAS craving item during the priming-induced craving session as well as (C) VAS-items of "craving", "liking", "anxiety" and "arousal" after the first sip of alcohol. The OSU6162-treated group rated significantly lower craving (Short-DAQ) immediately after finishing the alcoholic drink compared to the placebo-treated group (A) and there was a trend towards decreased craving in the OSU6162- compared to the placebo-treated group using the VAS at the same time-point (B). The OSU6162 group further rated significantly lower subjective liking, and a trend toward lower craving, after the first sip of alcohol (C). Values are presented as mean ± s.e.m; *p<0.05 compared to corresponding placebo.

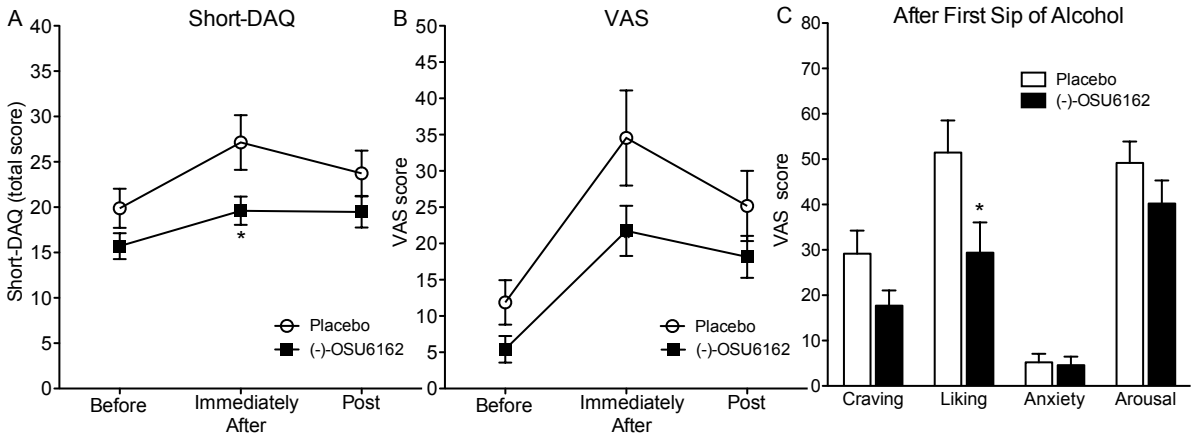
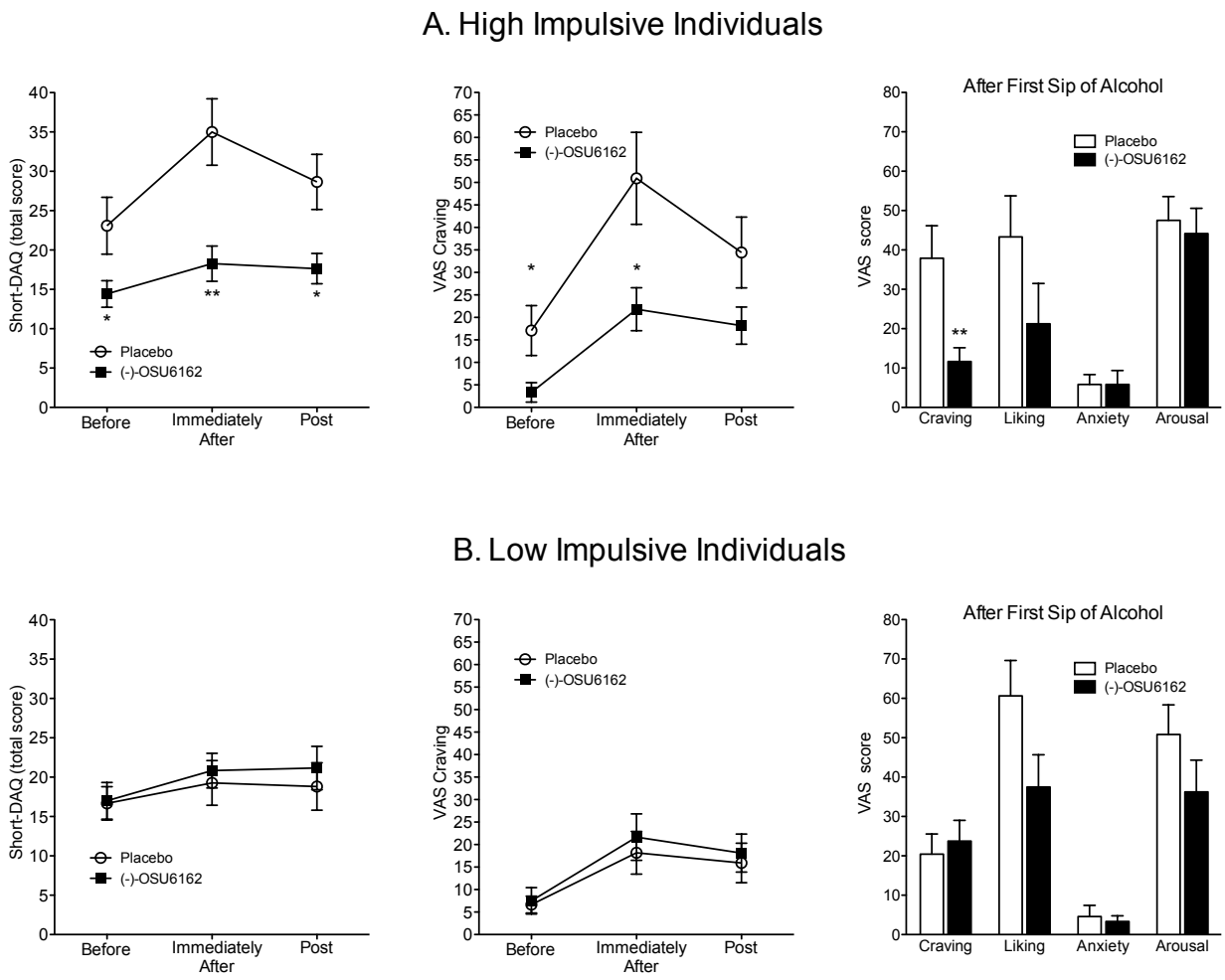


**Figure 6.** Mean craving total score on the shortened version of the Desire for Alcohol Questionnaire (short-DAQ) and VAS craving item in (A) high and (B) low impulsive alcohol dependent individuals during the priming-induced craving session. (A) OSU6162 significantly reduced craving in the high impulsive alcohol dependent individuals compared to placebo during the priming-induced craving session, including craving after the first sip of alcohol (right panel). (B) No significant difference in craving was found at any time-point between the OSU6162- and placebo-treated group in the low impulsive alcohol dependent individuals. Values are presented as mean ± s.e.m; *p<0.05 and **p<0.01 compared to corresponding placebo.




One patient in each treatment group responded yes to the question of subjective 'high'/'rush' when taking the medication ($\chi^2$ (1)=0.0; p=1.0), and there was no statistically significant difference between treatment groups regarding their guessed treatment assignment ($\chi^2$ (1)=0.42; p=0.52). In general, the OSU treatment was well tolerated and no severe adverse events were reported during the study period. Most reported side effects were mild and non-specific (e.g., fatigue, headaches, gastrointestinal symptoms) and there was no statistically significant difference in the frequency of such side effect between the OSU and placebo group.

## 5.4 STUDY IV

There were no statistically significant differences between the OSU and placebo groups at baseline for any of the neuropsychological test outcomes (Table 6).

