From social drinking to alcohol addiction

Decision making and its neural substrates along a spectrum from social drinking to alcohol addiction

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Hanna Karlsson

Department of Biomedical and Clinical Sciences,
Center for Social and Affective Neuroscience
Faculty of Medicine and Health Sciences
Linköpings universitet, SE-581 83 Linköping, Sweden
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Study 2 “Choice of alcohol over a natural reward: an experimental study in light and heavy social drinkers” is accepted and soon to be published in Psychopharmacology by Springer Nature.
Abstract

For a minority of alcohol users, the initial sip of alcohol marks the start of a life-threatening process. This thesis studies cognitive mechanisms pertinent to alcohol addiction and its development, using a spectrum of individuals that range from healthy social drinkers, through people with hazardous use, to those suffering from alcohol addiction.

Decision making can be altered in addiction, but less is known on the direct pharmacodynamic effects of alcohol intake in healthy people. Study 1 addressed decision making under the effects of moderate alcohol intoxication in healthy social drinkers using established behavioral economics tasks. The investigated processes encompassed both personal and social aspects of decision making. Within the personal domain, impulsivity and risk taking were investigated, while in the social domain, prosocial attitudes along with moral judgment were assessed. Moderate alcohol intoxication was found to impact only the social domain, leading to increased prosocial and utilitarian behaviors, but did not affect measures of impulsivity.

Choosing alcohol over other natural rewards despite negative consequences is a central phenomenon of alcohol addiction. Two studies of this thesis investigated choice preference for alcohol compared to snack, using a cost manipulation paradigm, in light and heavy drinkers. Study 2 was a laboratory experiment whereas Study 3 was an imaging experiment for characterization of neural substrates. Cost was an important predictor of choice, as in both groups, alcohol choice was sensitive to cost in a parametric manner. This was mirrored in the brain by activity in value-based and salience regions, including orbitofrontal cortex and insula. In Study 2 we found that heavy drinkers showed generally higher alcohol choice preference and attenuated cost sensitivity. Failure to replicate this finding in Study 3, was possibly due to the artificial scanner environment.
Craving is a key component in the cycle of addiction and a determinant of relapse, making it an important target for treatment interventions. **Study 4** was a randomized sham-controlled trial using repetitive transcranial magnetic stimulation (rTMS) targeting the insula as a method to reduce craving and alcohol use in people suffering from alcohol addiction. An overall decrease in alcohol consumption and craving were seen, but did not differ between sham stimulation and rTMS targeting the insula.

In summary, this thesis provides some insights into cognitive mechanisms related to alcohol addiction and processes that may be implicated in its development. During a moderate acute alcohol intoxication in healthy social drinkers, social decision-making is influenced, leading to increased utilitarian and altruistic behaviors. Thus, deficits in prosocial behaviors in people with alcohol addiction are unlikely to result from direct pharmacodynamic effects of alcohol, but are rather likely to reflect a selection of vulnerable individuals, consequences of the addictive process, or both. In individuals at risk of developing alcohol addiction, the sensitivity to the costs associated with choosing alcohol over an alternative reward is largely preserved, though it might be reduced compared to light, non-problem drinkers. Modulation of the insula cortex with TMS was not successful in decreasing alcohol use in individuals with alcohol addiction.

Keywords: alcohol, heavy drinking, alcohol addiction, decision making, alcohol choice, fMRI, rTMS
Sammanfattning


Att välja alkohol framför livets övriga belöningar är ett av kärnsymptomen vid alkoholberoende. Personer med beroendesjukdom hamnar ofta i att välja alkoholen framför exempelvis fritidsintressen, arbete och familj, varför det är viktigt att studera val av alkohol när andra belöningar också finns tillgängliga. Vi rekryterade 30 personer med låg alkoholkonsumtion och 30 personer med hög konsumtion av alkohol. I uppgiften Concurrent Choice Alcohol Food (CCAF) fick deltagarna samlta poäng för alkohol eller snacks. De fick reda på att ju fler poäng de samlade för en belöning, desto större chans hade de att få just den belöningen i slutet av

I den tredje studien tittade vi på förändringar i hjärnans struktur och funktion som kan förklara hur vi väljer alkohol och andra belöningar. Detta gjordes genom att uppgiften från studie två, CCAF, genomfördes på en ny grupp personer som samtidigt undersöcktes i magnetkameran. Studien visade dels att olika hjärnregioner används när vi väljer alkohol jämfört med när vi väljer snacks, men också att vissa hjärnregioner aktiverades mer ju fler poäng det gick att samla för alkohol.

List of original papers

I. Acute effects of alcohol on social and personal decision making
Hanna Karlsson, Emil Persson, Irene Perini, Adam Yngve, Markus Heilig, Gustav Tinghög
Neuropsychopharmacology 2021

II. Choice of alcohol over a natural reward: an experimental study in light and heavy social drinkers
Hanna Karlsson, Sarah McIntyre, Sarah Gustavsson, David Andersson, Ilona Szczot, Markus Heilig, Irene Perini
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III. Neural substrates of choosing alcohol over a palatable food reward in humans
Irene Perini, Hanna Karlsson, Sarah McIntyre, Markus Heilig
Manuscript

IV. Repetitive transcranial magnetic stimulation targeting the insular cortex for reduction of heavy drinking in treatment-seeking alcohol-dependent subjects: a randomized controlled trial
Irene Perini, Robin Kämpe, Theodor Arlestig, Hanna Karlsson, Andreas Löfberg, Michal Pietrzak, Abraham Zangen, Markus Heilig
Neuropsychopharmacology 2020
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Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder
APA: American Psychiatric Association
AUD: Alcohol Use Disorder
AUDIT: Alcohol Use Disorder Identification Test
AUQ: Alcohol Urge Questionnaire
BAES: Biphasic Alcohol Effects Scale
BART: Balloon Analogue Risk Task
BOLD: Blood Oxygen Level Dependent
BrAC: Breath Alcohol Content
CCAF-task: Concurrent Choice Alcohol Food task
CGI: Clinical Global Impression
CPRS-SA: Comprehensive Psychopathological Rating Scale
DEQ: Drug Effect Questionnaire
DSM-5: Diagnostic and Statistical Manual of Mental Disorders 5
DUDIT: Drug Use Disorder Identification Test
FDA: Food and Drug Administration
fMRI: Functional Magnetic Resonance Imaging
FTQ: Family Tree Questionnaire
GABA: γ-Aminobutyric Acid
GCP: Good Clinical Practice
HD: Heavy Drinker
ICD: International Statistical Classification of Diseases
LD: Light Drinker
LME: Linear Mixed Effect model
MINI: Mini International Neuropsychiatric Interview
mPFC: Medial Prefrontal Cortex
MRI: Magnetic Resonance Imaging
NEO-FFI: NEO Five-Factor Inventory
PACS: Penn Alcohol Craving Scale
PETH: Phosfatidylethanol
PFC: Prefrontal Cortex
RCT: Randomised Controlled Trail
rTMS: Repetitive Transcranial Magnetic Stimulation
SCL90: Symptom Checklist 90
SUD: Substance Use Disorder
TI: Temporal Interference
TLFB: Time Line Followback
WHO: World Health Organization
Introduction

From social drinking to alcohol addiction

Alcohol is a commonly consumed drug in Western societies and fermented beverages have been documented as far back as during the Neolithic period [1]. Worldwide, almost half of the population aged over 15 years are currently social drinkers and on average, 6.4 liters of pure alcohol is consumed annually per person [2]. The use of alcohol is the highest in Europe. In Sweden, 81% of people over 15 years have consumed alcohol during the last year, and the annual average use of pure alcohol is 8.5 liters per capita [3].

For most people, alcohol use is a positively reinforced, recreational activity that people typically engage in social settings. However, some people escalate their alcohol use to levels considered hazardous. In Sweden, hazardous levels have long been defined as a use that equals to or exceeds fourteen or nine standard units (12 g / unit) of alcohol per week, for men or women, respectively [4]. Over time, a significant minority of users develops a clinically significant condition that through the years has been referred to by multiple labels. The term alcoholism, still in use by the general public and by the largest client organization, Alcoholics Anonymous, is increasingly considered derogatory, and to be avoided in a scientific context [5]. “Alcohol dependence”, an influential conceptualization of the clinical syndrome introduced by Griffith Edwards [6] was long used as a clinical diagnostic category in the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV manual of the American Psychiatric Association (APA) [7], and remains in use in the World Health Organisation (WHO) International Classification of Diseases (ICD) [8]. With arrival of the DSM-5, the APA manual introduced the broader concept of Alcohol Use Disorder (AUD), with the moderate and severe cases corresponding to alcohol dependence [9]. In the following, unless there is reason to do otherwise, I use the term “alcohol addiction”, equating it to “alcoholism”, “alcohol dependence” or “moderate-to-severe alcohol use disorder”. For a more detailed discussion of how these concepts and
terms are related to each other, see [10] and Figure 1. For diagnostic criteria, see next section.

As for most complex disorders, genetic and environmental factors affect the development of alcohol addiction. About 50% of the variance in risk for alcohol addiction is explained by genetics [11, 12]. Environmental factors such as early-life trauma [13], stress, family background and peer group are well documented risk factors to develop alcohol addiction [14]. Genetic predisposition and environmental factors interact and influence the development of disorder.

