Interactions between genes and alcohol on aggressive behavior and anger related traits:

The oxytocin receptor gene as a candidate

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ACADEMIC DISSERTATION

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LIST OF ORIGINAL PUBLICATIONS

This doctoral thesis is based on the following articles, referred to in the text by their Roman numerals.

I Johansson, A., Santtila, P., Corander, J., Jern, P., von der Pahlen, B., Varjonen, M., & Sandnabba, K. (2011). Controlling anger in self-reported sober and alcohol intoxicated states: Moderating effects of trait anger and alcohol consumption. *Scandinavian Journal of Psychology, 52,* 382-388.

II Johansson, A., Santtila, P., Corander, J., Alanko, K., Jern, P., von der Pahlen, B., & Sandnabba, N. K. (2010). Genetic effects on anger control and their interaction with alcohol intoxication: a self-report study. *Biological Psychology, 85,* 291-298.

III Johansson, A., Bergman, H., Corander, J., Waldman, I. D., Karrani, N., Salo, B., Jern, P., Ålgars, M., Sandnabba, K., Santtila, P., & Westberg, L. (2012). Alcohol and aggressive behavior in men – moderating effects of oxytocin receptor gene (*OXTR*) polymorphisms. *Genes, Brain and Behavior, 11,* 214-221.

IV Johansson, A., Westberg, L., Sandnabba, K., Jern, P., Salo, B., & Santtila, P. (In press). Effects of oxytocin receptor gene (*OXTR*) polymorphisms on self-reported aggressive behavior and anger: Interactions with alcohol consumption. *Psychoneuroendocrinology.*

SVENSK SAMMANFATTNING

Bakgrund: Det är välkänt att alkoholanvändning ökar aggressivt beteende. Vidare tyder studier även på att alkoholberusning ökar känslan av ilska. Alkoholens effekter med avseende på ilska och aggressivt beteende skiljer sig dock mellan olika individer. Medan berusning ökar aggressivt beteende och ilska för vissa, medför den inte sådana förändringar hos andra. Majoriteten av de studier som försökt kartlägga varför vissa beter sig mer aggressivt under alkoholberusning medan andra inte gör det har koncentrerat sig på fenotypiska faktorer utan att beakta möjligheten att genetiska varianter kunde moderera sambandet mellan alkohol och aggressivt beteende.

Målsättning: Den övergripande målsättningen med föreliggande avhandling var att undersöka effekten av alkoholanvändning på aggressivt beteende, tendens att känna ilska samt på kontroll av ilska. Mera specifikt var målsättningen att undersöka om alkoholanvändning har olika effekt på aggressivt beteende, tendens att känna ilska samt på kontroll av ilska, som funktion av vilka genetiska varianter individen bär på. Som kandidatgen för dylika interaktiva effekter med alkoholkonsumtion analyserades polymorfismer i oxytocinreceptorgenen (*OXTR*).

Försökspersoner: Avhandlingens analyser baserade sig på två sampel. Det första samplet var ett populationsbaserat urval av finska tvillingar och deras syskon i åldrarna 18-49 år som fyllde i ett frågeformulär. Frågeformuläret besvarades av totalt 3923 män och 6601 kvinnor, den sammanlagda svarsprocenten var därmed 45 %. Av deltagarna gav 4278 individer även ett DNA-salivprov. Olika delar (*n* varierade mellan 3577 och 8964 för delstudierna) av detta populationsbaserade urval användes i avhandlingen, beroende på vilken analysmetod som tillämpades samt svarsprocenten för enskilda instrument i frågeformuläret. Det andra samplet som användes i avhandlingen bestod av 116 manliga högskolestuderande i åldrarna 18- till 30-år som deltog som försökspersoner i en experimentell studie och gav ett DNA-prov för genetiska analyser.

Metoder: Enkätsvar gällande alkoholanvändning, aggressivt beteende och ilska samlades in från försökspersonerna i det populationsbaserade urvalet. Ett experimentellt upplägg användes i det andra urvalet, där aggressivt beteende mättes enligt ett laboratorieparadigm. Försökspersonerna delades slumpmässigt in i två olika grupper, varav ena gruppen tilldelades

en alkoholhaltig dryck medan den andra gruppen tilldelades en ”placebodryck” (en dryck som inte var alkoholhaltig men som hade en arom av alkohol). Genetiska effekter beräknades både med hjälp av kvantitativa genetiska metoder och molekylärgenetiska associationsmetoder.

Resultat: I självrapportering uppgav försökspersonerna att de kontrollerar sin ilska mindre när de är alkoholberusade än när de är nyktra. Denna skillnad i kontroll av ilska var mera utpräglad för individer med en tendens att reagera på situationer med ilska än för individer utan en dylik tendens. Individer som uppgav sig konsumera förhållandevis mycket alkohol rapporterade även större skillnader i kontroll av ilska mellan nyktra och berusade tillstånd. Resultaten visade vidare att gener påverkar kontroll av ilska både gällande nyktra (heritabilitet 27 % för män och 34 % för kvinnor) och berusade tillstånd (29 % för män och 37 % för kvinnor). Den resterande variationen i kontroll av ilska förklarades av unika omgivningseffekter. Majoriteten av de genetiska effekterna för kontroll av ilska var gemensamma för det nyktra och berusade tillståndet, det vill säga det antas att det huvudsakligen är samma gener som påverkar kontroll av ilska vid såväl nyktra som berusade tillstånd. Vidare visade resultaten att gener påverkade den skillnad i kontroll av ilska som rapporterades gällande nyktra och berusade tillstånd. En sannolik tolkning av resultatet är att gener modererar den effekt alkohol har på kontroll av ilska, men alternativa tolkningar kunde inte uteslutas. En *OXTR*-polymorfism (rs4564970) modererade effekterna av alkoholkonsumtion på aggressivt beteende. Både rs4564970 och rs1488467 polymorfismerna modererade effekterna av alkoholkonsumtion på tendensen att känna ilska. Resultaten antydde att individer som bär på åtminstone en cytosin-allel är mera känsliga för alkoholens höjande effekter på aggressivt beteende samt ilska jämfört med individer som bär två guanin-alleler vid både rs4564970- och rs1488467-polymorfismerna. Dessa polymorfismer hade ingen effekt på skillnaden i kontroll av ilska mellan de självrapporterade nyktra och berusade tillstånden, vilket antogs antyda att dessa två *OXTR*-polymorfismer modererar effekterna av alkoholkonsumtion på underliggande känslor till skillnad från kontroll av sådana känslor.