On the SST main outcome SSRT, there was a statistically significant main effect of time ($F(1,47)=6.7$; $p=0.013$) indicating a general reduction in SSRT from baseline to test day (baseline: 212 ms; test day: 189 ms), but there was no significant main effect of treatment ($F(1,47)=0.0$; $p=0.926$) or treatment*time interaction ($F(1,47)=0.0$; $p=0.840$). No other significant main effects of treatment or treatment*time interactions were found for the other SST outcomes (all $p>0.05$).

In the SOC task most difficult 5-move-problems solved in minimum moves, there was a significant treatment*time interaction ($F(1,46)=0.5$; $p=0.480$) with OSU treated patients solving more problems on test day compared to placebo ($F(1,47)=4.3$; $p=0.043$). In addition the OSU group had a significant improvement across the treatment period, solving more problems at test day compared to baseline ($F(1,23)=13.3$; $p=0.001$) while no difference was found between test day and baseline for the placebo group ($F(1,23) = 0.00$; $p = 1.00$). For mean number of moves on the 5-move-problems, there was a significant main effect of time ($F(1,45) = 7.5$; $p = 0.009$) indicative of a general reduction across test sessions, but no significant main effect of treatment ($F(1,45) = 0.2$; $p = 0.664$) or treatment*time interaction ($F(1,45) = 2.5$; $p = 0.120$).

In the ERT task, there was no significant treatment*time interaction for percentage correct trials ($F(1,47) = 1.8$; $p = 0.187$). There were however for mean response latency a significant treatment*time interaction ($F(1,47) = 6.7$; $p = 0.013$), indicative of a greater reduction in response latency in the OSU group (mean difference: −416 ms; $F(1,23) = 91.5$; $p < 0.001$) compared to the placebo group (mean difference: −242.5 ms; $F(1,24) = 23.5$; $p < 0.001$). Finally, in the verbal divergent thinking task the OSU group generated significantly greater number of semantic categories compared to the placebo group ($F(1,44)=10.1$; $p=0.003$) but no effect was seen on the figural task ($F(1,44)=0.0$; $p=0.862$).

There were significant main effects of time, suggestive of general improvement on test day compared to baseline for the RVP and AST attention tasks, Digit span verbal working memory task and the ERT percentage correct trials outcomes. In contrast, a general worsening on risk taking and willingness to bet was seen overall on the CGT task. No significant treatment*time interactions were found in any of the other neuropsychological task outcomes. See Table 6 for all neuropsychological task outcomes at baseline and test day.

**Table 6.** Behavioral outcomes on tasks of cognitive function in alcohol dependent patients before and after 14 days treatment with OSU6162 or placebo. Effect sizes for between-group differences at test day are reported as Cohen's d. Values are presented as mean (standard deviation) or fractions.
Abbreviations: SST – Stop Signal Task; SSRT – Stop Signal Reaction Time; RT – Reaction Time; IED – Intra-Extra Dimensional Set Shift; RVP – Rapid Visual Processing; AST – Attention Switching Task; SWM – Spatial Working Memory; ERT – Emotion Recognition Task; DTT – Divergent Thinking Task.

| | **OSU6162** | | **Placebo** | | **Sig. Baseline** | **Sig. Test day** | **Effect Size** |
|---|---|---|---|---|---|---|---|
| | Baseline | Test day | Baseline | Test day | | | |
| **SST** | | | | | | | |
| SSRT | 209.1 (51.5) | 189.5 (62.8) | 212.2 (70.3) | 189.2 (52.8) | p=0.863 | p=0.840 | d=0.01 |
| Median go RT | 489.7 (174.5) | 448.3 (173.5) | 421.9 (131.0) | 388.1 (117.4) | p=0.130 | p=0.780 | d=0.41 |
| Proportion successful stops | 0.52 (0.12) | 0.53 (0.10) | 0.49 (0.10) | 0.49 (0.08) | p=0.261 | p=0.707 | d=0.44 |
| **IED** | | | | | | | |
| ED stage errors | | 10.8 (11.7) | | 8.2 (9.2) | | p=0.433 | d=0.25 |
| Pre-ED errors | | 6.7 (2.8) | | 5.6 (2.1) | | p=0.148 | d=0.44 |
| Stages completed | | 8.5 (0.9) | | 8.8 (0.6) | | p=0.280 | d=0.39 |
| Total response latency | | 156699 (36836) | | 156861 (37339) | | p=0.989 | d=0.00 |
| **CGT** | | | | | | | |
| Overall proportion bet | 0.57 (0.1) | 0.59 (0.1) | 0.51 (0.1) | 0.55 (0.1) | p=0.072 | p=0.537 | d=0.40 |
| Deliberation time | 2254.8 (630.7) | 1847.6 (464.1) | 2257.7 (630.3) | 1855.0 (436.5) | p=0.998 | p=0.970 | d=0.02 |
| Risk adjustment | 1.5 (0.6) | 1.5 (0.6) | 1.7 (0.9) | 1.7 (0.9) | p=0.469 | p=0.686 | d=0.26 |
| Risk taking | 0.61 (0.1) | 0.64 (0.1) | 0.55 (0.1) | 0.60 (0.1) | p=0.081 | p=0.511 | d=0.40 |
| **SOC** | | | | | | | |
| 5 move problems solved in minimum moves | 2.2 (1.0) | 3.0 (1.0) | 2.4 (1.0) | 2.4 (1.2) | p=0.473 | p=0.012 | d =0.54 |
| 5 move problems mean moves | 7.0 (1.4) | 5.9 (1.2) | 6.5 (1.1) | 6.2 (1.1) | p=0.193 | p=0.120 | d =0.26 |
| **RVP** | | | | | | | |
| Probability of hit | 0.59 (0.2) | 0.65 (0.2) | 0.60 (0.2) | 0.73 (0.2) | p=0.852 | p=0.400 | d =0.40 |
| Probability of false alarm | 0.0046 (0.006) | 0.0054 (0.006) | 0.0044 (0.004) | 0.0031 (0.004) | p=0875 | p=0.214 | d =0.45 |
| Mean latency | 426.8 (90) | 399.7 (95.8) | 420.0 (81) | 393.8 (52.2) | p=0.783 | p=0.961 | d =0.08 |
| **AST** | | | | | | | |
| Percentage correct trials | 94.7 (5.8) | 96.6 (2.1) | 93.2 (7.0) | 95.5 (8.3) | p=0.415 | p=0.794 | d =0.18 |
| Mean latency | 679.1 (174) | 600.0 (165) | 682.8 (194) | 583.9 (152) | p=0.944 | p=0.448 | d =0.10 |
| **Digit span** | | | | | | | |
| Total score | 16.5 (3.6) | 17.4 (3.1) | 15.6 (3.5) | 16.6 (3.9) | p=0.397 | p=0.877 | d =0.23 |
| Backward score | 7.0 (2.3) | 7.3 (1.8) | 6.6 (2.3) | 7.3 (2.5) | p=0.541 | p=0.478 | d =0.00 |
| Forward score | 9.5 (2.1) | 10.0 (1.9) | 9.1 (1.7) | 9.4 (1.9) | p=0.394 | p=0.631 | d =0.32 |
| **SWM** | | | | | | | |
| Between-errors | 19.4 (15) | 16.9(13) | 19.0 (13) | 20.6 (18) | p=0.909 | p=0.369 | d =0.24 |
| Within-errors | 1.3 (2) | 0.8 (1) | 2.1 (4) | 1.0 (2) | p=0.420 | p=0.586 | d =0.13 |
| Strategy score | 29.4 (8.6) | 30.3 (6.3) | 28.9 (8.0) | 29.7 (8.7) | p=0.823 | p=0.9937 | d =0.08 |
| **ERT** | | | | | | | |
| Percentage correct trials | 63.3 (9.2) | 66.1 (10.4) | 63.3 (10.1) | 68.0 (10.0) | p=0.996 | p=0.187 | d =0.19 |
| Mean latency | 1840.3 (478) | 1425.3 (406) | 1931.5 (725) | 1689.0 (738) | p=0.607 | p=0.013 | d =0.44 |
| **DTT** | | | | | | | |
| Verbal score | | 5.7 (2.1) | | 3.9 (1.6) | | p=0.003 | d =0.96 |
| Figurative score | | 5.2 (2.7) | | 5.0 (2.3) | | p=0.862 | d =0.08 |

## 5.5 STUDY V

Figure 7 illustrates the Consolidated Standard of Reporting Trials (CONSORT) flowchart. Of 227 participants who underwent telephone screening, 64 came to the clinic for screening visit and 50 were randomized to working memory training or control training. There were no statistically significant differences between treatment groups at baseline regarding sociodemographic variables, drinking levels, craving or working memory capacity (Table 7). Eleven participants failed to complete the study protocol (i.e., complete minimum 20 training sessions during the five weeks), but no statistically significant difference in dropout rate was found between treatment groups (p=0.733). Since the ITT and PP analyses yielded similar results, only the PP analysis is reported.