The pathophysiology behind alcohol addiction is not yet fully understood, but positive and negative reinforcement is thought to be central in the development and maintenance of the disorder. All higher animals, including humans, have mechanisms that generate pleasure, often referred to as “reward systems”, that have evolved to promote the pursuit of rewards that favor survival and reproduction. The reward system is activated when people, for example, pursue opportunities to eat food or have sex. That said, this same system can also lead to maladaptive pursuits like addictions. Drugs including alcohol can initially positively reinforce behavior through activation of brain reward systems, but persistent drug use in individuals with addiction is often independent from the pleasurable effects of the drug [15]. Intake of alcohol triggers release of endogenous opioids from neurons originating from the lateral hypothalamic area and projecting to the ventral tegmental area (VTA). By activating inhibitory opioid receptors on inhibitory γ-gamma-aminobutyric acid (GABA) interneurons within the VTA, this, in turn, removes the inhibitory GABA tone on mesolimbic dopamine neurons, ultimately resulting in dopamine release in the nucleus accumbens [16-18].

Several influential frameworks have been proposed to conceptualize addiction [19-21]. I have primarily focused on the incentive sensitization theory postulated by Berridge and Robinson, as it is the most relevant in the interpretation and discussion of Studies 2 and 3. This theory conceptualizes drug “reward” as two components, “liking” and “wanting”, that are mediated by dissociable brain mechanism [22]. The concept of “liking” relates to the hedonic reactions to a reward, such as lip-licking
to sweet taste rewards and other orofacial expressions that are conserved across rodents and primates [23]. These orofacial “liking” expressions are generated by opioid and endocannabinoid stimulation of pleasure-generating hotspots in the brain, the latter including portions of the nucleus accumbens, ventral pallidum and orbitofrontal cortex. The "wanting" component relates to the motivational drive that promotes the pursuit of rewards, or “incentive salience”, a kind of incentive motivation mediated by the mesolimbic system and triggered by reward-related cues.

In this framework, addiction can be viewed as the result of excessive incentive salience to drug cues, or “incentive sensitization”. Incentive sensitization posits that repeated exposure to drugs can lead to an increased sensitivity, mediated by upregulated dopaminergic activity, to drug cues, ultimately promoting pathological “wanting” of the drug. This can happen despite the fact that pleasurable drug effects, or “liking”, may in fact have declined, and independently from conscious efforts to stop taking drugs [24, 25]. Critically, negative states can enhance this phenomenon [26, 27], consistent with a process of negative reinforcement. Negative reinforcement is defined as the process by which removal of an unpleasant stimulus or state increases the probability of a response [28]. Negative reinforcement models commonly claim that the negative affect itself, particularly during withdrawal, triggers drug seeking [28] rather than amplifying incentive sensitization [27]. Despite those differences, both conceptualizations emphasize the influence of negative affect in shaping addictive behaviors. This aligns with the perspective that persistent drug seeking does not seem to arise from an automatic, compulsive mechanism, where negative consequences are simply discounted; instead, it is intricately related to them.
Figure 1. The putative relationship between risky substance use, substance use disorder and addiction [10].

Clinical definitions and treatment options

Alcohol addiction is a chronic relapsing disorder in which loss of control over intake, choice of alcohol over natural rewards and excessive use despite negative consequences are central characteristics [7, 29, 30]. In a clinical context, it is observed that what was once significant in a person’s life, such as work, family, and even basic necessities like food, gets overshadowed and replaced by activities related to alcohol. In addition, people with alcohol addiction often develop severe psychiatric and medical comorbidities, as well as interpersonal difficulties [31-33]. These issues are in themselves also triggers of relapse into heavy drinking [34]. To suffer from alcohol addiction shortens life by an average of 20–25 years compared to the corresponding population without an alcohol addiction [35-37].

Although biomarkers for alcohol use exist, such as phosphatidylethanol (PEth), and can help in the assessment of a high use of alcohol [38], there are no biomarkers for alcohol addiction. Thus, clinical diagnosis is established based on criteria that rely on the presence of clinical symptoms.
The DSM manual developed by the APA, and the ICD developed by the WHO are most commonly used for diagnosis. DSM-5 criteria for moderate-to-severe AUD were used to operationalize and diagnose alcohol addiction in Study 4. The criteria for substance use disorder (SUD) are the same for across substances including alcohol, and the AUD are listed below. The presence of two to three criteria classify as mild, four to five criteria as moderate and six to eleven as severe SUD [7].

DSM-5 Alcohol Use Disorder criteria:

A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a 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 alcohol, use alcohol, or recover from its effects.
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 the effects of alcohol.
7. Important 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, as defined by either of the following:
   a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
   b. A markedly diminished effect with continued use of the same amount of alcohol.

11. Withdrawal, as manifested by either of the following:
   a. The characteristic withdrawal syndrome for alcohol
   b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

There are currently three pharmacological treatments for alcohol addiction approved by the US Food and Drug Administration (FDA), and four approved by the Medical Products Agency in Sweden [39]. Disulfiram, also known by the brand name Antabuse, discourages from drinking by inhibiting the enzyme aldehyde dehydrogenase and causing unpleasant symptoms after alcohol intake. Significant treatment effect of disulfiram are only seen with supervised administration by qualified health care personal [40]. Acamprosate (brand name Campral) reduces glutamate transmission and has been shown to significantly increase abstinence rates [41]. Naltrexone (brand name Revia) is an opioid antagonist with a particularly good effect in reducing alcohol use in males, in particular those with a family history of alcohol addiction, in whom use is initially driven by pronounced rewarding effects of alcohol [41-43]. Nalmefene (brand name Revex), another opioid antagonist, is approved for targeted use, i.e. use in situations where a person is at risk of relapse; while not part of the indication, similar effects have been shown using naltrexone [42, 44]. In addition to the medications approved for alcohol addiction, there is some scientific support for off-label use of treatments approved for other indications, including baclofen, topiramate and varenicline [45]. There are also behavioral treatments with good scientific support such as motivational interviewing, community reinforcement approach and relapse prevention based on principles of cognitive behavioral therapy [45].
Although pharmacological treatments for alcohol addiction exists, they are limited in effect size and clinical uptake [41]. Perhaps one of the greatest challenges to the treatment of alcohol addiction is that available evidence-based treatments are not offered to an adequate extent [10, 35, 46, 47]. A major reason why neither Sweden nor other countries are successful in providing treatment to the vast majority of people with alcohol addiction is the stigma that continues to surround this condition and other addictions [35, 48]. This causes people to seek care late in the progression of addictive disorders or not at all, and is a reason the quality of care they receive, if any, is substandard. Understanding the psychological and biological mechanisms underlying alcohol addiction and its development could contribute to reducing stigma associated with the condition.
Cognitive processes of interest

Every day unfolds as a series of moments where people find themselves navigating through multiple choices, each holding the power to shape the course of their lives. Whether it is choosing to drink another glass of wine, decide to impulsively spend money, or engage in a conflict with a colleague, the cumulative effect of daily decisions can be profound. Each choice triggers a consequence that ultimately has an impact on the life of the person making it, and those of others. Daily choices also affect the initiation and maintenance of problematic drinking. Animal studies have recently highlighted the importance of choices between drug and non-drug rewards. Surprisingly, even animals that self-administrate highly addictive drugs such as cocaine or heroin will essentially discontinue this behavior when offered a choice of alternative rewards [reviewed e.g. in [49]]. This thesis targets some of the cognitive processes that are relevant in alcohol addiction and potentially in its development. These processes include decision making under the influence of alcohol, value-based choice of alcohol compared to food, and craving.

Decision making

People with alcohol addiction face various difficulties that can have far-reaching effects on their relationships, work, and overall quality of life [50, 51]. They may exhibit, often under the influence of alcohol, behaviors that contribute to a range of detrimental choices, including engaging in risky activities, neglecting responsibilities, or having confrontational attitudes. These choices affect both the lives of the individuals making them, and the lives of people around them. They can ultimately lead to social exclusion and marginalization, central factors for the initiation and maintenance of alcohol addiction [52].

But when do “bad choices” start? When designing Study 1 we wanted to understand whether alcohol intoxication alone could alter some of the decision-making processes often affected in people with alcohol addiction. We used established behavioral economic tasks to investigate decision making in personal and social domains, in a controlled experimental setting that allowed causal inference. To parse out effects of alcohol from those of alcohol addiction, rather than recruiting people diagnosed with
alcohol addiction, we investigated a large sample of healthy social drinkers during acute alcohol intoxication. People with alcohol addiction have grey matter loss mainly in the prefrontal cortex (PFC), insula and the posterior cingulate cortex [53], regions that are central for decision-making [54-56]. Therefore, in people with alcohol addiction, it becomes impossible to disentangle the consequences of neural damage from the acute effects of alcohol, potentially confounding any conclusions that are made regarding the effects of intoxication. In addition, people with elevated genetic risk of developing alcohol addiction may also have pre-existing impairments of decision making. Thus, even absent impairments secondary to developing addiction, any abnormalities seen in patients with this condition could reflect selection rather than alcohol effects.