Slutsatser: Resultaten antydde att alkoholens effekter på ilska och aggressivt beteende varierar mellan individer, som funktion av vilken genetisk variant av två olika *OXTR*-polymorfismer de bär på. Resultaten antydde även att det är sannolikt att gener interagerar med alkohol i påverkandet av kontroll av ilska, men vidare forskning krävs för att identifiera specifika polymorfismer för denna interaktion.

ABSTRACT

Background: The association between alcohol intake and aggressive behavior is widely acknowledged. Trait anger and anger control are closely related to aggressive behavior, and alcohol has been shown to also increase anger. It is, however, clear that individuals react differently to alcohol; it does not enhance anger and aggressive behavior for all individuals. The majority of studies investigating why people differ in their reactions to alcohol have concentrated on phenotypic factors, without taking genetic moderation into consideration.

Aims: The general aim of the thesis was to explore effects of alcohol consumption on aggressive behavior and anger related phenotypes. Specifically, it was investigated if alcohol has different effects on anger and aggressive behavior for individuals based on their genetic variants. The oxytocin receptor gene (*OXTR*) was analyzed as a candidate gene for such interactive effects with alcohol.

Subjects: Two different samples were used. The first was a Finnish population-based sample of male and female twins and their siblings (age range 18 to 49 years) who responded to a questionnaire. Altogether 3923 men and 6601 women responded yielding an overall response rate of 45%. Furthermore, a DNA sample was collected from 4278 of the participants. Of the individuals in this population-based sample, subsamples (*n* between 3577 and 8964) were used for the thesis depending on method used and responses available on specific instruments in the questionnaire. The second sample consisted of 116 male university students (age range 18 to 30 years) who participated in an experimental study and gave a DNA sample for genetic analyses.

Methods: Survey data of alcohol use, aggressive behavior and anger were obtained from the population-based sample. In the second sample, an experimental method was used where participants were randomly allocated to either a group receiving alcoholic beverages or a group receiving placebo. Aggressive behavior was measured using a laboratory paradigm. Both quantitative genetic and molecular genetic association methods were used.

Results: The participants reported that they control their anger less when they are intoxicated than when they are sober, this difference being more pronounced for individuals with high levels of trait anger and alcohol consumption. Genes were found to influence anger control both regarding the sober and intoxicated states. For men, genes explained 27% of the

variation in anger control for the sober state and 29% for the intoxicated state. Similar effects were found for women with the overall genetic effect being 34% for anger control regarding the sober state and 37% for anger control regarding the intoxicated state. The rest of the variance was influenced by nonshared environmental effects. The majority of the genetic effects for anger control were common for the sober and intoxicated states. Moreover, genetic effects of moderate size were found to explain variance in the difference in anger control between the sober and intoxicated states. A likely explanation for this result is that genes moderate the effect alcohol has on anger control. However, alternative explanations could not be excluded. An *OXTR* polymorphism (rs4564970) was identified as a moderator of the effects of alcohol consumption on aggressive behavior. Both the rs4564970 polymorphism and the rs1488467 polymorphism were found to moderate the effect of alcohol consumption on the propensity to react with elevations in anger. The results suggested that carriers of at least one cytosine allele on these polymorphisms are more susceptible to the effects of alcohol on increasing aggressive behavior and anger than individuals homozygous for the guanine allele. These polymorphisms did not influence the difference in anger control between sober and intoxicated states and thus, they were hypothesized to moderate the effects of alcohol intake on underlying feelings rather than control of these feelings.

Conclusions: The results indicate that alcohol has different effects on anger and aggressive behavior for individuals, depending on their genetic variants on two *OXTR* polymorphisms. The results also suggest that it is likely that genes interact with alcohol consumption in influencing anger control, but it will be a task for future studies to identify polymorphisms with such an effect.

ABBREVIATIONS

A	Adenine
A	Additive genetic effects
BAC	Blood alcohol content
C	Cytosine
C	Shared environmental effects
D	Dominant genetic effects
DNA	Deoxyribonucleic acid
DZ	Dizygotic, fraternal
E	Nonshared environmental effects
G	Guanine
G x E	Gene-environment interaction
LD	Linkage disequilibrium
MZ	Monozygotic, identical
OXT	Oxytocin
OXTR	Oxytocin receptor
OXTR	Oxytocin receptor gene
PFC	Prefrontal cortex
rGE	Gene-environment correlation
SNP	Single nucleotide polymorphism
T	Thymine

1 INTRODUCTION

Although aggressive behavior can, in some instances, be considered an adaptive reaction to a situation, for example, when self-defense is called for, it often has serious consequences both for the individual and for society (Krug, Dahlberg, Mercy, Zwi, & Lozano, 2002). Many aggressive acts are committed under the influence of alcohol, and experimental studies have shown that the effect of alcohol on enhancing aggressive behavior is causal (for reviews see Bushman & Cooper, 1990; Chermack & Giancola, 1997; Exum, 2006; Ito, Miller, & Pollock, 1996). Although researchers agree that alcohol enhances aggressive behavior overall, it is evident that it does not do so for all individuals (e.g. Ito et al., 1996) and several studies have been conducted trying to identify moderators of the link between alcohol and aggressive behavior. Most of these have, however, concentrated on examining moderators on a phenotypic level, omitting possible genetic moderators.