**Figure 7.** CONSORT (Consolidated Standards of Reporting Trials) chart illustrating the flow of study participants.
Abbreviations: AUD, alcohol use disorder; WM, working memory; ITT, intention to treat; PP, per protocol.

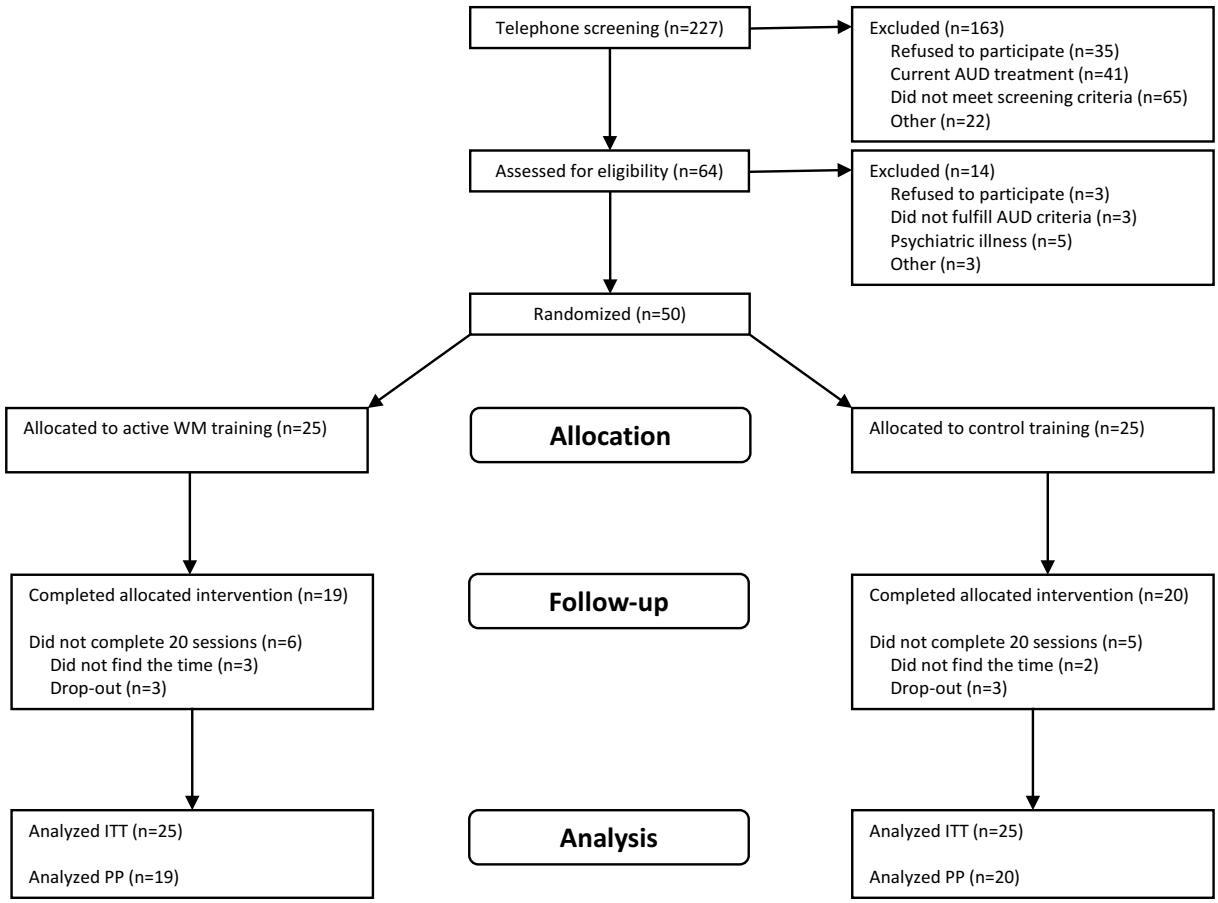


**Table 7.** Sociodemographic and clinical characteristics of the entire sample of study participants at baseline. Continuous outcomes are presented as mean (standard deviation). There were no statistically significant differences between groups on any of the outcomes.
Abbreviations: AD, alcohol dependence; OCDS, obsessive-compulsive drinking scale; TLFB, Timeline Follow-back. N.S., no statistically significant difference.

| | **Active training** | **Control training** | **Significance** |
|---|---|---|---|
| Males / Females | 13/12 | 12/13 | N.S. |
| Age | 49.6 (6.1) | 49.8 (8.7) | N.S. |
| Education | | | N.S. |
| - Elementary School | 4.0 % | 8 % | |
| - High school | 40.0 % | 36 % | |
| - University/College | 56 % | 56 % | |
| Marital status | | | N.S. |
| - Never been married | 8 % | 16 % | |
| - Married/partner | 76 % | 48 % | |
| - Divorced | 16 % | 32 % | |
| - Widow | 0 % | 4 % | |
| Daily nicotine use | 48% | 50% | N.S. |
| Previous treatment for AD | 40 % | 28 % | N.S. |
| Age at first drink | 13.9 (1.9) | 14.8 (1.9) | N.S. |
| Age when alcohol problem began | 34.0 (10.8) | 32.7 (12.7) | N.S. |
| AD DSM-IV criteria | 5.1 (1.2) | 4.8 (1.3) | N.S. |
| Heredity AD | 87 % | 88 % | N.S. |
| OCDS total | 22.7 (7.0) | 21.9 (5.4) | N.S. |
| TLFB 90 Drinks | 421.7 (211) | 358.1 (156) | N.S. |
| TLFB 90 Drinking days | 64.3 (21.6) | 63.2 (20.1) | N.S. |
| TLFB 90 Heavy drinking days | 49.8 (28.2) | 45.0 (28.0) | N.S. |
| TLFB 90 Drinks per drinking day | 6.5 (2.9) | 6.0 (2.0) | N.S. |
| Alcohol free days before inclusion | 4.1 (2.7) | 3.6 (0.89) | N.S. |
| Digit span total | 15,7 (3,6) | 16,0 (3,5) | N.S. |
| Digit span forward | 9,8 (1,9) | 9,0 (2,1) | N.S. |
| Digit span backward | 5,9 (2,2) | 6,9 (2,0) | N.S. |

For the verbal working memory Digit span task total score, there was a statistically significant treatment*time interaction ($F(1,37)=6.1$; $p=0.018$), driven by a significant improvement on test day compared to baseline only in the active treatment group ($F(1,18)=14.4$; $p=0.001$) but not in the control group ($F(1,19)=0.5$; $p=0.50$). The treatment effect was mainly driven by improvement in the backward score for which the treatment*time interaction was significant ($F(1,37)=6.1$; $p=0.018$), while no significant interaction for found for the forward score ($F(1,37)=1.2$; $p=0.273$). In the spatial working memory task, there were no significant time*treatment interactions for any of the error or strategy outcomes (all $p>0.05$).