**Personal decision making: impulsivity and risk taking**

To investigate decision making in the personal domain we used tasks that examine waiting impulsivity and choice under risk. In behavioral economics terms, waiting impulsivity is commonly defined as the tendency to choose smaller and more immediate rewards over those that are larger but more distant in time [57]. As stated above, alcohol addiction is associated with grey matter loss in the PFC, which results in impaired cognitive control, including delay discounting [58]. Accordingly, Attention Deficit Hyperactivity Disorder (ADHD), a condition characterized by increased impulsivity, is associated with increased rates of alcohol addiction [59, 60]. Although alcohol is commonly held to increase impulsivity, available studies make it difficult to disentangle to what extent impulsivity is a cause vs. a consequence of alcohol use [61], highlighting the importance of investigating impulsivity as a trait.

Prior studies have shown mixed results on waiting impulsivity during acute alcohol intoxication. One study showed increased impulsivity [62], one decreased impulsivity [63] and five none or very little effect of alcohol intake on impulsivity [64-68]. In addition to being inconsistent, these studies are also limited by small sample sizes. To fill this knowledge gap, we tested a large sample using an established task that assesses impulsivity by investigating participants’ preferences for real monetary rewards disbursed at different points in time [69, 70].
Risk taking represents a different dimension of impulsive behavior. It has been shown that alcohol use is positively correlated with a variety of risk taking behaviors, such as crime, violent behavior, high-risk sexual behavior and high risk driving that results in motor vehicle accidents [71]. Critically, the mortality and morbidity in alcohol addiction is partly attributable to the relationship between alcohol use and high-risk behavior. Clinically, risk typically refers to exposure to harm or loss in a broader sense, while in neuroeconomic contexts, it is defined more specifically as variability of possible monetary outcomes [72]. At group level, people show loss aversion i.e., they tend to dislike losses more than they like gains of the same magnitude. Prospect theory has established that people assess their loss and gain perspectives in an asymmetric manner, resulting in a greater risk aversion for gains than for losses [73]. To assess the acute effects of alcohol on risk taking, we used two different tasks. One risk task covers cognitive and intuitive aspects of decision making via prospect theory gambles [73]. The second task, the Balloon Analog Risk Task (BART) [74], primarily taps into more intuitive, affect-laden decision making.

Just as with impulsivity, evidence regarding the effects of alcohol intoxication on risk taking in healthy volunteers is mixed. Two studies prior showed increased risk taking [66, 75], whereas some other studies showed no altered risk taking during alcohol intoxication [62, 68, 76, 77]. Among moderate powered studies, Bernhardt et al. [68] used a within-subject design in 54 adolescent males, showing no effects of alcohol intake versus placebo on waiting impulsivity or risk taking. Conversely, in a study using the BART task with 142 individuals, increased risk taking was observed after administration of alcohol at dose of 0.6 g/kg compared to placebo [78]. Overall, the majority of studies investigating risk taking have been constrained by small sample sizes, and well-powered studies available are inconsistent.

**Social decision making: prosocial behavior and moral judgment**

Beyond personal decision making, we also tested “social” decision making, which we define as the cognitive processes leading to choices that impact others. As mentioned above, progressive social exclusion [52]
and impairments in social functions are often observed in alcohol addiction [79]. Impairments in prosocial behaviors have been reported in alcohol use disorder [80], but little is known regarding effects of alcohol intoxication on these processes in social drinkers. Our focus was on processes which are central for human social interaction, specifically altruism [81] and moral judgment.

Altruism is a form of prosocial behavior that implies accepting a personal cost to benefit others [82], whereas moral judgment refers to the process where an opinion is formed whether an act is right or wrong. Deontological and utilitarian moral theories provide two different approaches to determining the morality of actions. In deontological ethics, the morality of an action is based on whether that action itself is right or wrong according to a set of rules or principles, irrespective of the consequences of the action [83]. Conversely, utilitarian ethics emphasizes the centrality of the consequences in decision making. Whether an action is acceptable depends on whether the aim is to maximize happiness or well-being for all affected individuals [84].

Only a few studies have examined moral judgment and altruism during acute alcohol intoxication [62, 77, 85, 86]. Two experimental studies showed no change in, or decreased altruism after alcohol use, but these were limited by small sample sizes. One experimental study showed no effect on moral decision making after alcohol intake, but also this study was limited by a small sample size. A study by Duke & Begue assessed moral judgment using an observational field paradigm, approaching people with a structured questionnaire in a bar environment [85]. This study showed that blood alcohol concentrations were positively correlated with utilitarian preferences. However, since the method was correctional, it cannot provide answers about the causal relationship between alcohol intake and moral decisions. Once again, the evidence on the effect of alcohol intoxication on moral judgment and altruism is limited and inconclusive.
Value-based alcohol choice preference

Multiple and diverse reward-predictive stimuli are constantly and concurrently present in the environment. The cognitive process behind the assessment of prospective rewards is a central modulator of behavior. As mentioned earlier, one of the central features of alcohol addiction, shared with other addictive disorders, is a consistent tendency to prioritize alcohol over healthier alternative rewards [30, 49], independently of the severe negative consequences associated with alcohol use [7]. In other words, people with AUD tend to choose alcohol in a “compulsive” manner [21]. Currently, there is no conclusive evidence regarding the mechanisms causing this consistent shift of choice preferences towards alcohol-related rewards. Several possibilities need to be considered. Pathological alcohol choice could e.g. be the result of attributing greater expected value to alcohol, consistent with the incentive sensitization theory of addiction, resulting in an increased ability of this reward to outweigh the negative consequences associated with its use. Another, mutually non-exclusive possibility is that choice preferences shift in alcohol addiction due to an excessive devaluation of the negative consequences.

Studies 2 and 3 in this thesis provide some insights into these questions in people at risk of developing alcohol addiction.

Animal models of compulsivity typically pair a foot shock when the animal chooses a drug [21]. A recent human study based on these animal models assessed compulsivity in light and heavy drinkers using a task where participants could earn alcohol or food points at the risk of receiving electric shocks delivered to the wrist. Results showed that, compared to light drinkers, heavy drinkers attempted to earn more alcohol points when those were associated with a high probability of receiving an electric shock, indicating a more compulsive behavior [87]. While this task was informative in establishing a compulsive behavior, it presented the reward related cues in a sequential order and not concurrently.

In fact, until recently, modern neuroscience has typically studied drug seeking and taking in the absence of other available rewards, despite early evidence that this is a critically important determinant of these behaviors [49, 88]. While this research originally focused on opioids and stimulants, it has then become apparent that the presence of an
alternative reward is equally important for alcohol seeking in experimental animals. For instance, a study in rodents by Augier et al. showed the importance of concurrently presenting an alternative reward to alcohol [89]. In the absence of alternative rewards, almost all rats acquire and maintain alcohol self-administration. However, this behavior is profoundly affected by the presence of a high value non-drug alternative. Augier et al. showed that when rats were presented with a mutually exclusive choice of alcohol and a highly palatable, non-caloric sweet solution, only 15% of the rats chose alcohol, while the remainder chose the sweet solution. This proportion of rats choosing alcohol in the presence of an alternative reward is similar to the percentage of human alcohol users who develop AUD, making this finding of particular translational value. Using this approach, this study also identified that decreased expression of the GABA transporter GAT-3 in the central nucleus of amygdala was the determinant of the alcohol-preferring phenotype [89].

In humans, a concurrent choice paradigm based on rodent choice models was designed by Hogarth et al. to address not only the overall preference for alcohol vs. food, but also the sensitivity to costs associated with choosing alcohol [90]. As this paradigm allowed the investigation of cost sensitivity in a setup where both alcohol and snack were presented concurrently, we used a modified version of this task, which we called the Concurrent Choice Alcohol Food (CCAF) task. In contrast to the model by Grodin et al., where the cost associated with alcohol was in the form of a potential physical threat, our cost manipulation was related to the ability to assess the relative value of the presented rewards. In the CCAF task participants chose to accumulate points associated with alcohol or snack images and could exchange these points for the respective reward at the end of the session. Sensitivity to cost was assessed by manipulating the points associated with alcohol and snack. The points could be the same for the two rewards, in favor of alcohol, or in favor of snack. Therefore, the relative cost of choosing alcohol was the highest in the latter condition, as alcohol choice here was associated with the loss of anticipated maximal earning of the alternative snack reward. We first characterized behavioral responses at the CCAF task in Study 2, and in Study 3 we studied the neural correlates of choice behavior in this task while participants lied in the magnetic resonance imaging (MRI) scanner.
Craving and relapse

One of the biggest challenges in addiction treatment is preventing relapse. For several drugs including alcohol, studies show that about 85% of patients relapse and return to drug use within a year of treatment [91]. A recent large systematic review and meta-analysis suggests that craving plays a significant role in relapse to drug use [92]. Drug craving is a complex psychological phenomenon and is generally defined as a strong desire to use a drug [93]. Although long questioned as a valid construct due to its subjective nature, craving is currently thought to be central to the disorder of addiction, and constitutes a diagnostic criterion in the DSM-5, defined as "a strong desire for drugs" [7]. People suffering from addiction describe craving as the cause of relapse in retrospective studies [94, 95]. It has also been shown that the clinical efficacy of treatment strongly correlates with its ability to reduce craving [96, 97]. Based on the strong evidence that craving is central to relapse, there are clear incentives to try to reduce craving to treat addiction.