Recently, an increasing number of studies have shown that genetic variants can act as moderators of environmental effects (Dick, 2011; Wermter et al., 2010). This means that individuals can react differently to the same environmental influences, based on their genetic variants (Dick, 2011; Rutter & Silberg, 2002; Moffitt, Caspi, & Rutter, 2006). Such interactions between genes and environmental factors have been found to influence numerous psychological traits, including aggressive and antisocial behaviors (Caspi et al., 2002; Edelyn, Joiner, Johnson, & Bender, 2006; Foley, et al., 2004; Nilsson, et al., 2006; Reif et al., 2007). Moreover, it was shown in a sample of heavy drinkers that the effects of alcohol on vigor and negative mood were moderated by the genetic variants of the individual (Ray et al., 2010), indicating that it is reasonable to expect that genes can affect the way we react to alcohol. This was also indicated by a recent study in a sample of alcoholic violent offenders (Tikkanen et al., 2009; 2010). Tikkanen et al. (2010) showed that the individual's genotype at the MAOA-LPR polymorphism interacted with alcohol consumption to predict violent recidivism.

The present thesis aimed at exploring the relationship between aggressive behavior as well as anger related traits and alcohol consumption. Both the propensity of an individual to react to situations by getting angry and his or her ability to control such feelings are related to aggressive behavior (Spielberger, 1999). In fact, anger can be seen as a prerequisite for some aggressive behaviors (Spielberger, 1999). Thus, anger related traits are important to take into account when trying to explain the relationship between aggressive behavior and alcohol (Parrott, Zeichner, & Stephens, 2003). A special focus of the thesis was to shed light on the

individual differences in alcohol-related aggressive behaviors and anger by exploring interactions between alcohol consumption and genetic effects, with the oxytocin receptor gene as a candidate.

1.1 Definitions of anger and aggressive behavior

According to an often used definition of aggressive behavior, these behaviors have in common that they are directed toward another individual with the intent to cause harm and that the opponent is motivated to avoid being the target of such behavior (Anderson & Bushman, 2002; Baron & Richardson, 1994; Bushman & Anderson, 2001; Geen, 1990). One difficulty with this definition is that since intent is an internal state, it is not easily inferred from behavior (Bushman & Anderson, 2001; Geen, 1990). Another element that can be added to the definition is expectations that the individual's behavior would actually lead to harm for the opponent (Geen, 2001). Further, Anderson and Bushman (2002) specified in their definition of aggressive behavior that the intent of the individual to cause harm should be considered at an immediate level (e.g. the intent of a thief is to harm the persons being robbed at an immediate level whereas it in the long-term can be to being able to pay his or her bills).

There are different types of behaviors that could be characterized as aggressive, and there have been several efforts to define subtypes of aggressive behaviors in the literature (Geen, 2001). One distinction often being made is between hostile (also referred to as affective, angry, impulsive) and instrumental aggressive behaviors (Anderson & Bushman, 2002; Geen, 2001). Hostile aggressive behavior is seen as impulsive and affected by underlying feelings of anger (Anderson & Bushman, 2002; Geen, 2001). Moreover, it is often a reaction to provocative situational factors. Instrumental aggressive behavior, on the other hand, is seen as a way to obtain a goal, for example, personal gain by robbing someone or by defending oneself (Anderson & Bushman, 2002; Geen, 2001), and is not necessarily preceded by feelings of anger. Another division sometimes used is that between reactive and proactive aggressive behaviors, of which the former refers to behaviors initiated as a response to a provocation whereas the latter behaviors are not in response to any apparent provocation (Geen, 2001). These two different ways to distinguish different forms of aggressive behavior are not mutually exclusive.

Hostile and reactive aggressive behaviors are often accompanied by feelings of anger (Geen, 2001). Different definitions and operationalizations of anger have been used, sometimes

resulting in conceptual confusion in the literature (Eckhardt, Norlander & Deffenbacher, 2004). Spielberger (1999) used state-trait personality theory to define state and trait anger (Eckardt et al., 2004). According to his definitions, state anger is seen as an emotional state of "*feelings that vary in intensity from mild irritation or annoyance to intense fury and rage*" (Spielberger, 1999, p. 1). Trait anger, on the other hand, reflects the propensity of an individual to react to situations with angry feelings (i.e. elevations in state anger) (Spielberger, 1999). The subjective feeling of anger is often accompanied by bodily and autonomic reactions, associated cognitions and beliefs and is conveyed to others by, for example, facial expressions (Eckhardt et al., 2004; Novaco, 1994). While aggressive behavior is motivated by a goal (i.e. to harm another being), anger as a feeling is not directed towards any specific goal (Giancola, 2002). Depending on an individual's disposition to express or control angry feelings, aggressive behavior may result (Spielberger, 1999). Not all uncontrolled feelings of anger will result in aggressive behavior, however. Instead a provoked person can resort to non-aggressive behaviors such as confronting the instigator without overt aggressive behavior (O'Connor, Archer, & Wu, 2001). Although there are dysfunctional elements to anger, the emotion itself is often present in everyday life and serves also adaptive functions (Novaco, 1994). Novaco (1994) summarizes the relationship between anger and aggressive behavior by stating that anger "*is a significant activator of and has a mutually influenced relationship with aggression, but it is neither necessary nor sufficient for aggression to occur*" (p. 33).

According to Anderson and Bushman (2002), anger can affect aggressive behavior by providing a justification for aggressive retaliation. It can also interfere with cognitive processes such as moral reasoning and thus affect if a person is likely to aggress or not, and "*allows a person to maintain an aggressive intention over time*" (Anderson & Bushman, 2002, p. 45).They also argue that anger can be used as a cue on how to react to and interpret, for example, ambiguous social situations and that it energizes behavior by increasing arousal levels. In the following sections of the introduction, results of previous studies will be discussed. In the original studies of the thesis, as well as in the thesis itself, aggressive behavior, trait anger, anger control and alcohol consumption was measured. However, relevant studies of other variables such as violence or antisocial behavior will also be discussed, since they are related to the traits examined in the present study. Short definitions of some of the terms used can be seen in Table 1.