For the main drinking outcome percentage of heavy drinking days, there was a statistically significant main effect of time ($F(1,37)=6.3$; $p=0.017$) in the direction of an overall reduction in heavy drinking (overall 8% reduction across treatment groups), but no significant main effect of treatment ($F(1,37)=1.8$; $p=0.186$) or treatment*time interaction ($F(1,37)=2.3$; $p=0.142$) was found. For the outcome drinks per drinking day, there was a trend toward significance for the treatment*time interaction ($F(1,37)=3.5$; $p=0.070$) in the direction of greater reduction in drinks per drinking day in the active treatment group (average -0.94 reduction) than the control group (average +0.15 increase). No significant treatment*time interactions were found for any other drinking outcomes (percentage drinking days, drinks per day), self-rated craving or mood during the treatment period.

For the cognitive test battery performed at baseline and on test day, including additional task of delay discounting (Kirby Monetary Choice questionnaire), there were no evidence of any treatment effect for any of the cognitive test outcomes. No treatment*time interactions were statistically significant (all p-values > 0.1). There were however significant main effects of time for the SST SSRT outcome ($F(1,35)=8.2$; $p=0.007$) and RVP probability of hit ($F(1,35)=4.6$; $p=0.04$), suggesting a general improvement across the study for these outcomes related to response inhibition and attention. In contrast, for the CGT outcomes overall proportion bet ($F(1,35)=6.7$; $p=0.014$) and risk taking ($F(1,35)=9.6$; $p=0.004$) there was an overall increase in risky decision making at test day compared to baseline.

# 6 DISCUSSION

## 6.1 ETIOLOGY OF COGNITIVE DEFICITS IN AUD

The first study of the thesis was, to our knowledge, the largest study to date investigating the relationship between parental SUD and offspring cognitive ability. By utilizing the unique Swedish national registries in a population-based sample of 3 million individuals, a robust negative association between parental SUD and cognitive ability in the offspring was found. Besides a large sample size, the study had several additional strengths. First, two different forms of general cognitive ability outcomes were used (conscription test score and grades) and since the results were similar irrespective of outcome, the observed association was likely not due to systematic bias in outcome assessment. Second, thanks to linkage between the different population-based registries it was possible to adjust for several important covariates in both parent and offspring. Finally, by including information regarding genetic relatedness in the family-based children-of-siblings analyses, the study could also assert that the observed association was likely driven by shared genetic factors between parental SUD and cognitive ability.

The observed negative association between parental SUD and offspring cognition at the population level has implications for health care, educational services and future research. It is important to acknowledge that children of SUD parents are not only in need of social and emotional support, but may also benefit from targeted educational interventions. Furthermore, the study found a dose-response relationship, indicating that having two parents with SUD had an even stronger negative effect on cognition compared to having only one SUD parent. This finding sheds new light on the large number of case control studies which have consistently found that AUD patients compared to healthy individuals exhibit poorer cognitive function across all assessed domains (91). However, very few of these studies have investigated to what degree such observed differences in cognitive function between patients and healthy individuals are due to family history of SUD. The current study highlights the importance for future clinical research studies on cognitive function in SUD, and perhaps also other psychiatric disorders, using case-control design to assess and take into account presence of family history.

Study I also found evidence of shared genetic factors between parental SUD and cognitive ability in offspring. This result corroborates studies showing a similar relationship within individuals (196–198), and cognitive deficits in family history positive healthy individuals (114,115) and further extending these findings to be valid also across generations suggesting that cognitive capacities could be genetically influenced traits elevating risk for developing SUD, i.e. putative endophenotypes in AUD. This finding has several implications for both research and clinical practice. First, these results suggest that cognitive symptoms could be present before the onset of SUD, making cognitive assessment a possible strategy to identify individuals at risk. Second, the findings are compatible with the notion that cognitive symptoms may be a core clinical feature of the SUD syndrome, and this could affect

diagnostic classification of the disorder. For instance, it is possible that SUD could be further classified based on different forms of cognitive profiles, but this is merely speculation at this point. Finally, the study shows that observable cognitive symptoms associated with family history of SUD are influenced by genetic factors, suggesting that they may continue to be present in SUD patients also after a long period of abstinence, highlighting the potential need to address such symptoms in the long-term care of SUD patients. One important caveat with study I however, was that two very general cognitive outcomes were used. The question of which specific cognitive domains and tests that can be used in clinical settings to characterize this putative cognitive endophenotype, was instead addressed in study II.

In study II, it was found that AUD patients compared to HC exhibited elevated self-rated impulsivity (BIS), poor response inhibition (SST), reduced attention (RVP) and a tendency to gather less information in decision making (IST). These findings of higher impulsivity and poor EF replicate the results from a large number of previous studies in AUD and HC (92,94,97,199). Furthermore, while previous studies investigating the effect of AUD on cognition often included patients with severe forms of AUD (e.g., subjects recruited at inpatient treatment facilities), study II included AUD patients with relatively stable income and social situation and without any psychiatric co-morbidity. Cognitive deficits were detectable at the group level also in this high-functioning patient sample, suggesting that cognitive assessment could also play an important role in AUD patients with less severe disease trajectories recruited from the community.

The main finding in study II was that taking into account family history status for AUD in the HC group revealed new patterns of differences in cognitive functioning. The FH+ group was similar to the AUD patients exhibiting higher self-rated impulsivity, poorer future planning capacity and prolonged emotional recognition time compared to the FH- group. However, other cognitive tests which were significant in the AUD versus HC analysis did not follow this pattern, such as the SST response inhibition task. These results lend themselves to comparison with the series of studies performed by Ersche and colleagues, who investigated patients with stimulant dependence, their unaffected siblings and healthy volunteers without any family history of SUD (200–202). The results parallel the findings from Ersche and colleagues of elevated self-rated impulsivity assessed by the BIS, including largest effect for the non-planning subscale, as a potential endophenotype (201). However, while Ersche and colleagues found that response inhibition, assessed by the same SST task, followed a similar pattern in stimulant dependent individuals (202), the current results did not reveal any such pattern. There are several possible interpretations of this discrepancy, but one possible explanation could be that individuals with different cognitive profiles are more likely to initiate and engage in certain forms of substance use. While acute alcohol intake impairs response inhibition (203), central stimulants such as amphetamine and methylphenidate can improve this cognitive domain (204,205), reflecting differences in the neurobiological mechanism of action of these substances which may appeal to individuals with different cognitive profiles. Our results could thus reflect a difference in the underlying genetic

architecture between AUD and central stimulant use disorder: While self-rated overall impulsive behavior seems to be a possible endophenotype in both disorders, response inhibition did not follow the same pattern in AUD, where it may rather be related to drinking or sub-clinical withdrawal.

The results of study II also suggest that future planning capacity, operationalized as poorer performance on the SOC tasks most difficult problems, may be a putative endophenotype in AUD. This finding corroborates previous case-control studies showing difficulties with future planning in not only AUD (97,110) but also other forms of SUD including opioids (206), ketamine (207) and amphetamine (206). Notably, in the first analysis (AUD versus HC) no difference emerged for this cognitive outcome – but it would have been a statistically significant difference if the HC group only consisted of FH- individuals. Once again, this highlights the need for research studies employing case-control design when evaluating cognitive deficits in SUD patients, to take into account family history status also in the control group, since otherwise potentially meaningful differences could go undetected.