In Study 4 we investigated whether craving for alcohol could be decreased by modulation of the insula using deep repetitive transcranial magnetic stimulation (rTMS) in people with alcohol addiction, and whether this would result in reduction in measures of alcohol use. Insula is a heterogeneous region, involved in interoception [98] and salience processing [99, 100]. It has been shown that activity in the insula correlates positively with craving for cocaine and cigarettes [101, 102] and with drugs in general [103]. The most causal evidence regarding the role of the insula in craving comes from a lesion study and a rTMS Randomized Controlled Trial (RCT) in smokers. Smokers with lesions in the insula were more likely to quit smoking effortlessly and without relapsing than those with lesions not involving the insula [104]. Accordingly, a rTMS study targeting the insula and PFC showed long-term reduction in smoking in individuals with nicotine addiction [105], a finding subsequently replicated in a larger multi-center study [106]. Based on the mechanistic evidence and causal findings, we investigated whether rTMS targeting the insula could be beneficial for individuals with AUD.
Aims

The overall aim of this doctoral thesis is to obtain an improved understanding of mechanisms that contribute to the development of alcohol addiction, and to explore a potential treatment option. Specifically, we aimed to address the following questions:

Study 1. Acute effects of alcohol on social and personal decision making
Does acute alcohol intoxication affect social and personal decision making in social drinkers?

Study 2. Choice of alcohol over a natural reward: an experimental study in light and heavy social drinkers
Do heavy drinkers show an altered alcohol choice preference for alcohol over a concurrently presented natural reward when compared to light social drinker?

Study 3. Neural substrates of choosing alcohol over a palatable food reward in humans
What are the neural correlates of alcohol choice preference?

Study 4. Repetitive transcranial magnetic stimulation targeting the insular cortex for reduction of heavy drinking in treatment-seeking alcohol dependent subjects: A randomized controlled trial
Does deep rTMS targeting the insula have potential in the treatment of alcohol addiction?
Study population

The study populations in the four studies reflect the dissertation’s overall goal of improving the understanding of how alcohol addiction develops. We used different populations across the clinical continuum, from non-problematic social drinkers, through heavy social drinkers, to patients with a clinical diagnosis. This allowed us to study cognitive processes of interest before these become potentially confounded by secondary effects of excessive alcohol use and associated lifestyle factors.

Specifically, Study 1 examined healthy social drinkers, to assess the effects of alcohol on decision making while excluding potential impairment to brain structure and function due to excessive alcohol use. In Studies 2 and 3, healthy social drinkers were compared to people who engage in harmful alcohol use. Harmful use was defined as women drinking more than nine glasses per week and men drinking more than fourteen glasses per week. The main purpose of using these two populations was to replicate prior behavioral findings [90], improve on the task, and determine its potential as a tool in characterization of the risk for alcohol addiction.

In Study 4, participants with a moderate to severe AUD according to the DSM-5 were included. Here, the aim was to target neural mechanisms previously postulated to contribute to craving and relapse, and to examine whether an intervention targeting these mechanisms would reduce alcohol use. People who in any way were at risk by participating in the respective studies were excluded from participation, as discussed further in the study summary and in the Ethics section.
Methods

The first and the last studies in this thesis were RCTs, in which experimental intervention or active treatment were compared with placebo under double-blind conditions. **Studies 2 and 3** were experimental studies conducted in laboratory and MRI settings.

In recent years a replication crisis has been described in psychological sciences, where many of the scientific studies are difficult or impossible to reproduce [107, 108]. Pre-registering hypothesis, study designs and planned analyzes are believed to improve the prospects of obtaining findings that can be replicated, and **Study 1** was pre-registered for this reason. **Study 4** was also pre-registered, as that is a regulatory requirement for clinical trials.

Various methods were used to answer the questions of this thesis, including tasks assessing behavior, questionnaires assessing drug use severity and personality traits and psychiatric symptoms, and methods for measuring and manipulating brain activity. Several of these methods were used repeatedly in the four studies, as shown in Table 1.
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*Table 1.* BART=Balloon Analogue Risk Task, CCAF=Concurrent Choice Alcohol Food, AUDIT=Alcohol Use Disorder Identification Test, DUDIT=Drug Use Disorder Identification Test, FTQ=Family Tree Questionnaire, DEQ=Drug Effect Questionnaire, BAES=Biphasic Alcohol Effect Scale, AUQ=Alcohol Urge Questionnaire, PACS=Penn Alcohol Craving Scale, SCL90=Symptom Checklist 90, MINI-Mini International Neuropsychiatric Interview, CPRSA-SA=Comprehensive Psychopathological Rating Scale Self-rating Scale For Affective Syndromes, CGI=Clinical Global Impression, NEO-FFI=NEO Five-Factor Inventory, fMRI=functional Magnetic Resonance Imaging, rTMS=repeated Transcranial Magnetic Stimulation.
Methods for assessing behavior

Behavior can be defined as all observable and measurable actions, reactions and activities performed by an individual in a given situation. In this thesis, observable behavior has been assessed using several tasks, of which the most relevant are described below.

Waiting impulsivity

In Study 1, we measured participants’ choice of financial reward delivered at different timepoints. In the task the participants made choices between smaller rewards that would be delivered sooner and larger rewards that would be delivered later [69, 70]. Two types of waiting impulsivity were assessed. Patience was based on the proportion of choices where the participant chose a larger reward disbursed two weeks after the day of the experiment rather than a smaller amount of money disbursed directly after completion of the experiment. The second assessment, present bias, describes a sharp rise in discounting rate for rewards delivered closer to now [69, 109]. This was measured by calculating the difference for each individual between patience and the proportion of choices where the participant chose a larger reward disbursed three weeks after the experiment rather than a smaller amount paid out one week after the experiment.

Risk taking tasks

Risk taking was assessed in Study 1 using two tasks. One was a task based on prospect theory [73]. Here, participants were given the choice of either accepting an amount of money with certainty or participating in a lottery. The choice was made in three different domains, one where the participants could win money, one where they could risk losing money, and one where they could either win or lose money in the lottery. The main dependent variable for each domain was the proportion of choices where the participant chose to participate in the lottery. The other task was the BART, which is a computer-based neuroeconomic task designed to experimentally investigate risk taking [74]. A picture of a balloon was shown on the computer screen for each trial. The participants were told that they could earn money by inflating the balloon. By pressing a button, the balloon was pumped up and became bigger, and each pump
increased the earnings by 0.10 SEK. With each pumping, the balloon also risked bursting. All money for a trial was lost if the balloon burst before the participant chose to stop that trial. The participants could choose to stop pumping at any time and by that collect the earnings for that trial. Risk taking was measured as the average number of pumps per trial, excluding trials on which the balloon exploded.

**Dictator game**

The dictator game is a paradigm that was used in Study 1 to assess altruistic behavior [110]. In the original version of the dictator game, the participant decides how a sum of money should be distributed between the participant and another person. We used a modified version of this task [111], where the participant got a sum of money and then decided how much to donate to charity organization and how much to keep for themselves. The main dependent variable in the task was the total amount of money donated to charity.

**Moral judgement**

In Study 1, we used four different types of sacrificial moral dilemmas, also known as “Trolley Problems”. These dilemmas examine choices between utilitarian and deontological moral decisions [112, 113]. In each dilemma, participants choose between saving a certain number of people by sacrificing one person. Killing one person to save several others is a utilitarian decision. In contrast, deciding to not kill one person is a rule-based deontological decision, following the principle that the action of harming another person is unacceptable, irrespective of the consequences. The classic version of the Trolley problems is the switch dilemma, in which a trolley is driving towards five workers on a track. If the participant does nothing the five workers will die, but the participant can choose to pull a switch to save the five workers. If the participant pulls the switch the train will change track and instead kill one person. Another version of the Trolley problems is the footbridge dilemma where the participant is standing on a bridge and instead can sacrifice one person by pushing that person in front of the train to save five other people. In Study 1 two additional scenarios were included built on the same principles as the switch dilemma. The main dependent variables were
calculated as the proportion of utilitarian choices made by each participant in all scenarios.

**Concurrent Choice Alcohol-Food task**

The CCAF task was modified from Hogarth et al. [90] and used in Studies 2 and 3. The modification included general simplification of the task conditions to optimize it for fMRI analysis, as ultimately, we were interested in probing the neural correlates of alcohol choice preference. Another notable modification was that reward related images were personalized. Before engaging in the task, participants chose their favorite snack and drink from a selection of four items per reward, and pictures used in the task were tailored to participants’ preference. In the task, participants collected points for either an alcoholic drink or a snack, and were told that the more points they collected towards a reward, the higher their chance to receive that reward at the end of the experimental session. Specifically, during each trial, participants were presented with two concurrent pictures showing their favorite snack and their favorite alcoholic drink. Each alcohol and snack picture was associated with either one or three points. When both pictures were associated with either one or three points, the relative point level was equal (0). When the relative point level differed, it could be in favor of alcohol (+2) or snacks (-2). The dependent measure here was percentage of alcohol choice, reflecting the proportion of trials in which alcohol was chosen instead of snack.
Methods measuring and manipulating brain activity

Alcohol addiction is a brain disorder, and methods for measurement and manipulation of neural activity were used in this thesis. Specifically, rTMS targeting the insula was used to investigate if craving and alcohol use could be reduced in people with alcohol addiction. In Study 3 fMRI was used to investigate the neural correlates of alcohol choice preference, and in Study 4 to assess insula activity after rTMS treatment.