Table 1
Definitions of Anger, Aggressive Behavior and Related Terms

Trait	Definition
State anger	An emotional state that can vary in intensity from irritation to fury (Spielberger, 1999).
Trait anger	The propensity of an individual to react to situations with elevations in state anger (Spielberger, 1999).
Anger control	The propensity for an individual to control his or her feelings of anger by preventing their expression (Spielberger, 1999).
Aggressive behavior	Behavior that is directed toward another individual with the intent to cause harm while the opponent is motivated to avoid such behavior (e.g. Anderson & Bushman, 2002; Baron & Richardson, 1994; Geen, 1990).
Violent behavior	A form of aggressive behavior with extreme harm as the goal (e.g. death or physical assault). All violence is aggressive behavior, but all aggressive behaviors are not classified as violence. (Anderson & Bushman, 2002).
Antisocial behavior	Includes aggressive behaviors but also other non-aggressive behaviors that are risky, manipulative, sensation seeking or behaviors that otherwise violate societal norms or personal or property rights of others (Burt, 2009; Ferguson, 2008). Differences in antisocial behaviors exist, and a distinction is made between, for example, aggressive antisocial behavior and non-aggressive rule-breaking antisocial behaviors (Burt, 2009).
Criminal behavior	Behaviors that are unlawful in a society and lead to conviction, arrest or incarceration (Rhee & Waldman, 2002). Aggressive behavior is related to criminal behavior (e.g. Loeber & Hay, 1997), but not all aggressive behaviors are criminal and not all criminal behaviors are aggressive.
Delinquent behavior	Unlawful behaviors committed as a juvenile (Rhee & Waldman, 2002).

1.2 Effects of alcohol on aggressive behavior and anger

It is well-known that alcohol consumption is related to aggressive and violent behavior, as indicated by, for example, survey studies, crime statistics, and experimental laboratory studies (for reviews see e.g. Bushman & Cooper, 1990; Chermack & Giancola, 1997; Exum, 2006; Ito et al., 1996). Studies suggest alcohol to be present in a large percentage of violent crimes (Chermack & Giancola, 1997; Pernanen, 1991). According to the U.S. Bureau of Justice Statistics (2010), 36% of victims of violent crimes perceived that the offender had been under the influence of alcohol at the time of the offence. This was in accordance with the estimate of percentage of state prisoners serving time for a violent offence who reported that they were alcohol intoxicated when committing their crime (37%; U.S. Dept. of Justice, Bureau of Justice Statistics, 2007). In Finland, the relationship between violent offences and intoxication of the offender seems to be even more pronounced; approximately 70% of individuals under suspicion for having attempted homicide and around 60% of individuals under suspicion for assaults had been under the influence of alcohol at time of the offence (Lehti, Sirén, Hinkkanen, & Aaltonen, 2010). Overall level of alcohol consumption prior to offence has also been shown to predict the type of violent offence (not alcohol related versus alcohol related) that a male offender was later incarcerated for (McMurran, 2007). Individuals with high alcohol consumption were more likely to have been incarcerated for violent offenses that were committed under the influence of alcohol (McMurran, 2007). Although this could also indicate effects of chronic alcohol use, it should be noted that violence seems to be best explained by the acute effects of alcohol rather than chronic ones (Arseneault et al., 2000; Collins & Schlenger, 1988). The violence triggering acute effects of alcohol were also supported in a study by Haggård-Grann, Hallqvist, Långström, and Möller (2006). Altogether 133 violent offenders were interviewed regarding offender- and offence-specific information and their use of alcohol and drugs. By comparing the exposure to alcohol during a time-period of 24h before the violent offence, with the exposure during a control period from the same individual, the researchers found that the risk of violence was 13.2-fold when alcohol had been consumed (Haggård-Grann et al., 2006).

High alcohol consumption has been shown to be related to aggressive behavior also in survey studies using samples of the general population (Bácskai, Czobor, & Gerevich, 2008; Wells, Graham, & West, 2000), and samples of regular pub users (Schnitzer et al., 2010). Furthermore, an individual's drinking frequency has been associated with number of fights in public venues in a general population sample (Wells, Graham, Speechley & Kovak, 2005). An

American population-based survey study of crime victimization showed that physical aggressive behaviors lead to more serious harm (e.g. physical injury) if the aggressor is alcohol intoxicated (U.S. Dept. of Justice, Bureau of Justice Statistics, 2010). Furthermore, the level of intoxication is positively associated with the severity of the aggressive acts, as shown both by a survey study (Wells & Graham, 2003) and an observational study (Graham, Osgood, Wells, & Stockwell, 2006). Inferences of causality in the relationship between alcohol and aggressive behavior cannot be drawn based on these types of studies, instead longitudinal and experimental studies have been conducted in order to try to answer the question of causality.

Results from longitudinal survey studies of the alcohol-violence relationship have been mixed. Many studies have examined the relationship between alcohol use and aggressive behavior only from one direction, without examining reciprocal effects, or effects in the opposite direction. Such studies include, for example, the studies by Ellickson, Tucker, and Klein (2003), and Resnick, Ireland, and Borowsky (2004), finding that alcohol use predicts violent behavior, and the study by Windle (1990) indicating that delinquency and antisocial behavior predict alcohol use. A study of 11-15-year-olds (N = 2586) examining if alcohol use predicts antisocial behavior, or vice versa, or if a reciprocal model would fit the data best, suggested that although antisocial behavior can predict alcohol use in the long term, in the short term, the reverse also applies (Young, Sweeting, & West, 2008). A recent longitudinal study of a representative sample of individuals (N = 10,828, ages 11-26) from the U.S. found that consistent alcohol use predicted violence whereas the reverse was not true (Maldonado-Molina, Reingle, & Jennings, 2011).