Finally, emotional recognition latency also exhibited a pattern compatible with an endophenotype. This is in line with previous studies since indices of emotional recognition has been shown be affected in AUD (208,209) and that poorer performance on emotional recognition tasks predicts worse treatment outcome in clinical settings (210). This finding however is more uncertain than the SOC finding. First, no effect of group, including AUD versus HC, was found for the main ERT task outcome of percentage correctly identified emotions. Secondly, when employing a more restricted definition of family history in the sensitivity analysis, the effect of family history on emotional recognition latency was no longer statistically significant. Thus, in addition to the general limitations of study II (discussed below in the Limitation paragraph), the finding of emotional recognition latency should be interpreted with extra caution.

The question of etiology of cognitive deficits in AUD represents a genuine and difficult scientific problem with important implications for the pathogenesis, classification and prevention of the disorder. However, when facing a patient suffering AUD who exhibits cognitive symptoms - the question of etiology becomes less pressing, and the most clinically important question arises: Can these cognitive symptoms be treated in a clinical setting?

## 6.2 TREATMENT OF COGNITIVE DEFICITS IN AUD

In the current thesis two conceptually different forms of interventions, pharmacological and working memory training, were evaluated as potential novel treatments for AUD. Importantly, cognitive assessment was performed at both baseline and after treatment to assess the intervention effect not only on traditional AUD outcomes (e.g., craving, drinking, mood) but also on cognitive functioning.

### 6.2.1 Pharmacological Intervention

Study III and IV, found that the monoamine stabilizer OSU reduced priming-induced craving, but not cue-induced craving, in an experimental craving laboratory test. The mechanism of action of this effect is not known, but given the important role of DA in reward (211), including acute alcohol intake (20,21), it is possible that OSU specifically blunted the rewarding properties of alcohol intake by inhibiting DA release in the mesolimbic DA system. This is also supported by the fact that the patients reported significantly lower 'liking' after the first sip of alcohol, and is in line with previous preclinical studies showing that OSU reduces alcohol-induced DA release in the nucleus accumbens in alcohol-naïve rats (152).

Another finding relevant for the current thesis was the subgroup analysis which found that poor baseline performance of response inhibition, an EF and core feature of impulsive behavior, robustly predicted positive treatment response to OSU. These results corroborate previous studies showing that baseline levels of impulsivity related outcomes predict pharmacological treatment response in AUD: Treatment with modafinil reduced drinking (138), SST performance (137) and working memory (139) in AUD patients, with a significant moderating effect of baseline performance of cognitive tests indicating that the positive treatment effect was found predominantly in patients with poorer baseline performance. In addition, studies of the partial DA agonist aripiprazole has suggested that higher baseline self-rating impulsivity assessed by the BIS (subscale non-planning, self-control) similarly predicts positive treatment outcome for craving and drinking in AUD (141,142). The neurobiological mechanisms behind these results are unknown, but preclinical studies have found that low D2 receptor availability is associated with both high trait impulsivity and greater cocaine intake in rats (212). Furthermore, chronic intermittent alcohol exposure in rats caused deficits in EF together with disrupted DA receptor signaling in the medial PFC (213), which has been repeatedly associated with EF also in humans (214). In AUD patients, ventral striatal brain activity, putatively mediated in part by dopaminergic signaling, was associated with self-rated impulsivity during a reward anticipation task (215). Furthermore, candidate gene studies have found associations between variation in genes related to the DA D2 receptor gene and impulsivity assessed by the BIS (216) and alcohol dependence (217). Finally, impulsivity is also associated with reduced D2 DA receptor levels (218), which has repeatedly been associated also with AUD (22–24). Taken together, these findings lend support to the notion that high baseline impulsivity could be a clinical marker of altered dopaminergic neurotransmission, involved in the development and maintenance of SUD (133). The results further add to previous studies by illustrating that OSU treatment has differential treatment effects in AUD based on baseline impulsivity – rendering the future question if specific genetic markers related to DA neurotransmission can predict cognitive deficits as well as treatment response to dopaminergic pharmacological agents.

Study IV found that OSU treatment did not cause any negative effect on any assessed cognitive domain. Rather, a positive treatment effect was found for future planning,

emotional recognition latency and divergent thinking capacity, suggesting that OSU treatment actually can improve certain cognitive domains. This is in contrast to previous studies of the traditional antipsychotic medication sulpiride, a primarily D2/D3 receptor antagonist, which has been shown to impair performance on both SWM and a future planning task (219). However, this was done in healthy volunteers and not in patients so it is not possible to directly compare these results. If the traditional antipsychotic mechanism of D2 receptor antagonism indeed does worsen performance on these cognitive domains, it is at least possible that some other proposed OSU mechanism may be involved in the current finding, for instance antagonism on the presynaptic autoreceptors (144,220,221), partial agonism at the 5HT2A receptor (220) or possibly its affinity for sigma receptors (222). Future neuroimaging studies are needed to fully understand the underlying neurobiological correlates of the treatment effect of OSU on the craving response and cognitive domains. For example, functional MRI could evaluate the effect of OSU versus placebo on alcohol cue/priming and cognitive task activation in brain areas involved in both the craving response (ventral striatum, anterior cingulate and the ventromedial PFC (38)) and EF (e.g., dorsolateral PFC, ventromedial PFC, inferior frontal cortex (214)) to shed further light on its pharmacological mechanism of action. Another interesting study would be to utilize PET neuroimaging to investigate acute or prolonged treatment effects of OSU on DA release and receptor availability in humans. Since AUD is associated with reduced striatal and prefrontal DA receptor availability and release (22–25,223), it would be interesting to assess whether OSU can counteract or normalize this hypodopaminergic state, as has been suggested by preclinical studies in alcohol-drinking rats (154).

The findings suggesting that OSU improves specific cognitive domains should be viewed in light of several limitations (see limitation paragraph for details) and interpreted cautiously. However, if replicated, such improvements in cognition could have important clinical implications. For instance, both future planning and divergent thinking/flexibility is crucial for the ability to both identify and utilize different craving coping strategies for instance in relapse prevention therapy (224). It is also interesting that two of the cognitive test outcomes that were improved by OSU treatment (SOC and ERT response latency) in fact also emerged as possible endophenotype candidates in study II, being significantly worse in both AUD patients and healthy volunteers with positive family history of AUD. If these findings are replicated it would suggest that pharmacological treatment with OSU could affect specifically genetically influenced traits elevating risk for AUD, but at this point this is merely a hypothesis for future research.

OSU had a generally mild side effect profile, without any severe adverse events recorded during the study, and no indication of intrinsic rewarding effects. Most relevant for the current thesis however, was that there was no evidence of negative cognitive effects of OSU on any of the assessed cognitive domains. Since cognitive side-effects can be clinically problematic (225), and early onset of any side-effects is a common reason for non-adherence to psychiatric medications (226), the observed lack of early side-effects supports the

feasibility of further evaluation of OSU in AUD patients. No treatment effect was however found on drinking during the treatment, but this was not unexpected given the short treatment period (14 days), and the study was not designed to detect differences in these outcomes. Future large-scale randomized placebo-controlled trials of OSU in AUD are needed to investigate the putative effect on drinking outcomes as well as to replicate the findings of potentially positive effects on cognitive domains of future planning, emotional recognition speed and divergent thinking capacity.

### 6.2.2 Cognitive Training Intervention

In study V, it was found that five weeks of working memory training improved verbal working memory function, but not spatial working memory, while no treatment effect was found on drinking, craving or mood. These results are in line with several previous studies showing that training working memory indeed improves working memory test performance in healthy volunteers (155,156,227), ADHD (158) and substance abuse populations such as heavy drinkers (166) and opioid dependent individuals (165). The treatment effect in study V was significant specifically for the backward Digit span test score, which has been proposed to be a more specific outcome for working memory since it requires active manipulation of received information (228). An important conclusion from these results is that it is possible to target and improve a specific cognitive domain, in this case working memory, in treatment seeking AUD patients.