Magnetic Resonance Imaging

MRI is a non-invasive method for studying the structure and function of the brain. MRI uses a strong magnetic field that is generated around a person, forcing protons in brain tissue to align with the field. Radio frequency currents are then sent as a pulse through the tissue. This excites the protons, making them spin out of equilibrium. When the radiofrequency pulse is turned off, the protons realign with the field, and this results in emission of weak radio waves as energy is released. This signal is picked up by detectors in a detector coil, and converted into images of the body’s organs and tissues, or functional measures, through computer analysis [114].

fMRI sequences allow acquisition of information on metabolic changes in the brain, providing an indirect measure of brain activity. Changes in fMRI signal are the result of a change in balance between oxygenated and de-oxygenated hemoglobin in brain vessels, the so-called Blood Oxygen Level Dependent (BOLD) signal. The BOLD signal is measured while the participant performs various tasks. By comparing the BOLD signal during a task and the BOLD signal during a control task or at baseline, it is possible to identify regions of the brain that are involved in performing that task. Compared to other available methods investigating brain function in humans, such as for example electroencephalography, MRI has a good spatial resolution but limited temporal resolution. From a “neural perspective” however, both spatial and temporal resolutions are limited [115]. The fMRI sequences applied here, on a 3 Tesla scanner, had a spatial resolution (voxel size) of 3 mm isotropic voxels, which can be compared to the size of a typical neuron, which ranges between 5-10 µm in diameter. The temporal resolution of fMRI is also highly limited
compared to a neural timescale. The hemodynamic response time is approximately five seconds following stimulus onset, while neural action potentials occur on a timescale of milliseconds [116]. To extract, to the extent possible, measures related to neural responses, the specific BOLD response to a stimulus is modelled such that the signal at time $t$, $y(t)$, is modeled as the convolution of a stimulus function $s(t)$ and the hemodynamic response function $h(t)$, i.e. $y(t) = (s * h)(t)$. An implication of this approach is that BOLD fMRI studies are sensitive to confounds when blood flow or oxygen extraction is affected by factors other than the specific stimuli used, such as e.g., drug effects on brain vasculature. If standard safety guidelines are followed, there are no known risks using MRI.

**Repetitive transcranial magnetic stimulation**

TMS is a non-invasive brain stimulation technique, in which an oscillating current is sent through a coil positioned on the head of the participant. Through induction, this generates magnetic pulses that reach brain regions targeted by the coil. As a result, an electric field is generated in axons that traverse the magnetic field at an angle. If this field is of sufficient intensity, neurons will be depolarized or hyperpolarized, depending on the stimulation frequency. For instance, a single pulse applied to the motor cortex can cause motor neurons to fire, resulting in a twitch of the corresponding muscle. When trains of pulses are repeatedly delivered (rTMS), effects on excitability can be obtained that persist for some time after stimulation has been terminated, typically approximately 50% of stimulation length. If multiple sessions of rTMS are carried out over days or weeks, effects on excitability are thought to potentially persist for much longer periods of time. This is thought to be the basis for the ability of rTMS to produce clinically meaningful therapeutic effects in depression and obsessive-compulsive disorder [117, 118].

The most common coil for TMS is a so-called “figure-of-eight” coil. When using this coil, the intensity of the magnetic field is maximal near the cortical surface of the brain and decreases exponentially as a function of distance into deeper regions. To modulate deeper regions, such as the insula, higher current must be passed through the coil. With a figure-of-eight coil, the levels of stimulation needed to reach the insula would be harmful for the overlying superficial brain regions. An H-coil has been
designed to produce a less steep decline of field intensity with distance, allowing stimulation of deeper regions without the need to drastically increase stimulation intensity [119]. While H-coils allows for stimulation of deeper regions, the stimulation can't be focal, as the TMS-induced electrical field extends across brain regions between the coil and the deep brain region of interest. Treatment with deep rTMS using a H-coil is considered safe when conducted within published international consensus safety guidelines [120, 121].

Questionnaires
In all four studies, self-reported measures were collected using established questionnaires. Variables related to alcohol and drug use, psychiatric symptoms and personality traits were used as outcome measures, manipulation checks, for baseline characteristics or as covariates in the analysis.

Alcohol and drugs
We used several questionnaires to measure different aspects of alcohol use, including effects of alcohol, craving and use. The Alcohol Use Disorder Identification Test (AUDIT) [122] was used in all studies and Drug Use Disorder Identification Test (DUDIT) [123] was used in Studies 2, 3, and 4 for screening. The AUDIT was developed by the WHO and is frequently used to identify hazardous or harmful alcohol use; the DUDIT, developed by Swedish researchers, is patterned on the AUDIT, in order to screen for hazardous use of addictive substances other than alcohol. Timeline Follow Back (TLFB) was used in Study 4 and is a validated method that is routinely used in FDA-regulated trials on alcohol addiction treatments [124]. TLFB is a tool to evaluate alcohol use over time by registering the frequency and volume of alcohol intake. In all studies, the Family Tree Questionnaire (FTQ) [125] was used to assess the family history of alcohol addiction. In Study 4 craving for alcohol was assessed with the Penn Alcohol Craving Scale (PACS) [126] and the Alcohol urge questionnaire (AUQ) [127]. In Study 1, the Drug Effect Questionnaire (DEQ) [128] was used to measure the subjective experience of drinking alcohol and the biphasic effects of the alcohol were measured using the Biphasic alcohol effect scale (BAES) [129].
Psychiatric symptoms

Psychiatric symptoms were assessed in all studies using questionnaires. In Study 1, the Symptoms Checklist (SCL90) was used to screen for psychiatric symptoms [130]. The primary purpose of using the questionnaire was to use psychiatric symptoms as covariates when analyzing the data and not for safety or inclusion reasons. Participants with risk scores for suicidality or a high probability of suffering from any clinically significant psychiatric disorder as assessed by a clinician received a shorter consultation. If they fulfilled criteria for a current psychiatric disorder or were at risk of suicide, they were excluded from the study and if necessary, the clinician referred the participant to health care for further help.

In Studies 2 and 3, a screening questionnaire for psychiatric symptoms was used to assess eligibility for participation. We used the Mini International Neuropsychiatric Interview (MINI) screen, a validated screening companion to the diagnostic MINI interview [131]. The full MINI interview [132] assesses the most common psychiatric diagnoses in DSM-5, and was used to evaluate inclusion and exclusion criteria in the clinical population in Study 4. The severity of depression and anxiety symptoms was obtained repeatedly during the study by self-report using the Comprehensive Psychopathological Rating Scale (CPRS-SA) [133] and global clinical impression was repeatedly assessed by a clinician by using the Clinical Global Impression (CGI) [134].

Personality traits

The NEO Five-Factor Inventory (NEO-FFI) [135] is an established questionnaire for assessing personality according to the five-factor model. The five different domains of personality have been used as a covariate in the statistical analyzes in all four studies.
Laboratory-based outcome measures

In some of the studies in this thesis, objective outcome measures were used as a complement to the subjective data from questionnaires described earlier. In Study 4, PEth in serum was analyzed as a measure of alcohol use and used as a co-primary outcome measure. PEth has high specificity and moderate sensitivity for the use of alcohol in the weeks before testing [38]. Measurements of alcohol concentration in exhaled air (BrAC) can be used to measure alcohol levels at the time when the sample is taken. BrAC was used as an objective manipulation check in Study 1. In all studies BrAC was measured as a screening tool to make sure that all participants were sober when starting the study or experiment.
Ethics

All studies included in this thesis have been approved by the Regional Ethics Review Board in Linköping or the Swedish Ethics Review Authority (Study 1 Dnr 2016/496-31, Studies 2 and 3 Dnr 2020-04019, Study 4 Dnr 2015/130-31). All studies were performed in accordance with the Declaration of Helsinki. Some ethical considerations regarding the work presented in this thesis are discussed below.

Moderate doses of alcohol to healthy participants

In Study 1, healthy subjects were randomly assigned to consume either alcohol or a placebo drink. The goal was to reach a breath alcohol concentration of around 0.6‰, a level commonly reached by non-dependent people in social situations. This drinking procedure has repeatedly been used in healthy adults without adverse effects [65, 136, 137]. Inclusion required that the participant had drunk any alcohol in the last three months, and, at some point, had consumed a similar amount of alcohol as that offered in the experiment. Participants that during screening reported physical illness, mental illness, suicidality, or pregnancy that would make the intoxication with alcohol a risk were excluded. If necessary, a referral for further health care was offered. To minimize discomfort and potential risks, participants were offered snacks and could stay at the center to sober up after finishing the experiment. Before and after the session, participants were told that they were not allowed to leave the experiment by car. With these safety measures, the risks of this procedure were considered very low.

Giving alcohol to heavy drinkers

In Studies 2 and 3, choice preference for alcohol over natural rewards was investigated using a choice task. People with heavy drinking were compared to people with light social drinking. Before the session, participants were presented with four different alcoholic drinks and four different snacks. They could smell and handle the drinks and snacks, which could trigger craving. At the end of the session, the participants were offered a standard glass of alcohol if they collected the most points for this reward category. This procedure was intended to increase the
participants motivation. Offering alcohol to individuals at risk of developing alcohol addiction may be perceived as problematic. However, a number of safety measures were taken, in line with guidelines from the American National Institute on Alcohol Abuse and Alcoholism [138]. People who had not drunk alcohol for the last three months or people who were actively seeking help for their alcohol use were excluded from the study. For participants who were heavy drinkers, the amount of alcohol in this study was negligible compared to their regular use, and should therefore not affect their risk of problems related to alcohol intake [139].