The results of experimental laboratory studies show that the acute effects of alcohol intoxication increase aggressive behavior, and that this effect is causal (for reviews see Bushman & Cooper, 1990; Chermack & Giancola, 1997; Exum, 2006; as well as the following individual studies, not included in the above mentioned reviews: Denson et al., 2008; Dougherty, Bjork, Bennett, & Moeller, 1999; Hoaken & Pihl, 2000; Giancola, 2002). Most experimental studies of the effects of alcohol on aggressive behavior have compared a group of individuals receiving alcoholic beverages to a group receiving a placebo beverage, and have found that individuals receiving alcohol show significantly higher levels of aggressive behavior than those receiving placebo (for reviews see Bushman & Cooper, 1990; Exum, 2006). It is primarily the pharmacological effects of alcohol instead of expectancy effects that influence aggressive behavior (see review by Exum, 2006). In addition, the effect

of alcohol on aggressive behavior seems to be greater when higher doses of alcohol are administered (see reviews by Bushman & Cooper, 1990; Ito et al., 1996). Alcohol also seems to increase aggressive behavior to a higher degree on the ascending limb of intoxication (Giancola & Zeichner, 1997). The results regarding the effect of alcohol on aggressive behavior on the descending limb are somewhat mixed, with a study by Giancola and Zeichner (1997) finding no such effects, while a study by Dougherty et al. (1999) found that the effect of alcohol on increasing aggressive behavior remained for several hours after the intake of alcoholic beverages.

The relationship between anger related traits and alcohol has not been as extensively studied as the one between alcohol and aggressive behavior. Experimental studies indicate that intoxicated participants seem to experience larger increases in anger after being provoked (Zeichner, Allen, Giancola, & Lating, 1994) and show more facial expressions of anger (Parrott et al., 2003) than sober participants. In addition, intoxicated individuals with high levels of anger control displayed fewer facial expressions of anger than intoxicated individuals with low levels of anger control (Parrott et al., 2003). Bond and Lader (1986) found somewhat contradicting results in their study. Although participants who received alcohol showed higher levels of aggressive behavior (measured using a competitive reaction time task), they reported themselves to be less furious (as opposed to calm) overall than participants in the placebo group. There were no significant differences between the groups (placebo, high-alcohol dose, low-alcohol dose) on related scales such as: angry-peaceful, affable-quarrelsome, and aggressive-cool-headed (Bond & Lader, 1986). Eckhardt (2007) obtained similar results as Bond and Lader (1986) in his experimental study of men with and without a history of domestic violence. In the study by Eckhardt (2007), alcohol did not have an effect on experienced anger after listening to vignettes of neutral situations or situations aimed at increasing husband anger and aggressive behavior (Eckhardt, 2007). Regarding the association between anger and frequency of alcohol consumption, Eftekhari, Turner, and Larimer (2004) found in a survey study using a sample of adolescent offenders that the expression of anger towards persons or objects was positively associated with more frequent alcohol use. Likewise, Foran and O'Leary (2008) found problem drinking to be negatively correlated with anger control in a sample of heterosexual couples with a young child.

Although alcohol increases aggressive behavior, and also seems to increase angry feelings at least in some instances, it is clear that it does not do so in all individuals (e.g. Giancola, 2002; Parrot et al., 2003). Instead, the effects of alcohol are moderated by a number of different

factors as will be described below (for reviews see e.g. Bushman & Cooper, 1990; Chermack & Giancola, 1997; Ito et al., 1996).

1.3 Moderators of the relationship between alcohol and aggressive behavior

One strong predictor of aggressive behavior is provocation (e.g. Anderson & Bushman, 2002; Geen, 2001). Likewise to sober conditions, provocation elicits aggressive behavior when individuals are alcohol intoxicated (e.g. review by Ito et al., 1996; and a later individual study by Hoaken & Pihl, 2000). There are, however, some discrepant results regarding whether the effect of alcohol on aggressive behavior is greater after low or high provoking conditions. Ito et al. (1996) reported in their meta-analysis that the difference in aggressive behavior between sober and intoxicated individuals seems to be smaller (although still significant) under highly provoked conditions in comparison to conditions with low provocation. The results of a later experimental study by Giancola et al. (2002) show the same pattern for men, and the authors note that this could be because whereas alcohol can explain a larger amount of the variance in aggressive behavior under low provoking conditions, the effect of provocation itself on aggressive behavior is so strong under high provoking conditions that alcohol might not add substantially to this effect. Another way to think about this is that alcohol would lower the threshold to be provoked to the degree that aggressive behavior would follow.

A later review of several meta-analyses (including the one by Ito et al., 1996, but not including the individual study by Giancola et al., 2002) contradicted this view, however, by noting that it seems that the relationship between alcohol, aggressive behavior and provocation depends on the experimental design, and that alcohol appears to have the largest effects in competitive reaction-time paradigms under highly provocative conditions (Exum, 2006). Thus, the effect of alcohol under low and high provoking conditions remains to be clarified.

Individuals with a general tendency to behave aggressively (i.e. dispositional aggressive behavior) are also prone to behave aggressively when alcohol intoxicated as shown both by an experimental (Eckhardt & Crane, 2008), and a survey study (Smucker Barnwell, Borders, & Earlywine, 2006). The measures of dispositional aggressive behavior did not specifically measure aggressive behavior when sober, which means that the association could be due to the measures of dispositional aggressive behavior capturing alcohol-related behavior. An experimental study by Dougherty et al. (1999) was, however, able to show that participants

with high levels of aggressive behavior in the placebo condition had the greatest increases in aggressive behavior when administered alcoholic beverages. Other risk factors for alcohol-related aggressive behavior include, for example, high irritability (Godlaski & Giancola, 2009), low executive cognitive functioning (Giancola, 2004; Godlaski & Giancola, 2009), high tendency for displaced aggressive behavior (Denson, White, & Warburton, 2009), a tendency for hostile rumination (Borders & Giancola, 2011) as well as low levels of empathy (Giancola, 2003). Alcohol-related aggressive incidents also more commonly take place after midnight, at weekends, at bars and more likely involve strangers than acquaintances (Wells & Graham, 2003).