In contrast to other studies (165), study V failed to detect any significant treatment effect on visuospatial working memory. The reason for this discrepancy is not entirely clear. A meta-analysis of cognitive deficits in AUD found similar overall effect sizes (approximately Cohen's d 0.35-0.55) for both verbal and visuospatial working memory and learning (91), suggesting that there is no general difference in impairment regarding verbal or visuospatial cognitive function in AUD. However after the study was published we collected data from healthy individuals (study II) and found that there actually was no statistically significant difference for neither verbal nor visuospatial working memory between the recruited AUD patients and healthy individuals and even a surprising trend toward better performance in the AUD group for spatial working memory. If there was no deficit in the patients to begin with, this could explain the lack of treatment effect on this cognitive domain.

There was no significant treatment effect of working memory training on any drinking outcome, which is in contrast to a previous study in heavy drinkers that found working memory training to reduce heavy drinking (166). One possible interpretation is that there actually is a true effect of treatment but that our study failed to detect it given the limited sample size. In support of this possibility is the fact that the raw scores indeed went in the direction of greater decrease in percentage heavy drinking days in the active treatment group (-11.5 %) compared to the control group (-3.4%), and the observed trend in the secondary outcome, drinks per drinking day, was also in favor of the active treatment group. However, it is also possible that there actually is no effect of working memory training on drinking in

AUD patients, which is supported by several recent studies showing lack of clinical effect of working memory training on substance use in different clinical SUD populations (169,170).

Finally, contrary to the hypothesis there was no effect of working memory training on any of the other assessed cognitive functions, i.e., the study failed to find any evidence of transfer effects. This is in contrast to previous studies which indeed have found that working memory training also improved attention (158,229–231) and general fluid intelligence (162,227). However, it is of relevance to highlight that there is an ongoing scientific discussion about the evidence of such transfer effects, with mixed results in different meta-analyses (162,163). Importantly, in a large-scale study of 11,430 individuals Owen and colleagues found that cognitive training for different cognitive domains (e.g., memory, planning and attention) only improved performance on the trained tasks, while there was no evidence of any transfer effects to other cognitive domains (232). Furthermore, several studies in SUD populations have failed to detect any transfer effects of working memory training to other cognitive domains (165,169,170), and our results are in line with this conclusion.

Even though the working memory training intervention was demanding for the participant, requiring them to perform 5 training sessions á 30-40 min per week, treatment adherence was acceptable with more than 75% completing the study protocol. No adverse events related to the cognitive training was reported. Taken together, the study found that it is clinically feasible to administer such a demanding cognitive training intervention to an outpatient AUD clinical population. However, based on the current study and growing numbers of studies that have failed to show beneficial treatment effects of working memory training in SUD patients, the research field should pose the question whether the focus of such cognitive training interventions should be exclusively on working memory, or perhaps rather on a broader/different set of cognitive domains, such as response inhibition, goal-directed training or cognitive bias modification training (44).

## 6.3 LIMITATIONS

The current thesis has several important limitations. In study I, a general limitation when utilizing national registries is the risk of misclassification, which could bias not only the overall population estimates but also mimic genetic confounding in family-based designs (233). The study however found that the results were similar in the sensitivity analysis where only parents who were fully covered by the registries their entire lives were included. Furthermore, the outcomes of general cognitive ability were very crude, and many other factors not actually related to genuine cognitive ability may have influenced the outcomes. For instance, individuals with high cognitive ability may actually want to perform worse on the conscription test to avoid military service. However, a strength in the current study was the use of two completely different cognition outcomes. Even though final grades and conscript test score were collected under completely different circumstances, they still correlated in individuals who provided data on both outcomes ($r=0.6$; $p<0.0001$), suggesting that they at least in part capture general cognitive ability. Another potential limitation is that

SUD patients with low cognitive ability may be at an extra elevated risk of being included in the registries. In the sensitivity analyses adjusting for parental cognitive ability however, the regression coefficients were similar as in the main analysis, suggesting that differential detection of only SUD individuals with low cognitive ability did not explain our findings. It is also important to note that study I was performed using data from Sweden collected approximately 1950-2000, and the findings do not necessarily transfer to other populations with different genetic constitution or sociocultural settings e.g., societies with different substance use cultures.

The limitations shared across the clinical studies in the thesis (study II-V), can broadly be categorized into limitations regarding statistics, participant generalizability and specific issues related to the design/setting of the treatment studies. First, an important limitation for all the clinical studies is the limited sample size. It is very important to note that for the two treatment studies (study III and V), the small sample sizes (n=56 and n=50) only had adequate power for detecting possible large treatment effect sizes. Lack of statistically significant differences between treatment groups should thus be viewed in light of the risk of type II errors. In addition, given the exploratory nature of these hypothesis generating studies (234) no adjustment for multiple comparisons was performed. The main reason for employing this approach, is that there is no consensus within the research field on how to treat the problem of multiple comparisons of highly intercorrelated cognitive outcomes. Therefore, it is common practice in the research field to simply report the unadjusted analyses (105,235,236), which also has the benefit of allowing for comparisons across studies.

The second limitation concerns the question of external validity. Small clinical studies require homogenous study populations, and therefore the included AUD patients all fulfilled extensive selection criteria. Thus, an important limitation is that the observed findings do not necessarily generalize to more clinically severe AUD patients with psychiatric and somatic co-morbidity.

Third, several methodological issues relate to the design and setting of the treatment studies that could have affected the study results. Cognitive testing was performed at both baseline and after treatment, allowing for practice effects which could have hidden potential treatment effects. In addition, the studies were performed at an outpatient research clinic with repeated visits during treatment, which allowed assessment of drinking levels during the study. However, it is likely that substance use could have had negative effects on treatment adherence, pharmacological effect and cognitive training performance. Thus, to isolate the treatment effect, an option would have been to perform the study at an inpatient facility in order to have control over substance intake. Finally, patients were recruited based on DSM diagnosis of AUD and not cognitive impairment. It is possible that only a subgroup of patients with detectable cognitive deficits will respond to treatment, which is further supported by the results in study III and previous research studies of pharmacological treatments (137–139,141,142) and working memory training (168). Future studies should

consider including only patients with specific cognitive impairments relevant for the intervention, for instance poor working memory, when evaluating a working memory training intervention.

## 6.4 REFLECTIONS AND FUTURE RESEARCH

To increase understanding of the research question of etiology of cognitive deficits in AUD, several different research methodologies are needed. Large-scale registry-based epidemiological studies using family-based designs represent a complementary research strategy, besides traditional clinical pharmacological and neuroimaging studies. For instance, by including cognitive outcomes at an earlier age and/or repeated longitudinal assessment it would be possible to disentangle the influence of genetic and environmental factors across different developmental phases. Furthermore, it would be interesting to also investigate the importance of family history of SUD on other psychiatric and neurological disorders characterized by more severe impairments in cognition, e.g., mental retardation or dementia.

Clinical studies evaluating the question of etiology are in general hampered by limited sample size and/or lack of uniform cognitive assessment (as discussed further below). Several large-scale consortia where many research groups collaborate are currently being organized in other areas of psychiatric research, e.g., the Psychiatric Genomics Consortium for large-scale genome-wise association studies (237). To fully understand and characterize the genetic and neurobiological underpinnings of putative cognitive endophenotypes in SUD, perhaps similar international collaborations between many research groups need to be created. Such collaborations would increase statistical power and improve the validity of inference and generalizability across different types of substance use disorder populations and sociocultural settings.