Our eligibility evaluation included evaluation of hazardous drinking using the WHO-recommended screening instrument, AUDIT. People whose AUDIT scores indicated hazardous or harmful drinking received feedback from an experienced clinician after completing the experiment, and were offered referral for treatment. This was done both in Studies 2 and 3. When conducting studies using these procedures, it is believed that participants may benefit from participating, rather than being at risk of exacerbating their issues. Evaluation and feedback that results in a brief intervention is a method known to promote reduced use [139, 140].

To trigger cravings in people with alcohol addiction

Every rTMS session in Study 4 started with a presentation of an alcohol cue as a craving provocation that aimed to increase the efficacy of rTMS. This procedure has earlier shown to increase effect of rTMS in a nicotine trial [105]. Participants were first asked to pour a glass of water and handle it for five minutes. They were then asked to choose their favorite alcohol beverage, pour a glass of the drink and handle it for 5 minutes without drinking it. All participants who experienced a strong craving after the procedure received support from an experienced clinician and the opportunity to stay at the center until the craving subsided. A clear reduction in alcohol use was later seen both in people who received active treatment and those who did not. An explanation for this could be that exposure to craving five days a week for three weeks with the support of a clinician can be seen as a cue exposure therapy. This is a behavioral treatment for alcohol addiction, in which patients get exposed to alcohol cues to extinguish conditioned craving responses [141].
Incidental findings in healthy volunteers

Two of the studies in this thesis included collection of MRI-data. The structural MRIs were evaluated by a radiologist, and in some cases the scan revealed incidental findings that could have a clinical significance. Participants were informed of any potentially clinically significant findings by an experienced physician and were followed up until resolution. This could cause anxiety and unnecessary examinations in a symptom-free person, and participants were informed about the risk before joining in the study. At the same time, this could also reveal a disorder at an early stage, offering the opportunity for timely intervention. In a similar way, participants in all studies were screened for psychiatric symptoms such as depression, anxiety and suicidality. This could feel exposing, as participants were asked to answer sensitive questions and were aware that study personal would read their answers. Participants reporting psychiatric symptoms were offered a consultation with an experienced clinician, and if needed, were referred to appropriate further care. While this procedure could cause some discomfort, participants reporting psychiatric symptoms could benefit, as this procedure served as the initial step towards seeking assistance and potentially improvement of symptoms.
Summary of papers

1. Acute effects of alcohol on social and personal decision making

This study was a preregistered randomized placebo-controlled study where we used a parallel group design. The study aimed to assess the acute effects of alcohol on social and personal decision making. It was published in Neuropsychopharmacology.

Methods

Study procedure. The study involved a single session comprising five phases: screening, questionnaires for baseline assessments, intake of drink, behavioral testing using decision making tasks performed at a computer, and a final phase with end-of-session questionnaires (Figure 2). Participants were randomized to receive an alcoholic drink corresponding to a breath alcohol concentration of about 0.6‰ or a placebo drink. After drink intake, participants carried out the tasks.

Participants. All prospective participants were evaluated for eligibility by a research nurse or a physician, then randomized to “alcohol group” (n = 128) or “placebo group” (n = 136).

Tasks. A series of a behavioral economic task were used to investigate impulsivity, risk taking, prosocial behavior and moral judgment are described in detail in the Methods section.

Figure 2. Study 1 timeline.
Results

Participants. We obtained expected BrAC values and subjective drink effects in both alcohol and placebo groups. In the alcohol group, a BrAC level of approximately 0.5‰ was reached when the behavioral testing started and remained stable until end of session. The alcohol group showed the expected stimulant and sedative effects of alcohol. In addition, a clear effect of alcohol on the “Feel drug” and “High” items of the DEQ was seen.

Tasks. Participants in the alcohol group exhibited more altruistic and utilitarian behaviors compared to those in the placebo group. Specifically, participants in the alcohol group donated more money to a charity. In sacrificial dilemmas, participants in the alcohol group chose more often to kill one person to save five people in all but the footbridge scenario. No effect of alcohol on risk taking or waiting impulsivity was found.

Conclusions

A robust effect of alcohol was found on both altruistic behavior and moral judgement, but no effects on risk taking or waiting impulsivity. This indicates that alcohol at low to moderate doses primarily affects decision making in the social domain, but not in the personal domain.
2. The behavioral mechanisms of alcohol choice preference

The study aimed to characterize choice preference for alcohol over natural rewards using a concurrent mutually exclusive choice task, and compare choice behavior between people with heavy compared to light social drinking. This study is provisionally accepted in Psychopharmacology pending revision.

Methods

Figure 3. Study 2 timeline.

Study procedure. The study involved a single session, with five phases. Participants underwent screening, and upon inclusion filled out questionnaires for baseline assessments. They then received instructions and picked their favorite drink and their favorite snack. Afterwards, they carried out the CCAF. Upon completion, they received a reward depending on their overall choice at the CCAF task (Figure 3).

Participants. 60 participants were grouped into light drinkers (LD, N = 30) and heavy drinkers (HD, N = 30) depending on the self-reported number of drinks per week. Heavy drinking was defined as 14 or more drinks per week for males and 9 or more drinks/week for women.

CCAF task. Participants carried out the CCAF task, described in detail in the Methods. Briefly, participants accumulated points associated with concurrently presented pictures of their favorite alcohol or snack rewards. Point values varied, so that they favored alcohol or snack, or were equal, resulting in three different relatively point levels. Percentage of alcohol choice was compared between groups and across relative point
levels, extracted for each participant. Correlations between percentage of alcohol choice and AUDIT scores were also analyzed.

**Results**

*CCAF task.* Percentage of alcohol choice was predicted by group, with increased alcohol choice preference in heavy drinkers. A robust overall sensitivity of choice behavior to relative point level was observed, with progressively higher alcohol choice as alcohol was associated to more points. While sensitivity to costs associated to choosing alcohol was present in both groups, it was significantly lower in heavy drinkers. Finally, percentage of alcohol choice correlated positively with AUDIT scores, replicating previous findings.

**Conclusions**

The relationship between severity of alcohol use and alcohol choice preference indicates good external validity of the task. In heavy drinkers, we found higher alcohol choice preference together with attenuated, but largely preserved, sensitivity to costs. Altogether these behavioral findings suggest that individuals at risk of developing AUD might attribute a higher relative reinforcing value to alcohol compared to natural rewards.
3. Neural substrates of choosing alcohol over a palatable food reward in humans

This project builds on Study 2 but extends the investigation to the neural correlates of alcohol choice preference by using fMRI. The manuscript associated to this study is in preparation.

Method

Study procedure. The experiment consisted of two visits. Similar to Study 2, during the first visit, participants were screened, filled out questionnaires and received task instructions. During the second visit, they chose their favorite drink and snack and were then invited to the MRI session, where they carried out the CCAF task. After scanning, snack or a drink associated with their wins was offered at the end of the session (Figure 4).

Participants. 61 participants were grouped into LD (N = 30) and HD (N = 31) as defined above, based on the self-reported number of drinks per week.

CCAF task. Task features and related measures followed those in Study 2, but the task was performed in the MRI-scanner.

Results

CCAF task. As in Study 2, alcohol choice preference was sensitive to relative point level in both groups. However, increased alcohol choice preference in HD compared to LD was not replicated.
Brain correlates to CCAF task. Brain activity in orbitofrontal cortex and insula was associated with relative point value during choice of alcohol, independent of group. Different neural signatures were also associated with choice of alcohol compared to snacks. When choosing alcohol vs. snacks, activation was seen in orbitofrontal cortex, midcingulate cortex, and dorsal striatum. No significant between-group difference in brain activity was observed.

Conclusions

Sensitivity to costs is generally preserved in individuals at risk of developing alcohol addiction, and it is processed by regions involved in value attribution and salience processing. The lack of between-group replication of the behavioral finding suggests that this result is more susceptible to potential sources of variance, which in this case could be attributed to the MRI environment and different participant characteristics with regards personality traits.
4. Repetitive transcranial magnetic stimulation targeting the insular cortex for reduction of heavy drinking in treatment-seeking alcohol dependent subjects: A randomized controlled trial

The aim of this double-blind RCT was to investigate the potential efficacy of rTMS targeting the insula in alcohol addiction. This study was published in Neuropsychopharmacology 2019.

**Method**

**Study procedure.** This project had three phases: screening, treatment and follow-up. During the screening phase, eligibility was assessed and upon inclusion baseline measures were collected, including structural MRI and resting-state scans. During the treatment phase, participants were randomized to receive active or sham rTMS. After the final treatment session, participants participated in another MRI session, where structural, resting-state, and task-based scans were collected. Participants returned for follow-up visits one, two, four, eight, and twelve weeks after the last treatment to assess the effects on alcohol use (Figure 5).

**Participants.** Treatment seeking patients with moderate to severe AUD (N = 56) were recruited. Participants were randomized to active or sham rTMS.

**rTMS stimulation procedure.**
Deep rTMS was delivered using an H8 coil bilaterally over the insula (Brainsway, Jerusalem, Israel). Stimulation parameters were patterned on a successful prior smoking cessation study. Stimulation was
delivered for approximately 20 min daily at 120% of individual motor threshold, five days a week, and for three weeks in total. A double-blinded randomization of active (10 Hz) versus sham operation modes was used. As described in more detail in the Ethics section, participants underwent a craving provocation before rTMS delivery.