1.3.1 The role of trait anger and control of anger

A few experimental studies have investigated the role of anger related traits in the alcohol-aggression relationship. Trait anger has been shown to moderate the effect of alcohol on aggressive behavior, so that alcohol is more likely to elicit aggressive behavior in individuals with high levels of trait anger compared to those with low levels of trait anger (Giancola, 2002). The effect of alcohol on aggressive behavior has been hypothesized to be especially pronounced in men with moderate levels of trait anger (Parrott & Zeichner, 2002), and when the trait anger is behavioral in nature (i.e. a tendency to express anger outwards e.g. by causing a scene) (Giancola, Saucier, & Gussler-Burkhardt, 2003). In a study by Tremblay, Mihic, Graham and Jelley (2007), participants read vignettes describing conflict situations with different situational factors while either imagining themselves to be sober or alcohol intoxicated. The results indicated that a motivational state (e.g. feelings of anger and preparedness to retaliate) of the participant had stronger effects on aggressive responses for participants that imagined themselves to be intoxicated compared to participant imagining themselves to be sober. In domestically violent men, high levels of trait anger and a large increase in feelings of anger after listening to neutral and anger evoking vignettes predicted verbal aggressive behaviors in those men who had received alcohol (Eckhardt, 2007). In addition, the tendency for a person to either control or express his or her feelings of anger further moderates the relationships between trait anger, alcohol and aggressive behavior. Parrott and Giancola (2004) found in an experimental study that trait anger predicted aggressive behavior only in intoxicated participants with low levels of anger control. Overall, those with high levels of anger control showed lower levels of aggressive behavior. A survey study by Norström and Pape (2010) found changes in heavy drinking to predict changes in

aggressive behavior strongest for individuals with high levels of suppressed anger. Trait anger was not measured in the study.

1.4 Gender differences

Gender differences in aggressive behavior have been frequently reported in the literature, and the general view is that men are more aggressive than women. Indeed, men show higher levels of direct and physical aggressive behaviors than women (see review by Archer, 2004; and later individual studies by Hess & Hagen, 2006; Smith & Waterman, 2006). Although men also seem to be verbally more aggressive than women, this difference is not as pronounced as for physical aggressive behaviors (see review by Archer, 2004). For indirect aggressive behaviors on the other hand, women appear to show somewhat higher levels than men (see reviews by Archer, 2004; Archer & Coyne, 2005; and a later individual study by Hess & Hagen, 2006). In contrast to direct aggressive behaviors, the aim of indirect aggressive behaviors is to harm individuals by affecting their reputation or by excluding them from the group or ignoring them (Archer & Coyne, 2005; Björkqvist, 1994).

Between-gender comparisons regarding anger are less clear-cut than comparisons regarding aggressive behaviors. A meta-analysis by Archer (2004) showed no differences in levels of anger between men and women. When outliers were removed, a small difference was seen with women showing somewhat higher levels of anger than men (Archer, 2004). This is in line with other studies, with the majority of the results showing no differences between men and women (Fischer & Evers, 2010; Maxwell, Sukhodolsky, & Sit, 2009). Regarding control and expression of anger, somewhat contradicting findings exist. In a study by Deffenbacher, Oetting, Lynch, and Morris (1996), there were no differences between men and women in control or expression of angry feelings. Another study found contradicting results with no differences between men and women on two out of four anger expression scales, but higher levels of anger expression and lower levels of anger control for men than for women on the other two scales (Spielberger, 1999). The opposite was, however, found by Maxwell et al. (2009). In this study, men showed higher levels of anger control than women. Deffenbacher, Oetting, Thwaites et al. (1996) conclude that they found few differences between men and women in anger or control or expression of angry feelings, and that the effects they found tended not to be replicated. It should be noted though that some situational factors could moderate the effect of gender on anger and aggressive behavior. For example, provocation has

been shown to reduce the difference between men and women on aggressive behavior (Bettencourt & Miller, 1996).

Results concerning gender differences in the effects of alcohol on aggressive behavior are also somewhat inconsistent. Still, survey and field studies suggest that alcohol increases aggressive behaviors both for men and women, but that this effect might be somewhat more pronounced for men (for a review see Giancola et al., 2009). A number of experimental studies have shown alcohol to increase aggressive behavior in women (e.g. Bond & Lader, 1986; Dougherty et al., 1999; Giancola et al., 2009; Hoaken, Campbell, Stewart & Pihl, 2003), but others have found that it only has an effect for men (Giancola, Helton, Osborne, Terry, Fuss & Westerfield, 2002; Hoaken & Pihl, 2000). In summary, alcohol seems to affect aggressive behavior also in women, but to a lesser extent than for men.

1.5 Explanations for alcohol-related aggressive behavior

A number of different models trying to explain the relationship between alcohol and aggressive behavior have been put forward throughout the years including models that emphasize, for example, the pharmacological effects of alcohol, expectancies about the effects of alcohol, the role of emotions such as anxiety, or cognitive factors (see review by Chermack & Giancola, 1997). Bushman (1997) divided these broadly into three categories: models of physiological (also known as pharmacological or direct) disinhibition, alcohol expectancy models, and indirect cause models. According to the physiological model, alcohol exerts a direct influence on aggressive behavior by affecting brain regions that are responsible for inhibitory control of behavior (Bushman, 1997; Chermack & Giancola, 1997). It is assumed that if the effect of alcohol would be direct, it would affect all individuals in the same way (Chermack & Giancola, 1997). Pharmacological (or direct) models have not received much support since studies have demonstrated individual variation regarding the effects of alcohol on aggressive behavior (Chermack & Giancola, 1997). The expectancy models posit, as the name suggests, that it is not the pharmacological effect of alcohol that elicits aggressive behavior, rather the expectancies that individuals have about the effects of alcohol (Bushman, 1997). Like the pharmacological models, expectancy models have not received much support (Bushman, 1997). Indirect cause models have, on the other hand, received support in the alcohol-aggression literature (Bushman, 1997; Heinz, Beck, Meyer-Lindenberg, Sterzer, & Heinz, 2011). According to indirect models, alcohol causes changes in