To date, there are only three principally different pharmacological treatments approved for AUD (40), and they predominantly focus either on increasing abstinence, or reducing heavy drinking and craving. The current thesis supports the notion that, besides drinking and craving, cognitive deficits could also be an additional viable treatment target when evaluating novel pharmacological interventions in AUD (44–46). There are several novel pharmacological targets that would be of great interest to explore further in future studies aiming to improve cognition in AUD. Psychostimulants such as methylphenidate, modafinil and nicotine can improve attention, memory and wakefulness in healthy volunteers, as shown in meta-analyses (238,239). Besides these classical cognitive enhancers, Fond and colleagues reviewed additional potentially interesting pharmacological agents that could enhance cognition in healthy volunteers (240). Even though there is an abundance of mixed and negative results in the literature, some positive findings emerged in the review: Drugs targeting the catecholamine system, such as the catechol-O-methyltransferase inhibitor tolcapone improves executive function and memory (241,242) while L-Dopa enhances memory encoding (243). In addition, novel pharmacological targets not traditionally considered cognitive enhancers in the research literature were melatonin which exerted a

positive effect on recognition memory (244), and acetyl salicylic acid which improved working memory (245). When evaluating potential cognitive enhancing drugs in AUD, it is also important to consider the important risk of addictive potential of the compound. Pharmacological agents without such addictive potential, but with potentially cognitive enhancing effects, such as the alpha2A adrenergic agonist guanfacine has shown to improve inhibitory control and attention shifting in cocaine use disorder (246). Another interesting pharmacological candidate is the norepinephrine reuptake inhibitor atomoxetine, which has been shown to improve response inhibition in healthy volunteers (247), ADHD (248) and Parkinson disease (235). Furthermore, atomoxetine has been shown to reduce attentional bias toward drug cues in cocaine use disorder (249), and would be interesting to investigate in AUD as well. Finally, it would be informative and clinically relevant to combine any potentially cognitive enhancing drug with evidence-based psychotherapy treatment. Whether drug-induced cognitive enhancing effects could improve adherence and outcome of for instance CBT based relapse prevention in AUD would be a highly interesting topic for future research.

The current thesis does not lend support for computerized working memory training in AUD per se, but study V did find that it was feasible to administer such a labor-intensive intervention to motivated AUD outpatients in a clinical setting. One possibility is to consider cognitive training programs specifically targeting other cognitive domains putatively more important in substance abuse, for instance response inhibition, goal-directed training or cognitive bias modification training (44). Another relevant aspect when creating cognitive training interventions is the actual design of the computer program. It has been suggested that when creating cognitive training programs, it is important not only to target specific cognitive domains but also that the prototype games are enjoyable for the individual user (250). Such games have shown some promising results in improving cognitive functions such as episodic memory and visuospatial abilities in individuals with mild cognitive impairment (251), and would be interesting to investigate also in AUD. Finally, it is important to note that there are other ways to influence cognitive function besides pharmacological treatment and cognitive training programs. For instance, an on-going study is evaluating the effects of aerobic exercise in AUD on several clinical treatment outcomes, including cognitive function (252). When it has been established which cognitive training interventions that are most promising in AUD, an interesting next step would be to combine such interventions with evidence based pharmacological treatment for AUD to investigate potential additive effects.

An important knowledge gap in the research field concerns the question of external validity of cognitive testing. What do the assessed cognitive deficits in clinical patients actually mean in real life? Indeed several studies have found that baseline cognitive impairments in AUD predicts poor treatment outcome in clinical settings (127–130,253,254), but the mechanism remains unknown. Do cognitive deficits directly increase the risk of relapse because of impairments in response inhibition in craving situations? Or do they cause difficulties in managing common daily activities and interpersonal relations, causing stress which in turn

leads to relapse? Future research could consider combining traditional cognitive testing in the laboratory, with more ecologically valid data collection methods for instance via smartphone apps and logs (255), in order to disentangle such mechanistic research questions.

Another important research question in need of further investigation is the temporal dynamics of cognitive deficits in AUD and other forms of SUD. Given that SUD is often conceptualized as a cyclic disorder of intoxication, withdrawal and pre-occupation/craving/negative affect (27), it is likely that the patterns of cognitive dysfunction is different in these different phases of the disorder. In addition, it is possible that certain patients only exhibit cognitive deficits during craving states, which could be investigated by combining cue- and priming-induced craving experiments with cognitive testing. Furthermore, even in the recovery phase after prolonged abstinence it is possible that different cognitive deficits will be more or less important. While there is evidence of some recovery of cognitive function over time (256), the only meta-analysis conducted found that even after prolonged abstinence of 1 year there are significant differences between patients and healthy controls, even though the effects are smaller compared to short-term abstinence (91). In both of the current thesis treatment studies it was found that certain cognitive domains improved spontaneously with time (e.g., response inhibition and attention), suggesting that they are more affected early in the abstinence phase. However, in both treatment studies it was found that AUD patients actually performed worse on the CGT task over time (higher proportion bet and more risk taking), suggesting that risky decision making could actually worsen during abstinence. An interesting idea for future research would be not only to assess cognitive function at baseline prior to treatment initiation, but also follow patients longitudinally with repeated cognitive assessments to fully understand which cognitive domains are predominately affected during the recovery phase.

Cognition has only recently been proposed as a putative treatment target in AUD and other forms of SUD (43–46), but very few randomized placebo controlled trials have been performed with cognitive test performance as outcomes. The current thesis lend support to the general notion that cognitive function is important both in the understanding of the etiology of AUD, as well as a putative treatment target. As more data accumulates within this field of research, it is possible that cognitive deficits in the future will be considered intrinsic and crucial aspects of AUD, as they are in other psychiatric disorders such as depression and schizophrenia.

## 6.5 OVERALL CONCLUSIONS

At the onset of the thesis, two research questions were presented:

1) What is the etiology of cognitive deficits in AUD?
2) Can cognitive deficits in AUD be treated, either by pharmacological or cognitive working memory training interventions?

The first broader question regarding etiology was addressed by study I and II. The conclusion from study I is that genetic factors may in part may explain the observed cognitive symptoms present in AUD patients. Importantly, the observed cognitive deficits in AUD patients are likely not only caused by the toxic effects of alcohol, but also influenced by genetic factors and may thus be present before the onset of the disorder, constituting a potential endophenotype in AUD. Study II suggests that certain specific cognitive domains (i.e., self-rated impulsivity, future planning, emotional recognition) may constitute such cognitive endophenotypes in clinical patients. More research is needed in order to fully understand and further characterize this putative endophenotype in AUD. These results have important implications for prevention, diagnostic classification and the treatment of AUD.

The second broader question regarding treatment of cognitive deficits in AUD was addressed by study III-V. The overall conclusion from study III-IV is that pharmacological treatments targeting the DA system, such as the monoamine stabilizer OSU, may be a promising strategy to treat certain cognitive deficits (e.g., future planning capacity, emotional recognition latency, divergent thinking). Furthermore, subgroups of high impulsive individuals may be more likely to respond to such dopaminergic pharmacological treatments. The results from study V showed that computerized working memory training can improve the cognitive domain of working memory, but did not support an effect of treatment on drinking or transfer effects to other non-trained cognitive domains. Overall the treatment studies found that it is possible in principle to influence different cognitive domains by both pharmacological and cognitive training interventions, and that the treatment effect may be moderated by baseline cognitive functioning. The findings highlight the importance of including cognitive assessments as both potential predictors of treatment as well as study outcomes, when evaluating novel interventions in SUD.