Outcome measures. Several outcome measures were included in this study, the most relevant are reported here. The primary outcome measure was alcohol drinking, assessed both with the selective biomarker PEth, and with self-reported heavy drinking, using the TLFB. In addition, acute and retrospective self-reports of craving, assessed using the AUQ and the PACS respectively, were also investigated. These measures were compared between groups at baseline, treatment, and follow-up sessions. Resting-state and task-based MRI data collected at follow-up were compared between groups.

Results

Participants. Of the 56 included patients, four were lost during screening and seven did not complete treatment. There were no clinically meaningful differences between active and sham groups in baseline characteristics.

Outcome measures: An overall decrease in alcohol drinking and craving was observed during treatment, with no difference between active and sham groups. Similarly, no treatment effects on task-based brain responses were found. However, between-group differences in resting-state connectivity between insula and posterior cingulate gyrus and precuneus were observed.

Conclusions

The findings of equally decreased drinking and craving during treatment, irrespective of whether participants received sham stimulation or rTMS, do not support efficacy of rTMS targeting the insula in alcohol addiction.
Discussion
This thesis examines some of the cognitive mechanisms involved in alcohol addiction, and processes potentially involved in its development. The work uses both correlational and causal approaches, and spans across the full spectrum of alcohol use severity. From the work presented here, we can draw four main conclusions. At least at moderate levels, acute alcohol intoxication in healthy social drinkers affects social decision making by increasing utilitarian and altruistic behaviors. In non-treatment seeking heavy drinkers many of whom meet criteria for an AUD diagnosis, cost sensitivity associated with choosing alcohol over a concurrently available alternative reward is largely preserved but might be decreased compared to light, non-problem drinkers. The modulation of insula using rTMS is not successful in decreasing alcohol use in people with AUD. These findings are discussed in more detail below.

Alcohol intoxication affects social decision making
In our preregistered randomized placebo-controlled study we observed an effect of acute alcohol intoxication in social, but not in personal decision making.

At the time when Study 1 was designed, to my knowledge only two previous studies had investigated effects of alcohol on moral judgement. One placebo controlled experimental study showed no effect after alcohol intake on moral decision making using the trolley dilemma [86], but this study was limited by a small sample size (N=48). Another study by Duke and Begue approached individuals in a bar using a structured questionnaire, and found that alcohol intoxication was associated with utilitarian decision making in the trolley dilemma [85]. Observational field studies have a lower degree of experimental control than laboratory-based studies, and cannot establish causality due to the potential for multiple confounders, such as selection bias. For instance, it is likely that people's tendency to drink to intoxication is not random, and may be associated with pre-existing personality traits that also influence moral judgment. This makes findings obtained using these approaches difficult to relate to ours. A recently published study with a design that was more comparable to ours in terms of intoxication level and sample size,
showed no effects of alcohol on moral decision making [142]. In this study, 329 individuals were divided into three groups (alcohol ~0.6‰, placebo, no-alcohol), and tested on the switch and footbridge dilemma. In our study we observed an effect of alcohol in the switch dilemma but not in the footbridge dilemma. Perhaps the major source of difference between the two studies has to do with the time interval between alcohol intake and task data collection, tapping into two essentially different states. Alcohol is stimulating during the ascending limb of the blood alcohol concentration, and sedative during the descending limb of intoxication [143]. The study of Paruzel-Czachura et al. reported a delay of one hour between alcohol intake and task performance, with descending BrAC from 0.69 to 0.54. In contrast, we used a time delay of 30 minutes and reported stable BrAC levels throughout the tasks. Therefore, the finding by Paruzel-Czachura et al. likely reflect the effects of intoxication during the “descending limb” whereas our experiment was performed during steady intoxication levels, which can possibly explain the different results in the two studies. An influential framework postulates that social behavior is controlled by two interacting systems that follow different operating principles. In this framework, a deliberate, reflective system generates behavioral decisions that are based on knowledge about facts and values, such as the value of the rule that acts resulting in the death of others are unacceptable. In contrast, an impulsive system elicits behavior through heuristic motivational orientations, such as “let’s do what seems best in the moment”, such as saving the maximum number of lives even if this undermines rules that are essential for the function of society in the long term [144]. It can be speculated that alcohol-induced stimulation during increasing blood alcohol levels shifts the balance between these two systems in favor of the latter, because cognitive control required for deliberative processes is loosened.

Only a few studies with low power have looked at moral decision making in alcohol addiction [145, 146]. Both show increased utilitarianism in alcohol addiction. These results are in line with the results we see in acute alcohol intoxication in healthy individuals. There is evidence that utilitarian decisions are associated with decreased interpersonal trustworthiness in group dynamics. To be seen as a trusted group member, making deontological rather than utilitarian decisions in a group is beneficial
An impaired ability to signal trustworthiness could contribute to social exclusion and marginalization. It is possible that the alcohol-related changes in social cognition contribute to the social exclusion seen in alcohol addiction [52].

Together with moral decision making, we also looked at measures of altruistic behavior, using a modified version of the Dictator game [111]. We found that alcohol intoxication increased altruistic behavior, in the form of donation to charity. In contrast, two earlier experimental studies show no or a tendency to a decreased effect on altruism after alcohol use, but these studies are limited by small sample sizes [62, 77]. A recent study used classic behavioral economic measures of altruistic behavior, reciprocal trust and fairness decision, and showed that people with AUD had lower prosocial behavior than controls [80]. This finding was robust across tasks and procedures, as it was first shown in a large cohort tested in a laboratory setting in Sweden, and replicated in another large cohort of American participants tested online. Findings reported by Jangard and colleagues are generally consistent with the observation that low agreeableness is a negative predictor of abstinence [149]. These findings suggest that alcohol addiction and personality traits associated with alcohol addiction risk, rather than alcohol effects per se, are associated with decreased prosocial behavior. In fact, even among participants in our study, we found an inverse correlation between measures of prosocial behavior and AUDIT scores, a measure of alcohol use problem that is associated with the risk of developing alcohol addiction. In contrast, people who are not at elevated risk of developing alcohol addiction, and who make up the majority of healthy controls, seem to experience prosocial effects when using alcohol. This may contribute to their willingness to use alcohol in the context of controlled drinking in social settings.

No effect of alcohol intoxication on personal decisions

In contrast to the findings on social decision-making, we saw no effect of moderate alcohol intoxication on personal decision making. Earlier studies found mixed results on risk and impulsivity, but were all limited by small sample sizes [62-68, 75-77, 150, 151]. Bernhardt et al. performed a moderately powered study with 54 participants in a within subject design and showed no effects on waiting impulsivity or risk [68]. This is in line
with the results in Study 1 and suggests that a moderate alcohol dose in healthy social drinkers has small or no effects on waiting impulsivity or risk taking. In Study 1, no effect on risk taking in the BART was seen. A previous well powered study comparing 142 participants in a between subject design was conducted by Rose et al. [78], showing in contrast to our study, increased risk-taking after alcohol intake. More studies are needed to understand how alcohol affects risk-taking in BART.

Alcohol addiction is known to be associated with generally increased impulsivity and risk-taking [152, 153]. Study 1 was designed to causally isolate the pharmacological effects of alcohol on decision making in social drinkers, because these do not present with chronic alterations in brain structure and function typical for individuals with alcohol addiction. Alcohol intoxication in social drinkers did not influence risk taking or impulsivity. Changes in these domains seen in people with alcohol addiction are thus possible effects of long-term exposure to alcohol, pre-existing vulnerability, or both.

Choosing alcohol: sensitivity to costs

Results of Studies 2 and 3 were consistent in the finding that alcohol choice preference was robustly affected by the relative cost in both light and heavy drinkers. In Study 2, we also found an increased overall alcohol choice preference in heavy drinkers, together with attenuated sensitivity to relative cost in this group compared to the light drinkers. Although the latter findings were not replicated in the scanner environment, we believe that this is likely to be driven by contextual differences between the studies. Irrespective of this, the observation that sensitivity of alcohol choice behavior to relative cost is largely preserved in heavy drinkers indicates that their excessive alcohol use is not likely due to loss of sensitivity to the cost of choosing alcohol, but rather due to increased decision utility for alcohol. This is in agreement with the overall conceptualization of excessive drug seeking and taking proposed by Ahmed [49].

The concept of decision utility was introduced by Kahneman and colleagues in the late 90’s. In their seminal paper, they described decision utility as one of the components of reward utility, of which the others are
predicted utility, experienced utility, and remembered utility [154]. While our task taps into predicted utility, which refers to “beliefs about the experienced utility of outcomes”, it strongly pivots on choice. Therefore, we believe that our task best captures decision utility, the form of reward utility that has the most direct link to a concrete decision-making process, and that does not necessarily correlate with subsequent experienced utility. Increased decision-utility for alcohol would be in line with the theory of incentive sensitization of addiction described in the Introduction. According to Berridge and Robinson, incentive sensitization is at the core of pathological “wanting” for the drug, and it is characterized by heightened sensitivity to drug cues following recurrent drug exposure. This theoretic framework is consistent with our findings in heavy drinkers from Study 2, and with the results from Hogarth et al. [90], showing that alcohol use severity was associated with alcohol choice preference.