different processes (e.g. cognitive, emotional or physiological), in turn increasing the likelihood that a person will behave aggressively (Bushman, 1997; Heinz et al., 2011), and assume that contextual factors interact with alcohol to affect aggressive behavior (Chermack & Giancola, 1997). The effects of alcohol can be pharmacological in nature, but it is not their direct effect, rather an indirect one, that influences alcohol related aggressive behavior according to these theories. The processes that are affected by alcohol are often thought to be cognitive in nature (Giancola, 2000). Recent attempts to theoretically describe the effects of alcohol on aggressive behavior have tried to integrate some of the earlier models. Heinz and colleagues (2011) name three recent multidimensional models that incorporate social and cognitive factors in the explanation of aggressive behavior under the influence of alcohol, namely the executive functioning framework (Giancola, 2000), the two-channel theory (Lange, 2002), and dual-process models (Wiers, Beckers, Houben, & Hofmann, 2009).

Giancola (2000) has attempted to integrate different cognitive aspects of alcohol related aggressive behavior in his executive functioning framework. According to his theory, many of the earlier models and studies on aggressive behavior when intoxicated involved cognitive domains that could be described as part of the more general construct executive functioning, a set of cognitive abilities mostly located to frontal brain regions, that help control and regulate other abilities and behaviors (Lezak, 2004). Executive functions include, for example, planning, cognitive flexibility, attentional control, evaluation of information, and goal setting (for a review, see Jurado & Rosselli, 2007). The framework stipulates that alcohol affects aggressive behavior by disrupting executive functioning, which in turn negatively affects four key abilities that influence if a person will act aggressively or not: attending to and appraising situational information, the ability to take the perspective of others, considering the consequences of one's actions and defusing a hostile situation (Giancola, 2000).

The two-channel theory involves the rationale behind expectation models in that it states that people often have strong mental representations of the usual effects of alcohol on aggressive behavior (Lange, 2002). For one individual, this can mean expecting that alcohol increases aggressive behavior, for another that it is associated with drowsiness. Alcohol affects aggressive behavior through two routes: by activating mental representations of associations between alcohol and aggressive behavior, and by impairing cognitive functions (Lange, 2002). Social situations are often ambiguous and alcohol intoxicated individuals have more difficulties trying to interpret these situations and solve the ambiguities (Heinz et al., 2011; Lange, 2002). Once the mental representations of alcohol related behavior (for example

aggressive behavior) have been activated in an individual, it becomes increasingly difficult to interpret ambiguous situations in ways that differ from the mental representations because of the impairing effects alcohol have on cognitive functioning. Therefore, intoxicated people tend to rely on the most salient information in ambiguous situations and interpret it according to activated mental representations (Heinz et al., 2011; Lange, 2002).

According to dual-process models, two types of processes influence aggressive behaviors (Wiers et al., 2009): impulsive and reflective. Whereas the impulsive process is a fast, automatic assessment of stimuli in terms of their affective and motivational relevance, the reflective process involves deliberation and goal regulation and depends on executive functioning (Heinz et al., 2011; Wiers et al., 2009). Since alcohol disrupts executive functioning, the theory posits that the behavior of an intoxicated individual is influenced by impulsive rather than reflective processes (Wiers et al., 2009). When behavior is directed by impulsive processes, social situations and stimuli are assessed relatively automatically in line with implicit alcohol-associations, which for some individuals can include aggressive associations (Wiers et al., 2009).

The executive function framework and the two-channel theory emphasize the importance of interpreting social cues in ambiguous situations when explaining aggressive behavior in alcohol intoxicated individuals. Furthermore, two-channel and dual-process theories try to explain why intoxicated individuals might be prone to interpreting ambiguous situations as hostile, as suggested in experimental studies. Attwood, Ataya, Benton, Penton-Voak and Munafò (2009) found that alcohol intoxicated participants (mis)interpreted ambiguous disgusted male faces as angry more often than sober controls. Alcohol-dependent individuals perform worse in recognizing emotional facial expressions (Foisy et al., 2007; Kornreich et al., 2003) as well as overestimate emotional intensity and show a bias towards angry expressions (Philippot et al., 2006) compared to controls. Difficulties in interpreting socially ambiguous situations have in turn been associated with aggressive behavior as shown by Coccaro, Noblett, and McCloskey (2009). In their study impulsive aggressive patients were shown to attribute more hostile intentions to provocateurs in socially ambiguous vignettes than healthy controls.

Although not directly discussing the role of anger, the above mentioned theories about the relationship between alcohol and aggressive behavior concentrate on hostile and reactive forms of aggressive behavior, which are often preceded or accompanied by feelings of anger

(Anderson & Bushman, 2002; Geen, 2001). It is reasonable to expect that the theories relate to anger as well. The impairing effect of alcohol on cognitive functioning is likely to influence anger, for example, by making the individual more prone to mistakenly interpret the intentions of others as hostile and provocative. Dual-process models have been proposed for anger as well (e.g. Wilkowski & Robinson, 2008). Likewise to aggressive behavior, these stipulate that information processing is influenced by two dual processes: an impulsive and a reflective one (Hofmann, Gschwendner, Friese, Wiers, & Schmitt, 2008). A study by Hofmann et al. (2008) showed that individuals have automatic representations of themselves as easily angered or not, and that cognitive functioning moderates the effect such automatic representations have on expression of anger in response to provocation, since reflective processes such as effortful control heavily depend on cognitive processes (Wiers et al., 2009). As noted earlier, alcohol intoxication is suggested as influencing individuals by making them more prone to impulsive processes because of the impairments in cognitive functioning that alcohol entails (Wiers et al., 2009), thus giving more room for implicit associations of oneself as easily angered or not to affect the outcome of behavior. Another impulsive and automatic process that has been linked not only to alcohol intoxication but also to trait anger is proneness to interpreting ambiguous situations as hostile (Attwood et al., 2009; Wilkowski & Robinson, 2008).