In clinical care of AUD patients, it is common practice to assess drinking, craving, anxiety and mood but little focus is placed on cognitive function. Cognitive function may in some cases be ‘the elephant in the room’ increasing risk of treatment failure, since cognitive deficits can make it impossible to formulate and adhere to any form of clinical treatment plan. The current thesis brings this neglected clinical topic to focus by highlighting that cognitive deficits in AUD are in part genetically influenced, and constitute a potential treatment target when evaluating novel interventions in AUD.

# 7 SWEDISH SUMMARY

Alkoholbrukssyndrom, som förut kallades alkoholberoende/alkoholmissbruk, är en psykiatrisk diagnos vars kännetecken är kontrollförlust, tolerans, abstinens och negativa psykiska, fysiska och sociala konsekvenser på grund av alkoholintag. Många patienter som lider av alkoholbrukssyndrom uppvisar också kognitiva problem, exempelvis svårigheter med impulskontroll, bristande uppmärksamhet och nedsatt minne. Det övergripande målet med denna avhandling var att besvara två forskningsfrågor: 1) Finns det genetiska faktorer bakom kognitiva problem vid alkoholbrukssyndrom? 2) Kan kognitiva problem behandlas farmakologiskt eller med hjälp av kognitiv träning?

Studie I var en storskalig epidemiologisk studie baserad på data från 3 miljoner unika individer ifrån svenska nationella register. Denna studie visade att om man har föräldrar med substansberoende (inklusive alkoholbrukssyndrom), så är detta associerat med lägre generell kognitiv förmåga (mätt som slutbetyg i nionde klass och begåvningstest vid mönstring). Detta samband blev gradvis svagare, när analysen gjordes om i kusiner vars föräldrar var mer och mer genetisk lika varandra (halvsyskon, helsyskon och slutligen enäggstvillingar), vilket tyder på att det finns gemensamma genetiska faktorer bakom ärftlighet för substansberoende och kognitiv funktion.

Studie II var en fall-kontroll-studie där patienter med alkoholbrukssyndrom (n=106) jämfördes med en grupp friska kontroller (n=90), som i sin tur delades in i två undergrupper nämligen de med ärftlighet för alkoholbrukssyndrom och de som saknade sådan ärftlighet. Alla studiedeltagare genomgick en psykiatrisk bedömning samt omfattande neuropsykologiska tester, som mäter impulsivt beteende, beslutsfattande, uppmärksamhet, minne och igenkänning av emotioner. Patienterna med alkoholbrukssyndrom och de friska med ärftlighet uppvisade liknande nivåer av förhöjd impulsivitet, försämrad förmåga till framtida planering samt längre svarstid för att känna igen olika emotioner jämfört med de friska utan ärftlighet för alkoholbrukssyndrom. Dessa kognitiva symptom skulle delvis kunna utgöra genetiskt betingade kognitiva egenskaper som ökar risken för att utveckla alkoholbrukssyndrom.

Studie III och IV var baserade på samma datainsamling ifrån en randomiserad kontrollerad prövning av en ny farmakologisk substans, nämligen monoaminstabiliseraren (-)OSU6162 (OSU). Syftet med dessa studier var att undersöka effekten av OSU på alkoholsug (studie III) och kognitiv funktion (studie IV). Patienter med alkoholbrukssyndrom (n=56) randomiserades till att erhålla behandling med OSU eller placebo i 14 dagar, och studien avslutades med ett experiment för att mäta alkoholsug. Patienterna genomgick också neuropsykologisk testning före och efter behandling. Studie III visade att behandling med OSU minskade alkoholsug efter intag av alkohol, och den främsta behandlingseffekten fanns hos patienterna med högst impulsivitet. Studie IV visade att behandling med OSU inte orsakade några negativa effekter på kognitiv funktion, utan tvärtom förbättrade förmågan till

framtida planering, svarstid för emotionell igenkänning samt kreativt/divergent tänkande. Sammantaget visade studie III och IV att OSU har potentiellt gynnsam behandlingseffekt på såväl alkoholsug som kognition, men större randomiserade kontrollerade prövningar krävs för att replikera dessa preliminära fynd, samt utvärdera klinisk effekt på drickande.

Studie V var en randomiserad kontrollerad studie som undersökte effekten av arbetsminnesträning vid alkoholbrukssyndrom på arbetsminne, drickande samt övriga kognitiva funktioner. Patienter med alkoholbrukssyndrom (n=50) randomiserades till 5 veckors behandling med antingen aktiv arbetsminnesträning eller kontroll-träning. Studiedeltagarna kom sedan en gång per vecka och rapporterade hur mycket alkohol de druckit samt självupplevt alkoholsug, och de genomgick omfattande neuropsykologisk testning både före och efter behandlingen. Arbetsminnesträning förbättrade verbalt arbetsminne, medan ingen statistiskt signifikant effekt av behandling syntes på drickande, alkoholsug eller någon annan kognitiv funktion. Studie V gav inte stöd åt hypotesen att arbetsminnesträning är en effektiv behandling vid alkoholbrukssyndrom, men studiens resultat måste tolkas i ljuset av flera viktiga begränsningar, såsom liten studiepopulation samt att patienter inkluderades i studien oberoende av om de hade en låg arbetsminneskapacitet eller ej.

Sammanfattningsvis visade denna avhandling att kognitiva problem hos människor med alkoholbrukssyndrom delvis beror på genetiska faktorer. Exakt vilka kognitiva symptom som är betingade av genetik är inte känt, men impulsivitet, förmågan till framtida planering samt emotionell igenkänning tycks vara exempel på sådana kognitiva symptom, men fler studier behövs för att replikera dessa preliminära fynd. Avhandlingens kliniska behandlingsstudier visade att kognitiva utfall kan användas både som prediktorer för behandlingssvar och som kliniska behandlingsutfall när nya farmakologiska och kognitiva träningsinterventioner ska utvärderas vid alkoholbrukssyndrom.

# 8 ACKNOWLEDGEMENTS

Research is based on collaboration, and I have had the joy to do my PhD together with many great people I would like to thank.

Nitya Jayaram-Lindström – thank you for your endless support, all hours of scientific struggles, late-night manuscript rounds, all jokes and laughs and cries, your friendship and excellent supervision through all these years.

Johan Franck – thank you for creating a fantastic clinical research environment, your clinical wisdom and supervision, and your extensive knowledge of psychiatry, history, art and ice cream.

Predrag Petrovic – thank you for good times on conferences, scientific discussions and your enthusiasm for research.

Johan Cullberg – thank you for your mentorship, for inspiring discussions, and for giving me important new perspectives on psychiatry.

Thank you to my research group, collaborators and colleagues at Beroendecentrum Sthlm: Joar, Christoffer, Simon, Maria, Maija, Amanda, Daniella, Rebecka, Nasim, Pia, Ida, Kristin, Charlotte, Angela, Anders, Margareta, Else-Britt, Camilla H, Anna-Lena, Zakarias, Åsa, Lise-Lotte, Jonnie, Antti, Paul, Ralf, Henrik, Brian, Torkel, Jussi, Bo, Arvid C, Örjan

Thank you to my friends: Arvid GS, Hugo, Fredrik, Karl (the 4 wise men), Karin Z, Kuba, Karin B, Gustav, Alexandra, Arvid F, Victor, Johannes, Elof, Camilla W and many more.

Thank you to my family: Mamma Gudrun and Javad, Jonas and Diane, Hamadi and Charlotte, Papoose Hassen, Carina and Eric, Ida and Daniel, Farnaz and Jens and Foad.

Linnéa, Yamina, Fiona: You are all that really matters. Love you more than anything else.

And with that, I just have two more words to say,

LOTFI OUT

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