Factors potentially influencing alcohol choice

While self-reported drinking was consistently higher in heavy compared to light drinkers in Studies 2 and 3, we could not experimentally replicate the increased preference for alcohol in heavy drinkers in Study 3. The results from Study 2 replicated previous findings from the original version of the task, which was tested in a population of British participants [90], strongly supporting the presence of a shift of choice preference in heavy drinkers. As discussed in detail in the manuscript, when the task was migrated to the scanner environment, the effect of relative point level was preserved, but we observed a marked drop in its effect size, from an $\eta_p^2 = 0.69$ to 0.10. This indicates that performance in this task was sensitive to potential sources of noise, whether contextual or individual. The effect size of the group effect (heavy vs. light drinkers) in Study 2 was considerably lower than that of relative point level ($\eta_p^2 = 0.13$). If it was attenuated to the same extent as the effect size of relative point level, our study was vastly underpowered to detect it. We speculate that this failure to replicate the between-group effect in Study 3 may be due to two potential sources of variance. An obvious difference in conditions between Studies 2 and 3 is that the task in Study 3 was performed in the MRI scanner. It is possible that the MRI environment may have affected behavioral responses, such that, while the overall pattern of sensitivity to relative cost was preserved, the less pronounced
difference in choice preference was attenuated to the point of no longer being detectable. A more salient cost manipulation, such as an immediate painful stimulus [87], might be more efficient in keeping the participants focused on the task while in the scanner.

In addition to context, differences in baseline characteristics across the studies may have contributed to the lack of between-group differences in alcohol choice preference. Despite using the same recruitment strategy and eligibility criteria, Studies 2 and 3 recruited participants who were comparable with regard to self-reported drinking and alcohol use severity, but differed in baseline characteristic known to be of relevance for alcohol use patterns. Specifically, in Study 2, heavy drinkers had significantly lower self-control, lower conscientiousness and increased extraversion compared to light drinkers. Lower levels of conscientiousness and higher extraversion are traits related to increased possibility to move from moderate to heavy alcohol use [149]. Impulsivity is associated to low conscientiousness and there is a large literature on the association between impulsivity and drug use [155, 156]. Thus, heavy drinkers in Study 2 had a personality profile typically associated with increased risk of developing alcohol addiction, whereas heavy drinkers in Study 3 did not show this profile. The reasons for these differences are unclear, but it is possible that they affected the results.

Is insula the island of addiction?

Because of its role in interoception [98], drug craving [103], and smoking cessation [104], it has been theorized that the insula contributes to the emergence of conscious drug urges and influences the decision making processes that lead to relapse [157, 158].

The RCT presented in Study 4 was built on the correlational and causal evidence cited above, in an attempt to test a potential new treatment for alcohol addiction. Despite the strong mechanistic rationale, we did not detect any impact of active rTMS compared to sham rTMS on alcohol use. Negative findings in experimental studies are challenging to interpret, as they may result from insufficient power, methodological limitations or unidentified factors, making it difficult to pinpoint the exact cause. Here, stimulation parameters were based on the seminal
randomized controlled trial showing reduced cigarette use following high-frequency rTMS targeting insula and PFC bilaterally [105]. In addition, patterned on the seminal Dinur-Klein et al. 2014 study, our participants were exposed to a cue provocation using alcohol cues before each rTMS session, as this was suggested to increase efficacy in the smoking cessation study [105]. Outcome measures of alcohol use included serum PEth, currently the most specific and quantitative biomarker of alcohol use [38], as well as self-reported heavy drinking days, using the TLFB [124], which is a standard tool in clinical trials of AUD. We believe that the lack of rTMS effect was unlikely to be a technical failure for the following reasons. First, we used validated self-report based as well as objective outcome measures that were highly correlated with each other and consistently failed to support a treatment effect. Second, the resting state findings showed that our stimulation appeared to influence insula function. Collectively, these observations argue against high frequency targeting the insula as a treatment for AUD.

Limitations intrinsic to the TMS technology may have contributed to these negative finding. One possibility is that our stimulation did not have sufficient specificity. The main limitation of deep rTMS is that, while it allows stimulation of deeper cortical regions, it doesn’t allow for focal stimulation. According to our electric field simulation, the stimulation we used targeted the whole insula, together with regions above it. As described in Study 4, the insula is heterogeneous in cytoarchitecture, function and connectivity and while its different subregions are interconnected, a more focal stimulation may be required to produce therapeutic effects. In addition, lateral and medial portions of the insula lie at different depths, which in our case resulted in uneven stimulation intensity. For its role in integrating interoceptive signaling [159], salience processing [99, 100], and its connectivity to premotor midcingulate regions [160], the anterior portion of the insula is of particular interest in the context of craving and motivated behavior. However, targeting exclusively this region was not possible with TMS at the time we designed this clinical trial. Recent advancements in neuromodulation techniques, allow for non-invasive deep brain stimulation, even at subcortical levels [161], using temporal interference (TI) [162]. TI would allow for a more precise stimulation in terms of both location and intensity. Therefore, TI
would make it possible to target the anterior portion of the insula at a stable intensity, providing a more conclusive understanding of the impact of the stimulation and on the role of that region in AUD.

Finally, an important possibility is that therapeutic effects in alcohol addiction may require modulation of insula function using inhibitory, low frequency stimulation, rather than then excitatory high frequency we applied. Indirect support for this notion is provided by two recent observations. First, a parallel study carried out by our group and collaboratoros within the EU Sybil-AA consortium followed a very similar clinical protocol, but targeted medial prefrontal cortex (mPFC) and anterior cingulate cortex with excitatory stimulation parameters, and this intervention did result in consistent reductions in both craving and alcohol use [105]; similar results have since also been reported by others [163]. Second, an extensive connectivity analysis of a brain “addiction network” identified both the insula and the mPFC as important nodes; however, these nodes were anti-correlated [164].

In addition to the reasons listed above, it’s possible that the stimulation of the insula alone was not sufficient to produce a treatment effect. As mentioned earlier, a coil that produces concurrent stimulation of the insula and the lateral PFC showed a robust effect on smoking cessation in the study by Dinur-Klein [105]. In Study 4 similar parameters and some design features including cue provocation as in the Dinur-Klein study were chosen. However, the insula coil used in Study 4 was designed to more selectively stimulate the insula, while avoiding stimulation of the lateral PFC. This could account for the difference in treatment effect between Study 4 and the Dinur-Klein study. PFC has been identified as an important region in addiction, in part due to its role in top-down regulation of reward-related behaviors, and its involvement in higher order executive function [58]. Furthermore, gray matter loss in the PFC is seen in alcohol addiction [53].
Conclusions and future directions

Although we found interesting effects of alcohol on social decision making in healthy people in Study 1, it is unclear how these data relate to clinical populations. Our findings, together with those obtained by others in people with AUD, suggest two possibilities. First, pre-existing factors associated with elevated risk of developing AUD may also be linked to attenuated prosocial behavior as a stable personality trait that precedes AUD. Second, with prolonged and excessive use of alcohol, persistent impairments in prosocial behavior may result. These two possibilities are not mutually exclusive. Ideally, what is needed to resolve this are longitudinal studies assessing prosocial behavior as people progress from being light drinkers, to heavy drinkers, and to fully developed alcohol addiction.

In Study 2, we found systematic differences in alcohol choice preference between heavy and light drinkers. This study was a follow-up to a previously conducted study in rats, where GABA signaling in the central amygdala was altered in animals that chose alcohol over high-value non-drug rewards [89]. Study 3, the subsequent fMRI study was designed to examine whether choice preference could also be examined in a scanner environment, whether a neural signature of alcohol choice could be identified, and whether that signature would include activity in the amygdala. Our data indicate that further task development is needed in order to simultaneously tap into differences in choice behavior between heavy and light drinkers, and obtaining brain measures of these differences. For this to be successful, refinement of several task parameters may be needed, including the salience of the reward stimuli, their magnitude, or procedures that increase motivation for obtaining the rewards.

Even absent brain signatures, behavior in the CCAF task may be useful as a biomarker in studies aimed at evaluating novel candidate treatments. Outside the scanner, alcohol choice in CCAF correlated with AUDIT scores and the choice of alcohol was increased in heavy drinkers. Based on this, the task could be used as a screening tool for early evaluation of candidate medications or other therapeutic interventions. If heavy drinkers would choose less alcohol in the task when they received a medication, this could predict reduction in choice of alcohol in real life.
A laboratory study using CCAF in a limited population could thus provide initial proof-of-principle in a shorter timeframe and at a lower cost than a full-scale clinical trial.

In Study 4 we found that 10Hz rTMS targeting the insula failed to produce beneficial effects on alcohol use in people with alcohol addiction. Our data were sufficiently consistent and robust to make us conclude that this intervention lacks potential as a clinical treatment. In parallel with our study, our group collaborated with Israeli colleagues on a study with rTMS directed at the medial prefrontal and anterior cingulate cortices [165]. This study showed potential as a treatment method for alcohol addiction as described above. The next step along the way to taking this treatment to clinical practice is a full-scale confirmatory multicenter trial. This is planned, and our center will be a part of that study. If the results are confirmed, rTMS is ready to reach the clinic as a new treatment method for alcohol addiction.
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References


27. Hogarth, L., Addiction is driven by excessive goal-directed drug choice under negative affect: translational critique of habit and


Papers

The papers associated with this thesis have been removed for copyright reasons. For more details about these see:

https://doi.org/10.3384/9789180754088
Decision making and its neural substrates along a spectrum from social drinking to alcohol addiction

Hanna Karlsson