Although the above mentioned theories do not directly discuss neurobiological aspects, they do so indirectly, since executive functions are strongly related to activation of the prefrontal cortex of the brain (Heinz et al., 2011). The necessity of including biological aspects, including genetic ones, has been emphasized, for example, by Chermack and Giancola (1997) and Heinz and colleagues (2011).

1.6 Neurobiological correlates

Although not measured in the present thesis, neurobiological correlates of anger and aggressive behavior are briefly outlined since they are related to the cognitive theories describing the relationship between alcohol and aggressive behavior.

In many theories, aggressive behavior has been related to executive functioning, especially during alcohol intoxication (e.g. Giancola, 2000; Lange, 2002; Wiers et al., 2009). A review by Coccaro, Sripada, Yanowitch and Phan (2011) emphasizes the relevance of those prefrontal cortical areas of the brain that are, for example, involved in decision making and

the assessment of social situations in order to evaluate whether or not to respond aggressively. The role of the prefrontal cortex (PFC) in aggressive behavior has been demonstrated in studies of individuals with prefrontal brain damage (for a review see Coccaro et al., 2011). Furthermore, individuals with high levels of aggressive behavior show lower-than-average baseline activity in the frontal cortex (for reviews see e.g. Coccaro et al., 2011; Nelson & Trainor, 2007). The PFC has also an additional role in aggressive behavior, in that it is involved in processes related to the regulation of emotions (Coccaro et al., 2011). In addition to the PFC, subcortical limbic regions such as the hypothalamus and amygdala have been implicated in anger and aggressive behavior, mainly because of their role in the experience of emotions (Coccaro et al., 2011; Nelson & Trainor, 2007). For example, amygdalectomy have been reported to reduce aggressive behavior (Coccaro et al., 2011). Results from functional magnetic resonance imaging studies are varied, with some studies finding an increase of amygdala activity as a response to negative pictures or social signals of threat in individuals with heightened levels of aggressive behavior, and others finding a decrease of amygdala activation (Coccaro et al., 2011). The relation between activation in the amygdala and that in prefrontal regions has been suggested to be of particular relevance for aggressive behaviors (e.g. Bufkin & Luttrell, 2005; Coccaro et al., 2011) since the frontal cortex provides inhibitory inputs to neural circuits involving the amygdala (Nelson & Trainor, 2007). Indeed, in comparison to controls, individuals with intermittent explosive disorder show increased amygdala reactions and reduced orbitofrontal cortex activation in response to angry faces (Coccaro, McCloskey, Fitzgerald, & Phan, 2007).

With regards to the relationship between alcohol intake and PFC functioning, it has been postulated that alcohol intake impairs cognitive functions subserved by the PFC, thus facilitating aggressive behavior (for a review see Giancola, 2000). In addition, already small quantities of alcohol have been shown to reduce activity in the medial PFC in response to errors of performance which was associated with decreased ability to adjust behavior after such errors (Ridderinkhopf et al., 2002, reviewed in Heinz et al., 2011). Furthermore, Heinz et al. (2011) suggest that alcohol intake also facilitates aggressive behavior by disturbing the inhibitory mechanism of the PFC on limbic regions, thus affecting limbic processing of threatening stimuli.

When it comes to neurotransmitters that affect anger and aggressive behavior, serotonin is one of the most studied ones. Studies suggest an inverse relationship between serotonergic activation and aggressive behavior, especially when it comes to hostile (impulsive) aggressive

behaviors (Yanowitch & Coccaro, 2011; Pihl & Benkelfat, 2005; Seo, Patrick, & Kennealy, 2008; Siegel, Bhatt, Bhatt, & Zalcman, 2007). Studies show that low cerebrospinal fluid levels of 5-hydroxyindoleacetic acid (5-HIAA; the main metabolite of serotonin), and altered serotonin receptor function are associated with aggressive-impulsive behaviors (Yanowitch & Coccaro, 2011; Pihl & Benkelfat, 2005). Furthermore, treatment with selective serotonin reuptake inhibitors (SSRI; increasing the extracellular availability and neurotransmission of serotonin) has an overall inhibitory effect on aggressive behavior (Carrillo, Ricci, Coppersmith, & Melloni Jr., 2009). Other neurotransmitters that have been indicated to affect aggressive behavior include the dopamine system, the gamma-aminobutyric acid (GABA), and noradrenergic systems (Pihl & Benkelfat, 2005; Siegel et al., 2007). The specific effects of GABA and noradrenaline on aggressive behavior are not, however, as pronounced as those of serotonin and dopamine (Miczek, Faccimodo, Fish, & DeBold, 2007; Yanowitch & Coccaro, 2011). Whereas the effects of serotonin and GABA on affect-related aggressive behaviors are seen as inhibitory, the effects of dopamine and noradrenaline are thought to be facilitative in nature (Siegel, et al., 2007). It should be kept in mind, however, that neurotransmitters show complex interactions with each other, and that their effects on behavior cannot be isolated (Pihl & Benkelfat, 2005; Seo, Patrick, & Kennealy, 2008). For example, the relationship between metabolites of dopamine and serotonin has been indicated as particularly relevant in explaining aggression related phenotypes (Anckarsäter, 2006; Nilsson et al., 2010; Pihl & Benkelfat, 2005). Although the association between the effects of alcohol on neurochemistry specifically with regards to anger and aggressive behavior is complex and not quite clear, effects of alcohol intake on the serotonergic, dopaminergic, noradrenergic, as well as GABAergic neurotransmitter systems have been noted in the literature (Heinz et al., 2011; Mukherjee, Kumar Das, Vaidyanathan, & Vasudevan, 2008; Valenzuela, 1997). For example, animal models indicate that although the GABA neurotransmitter shows suppressive effects on aggressive behavior in general, increased $GABA_A$ receptor activation as a result of alcohol is associated with aggressive behavior (Miczek, DeBold, van Erp, & Tomatzky, 1997; Miczek, Fish, & DeBold, 2003).Other factors that influence aggressive behavior include the steroid hormones testosterone and cortisol (van Honk, Harmon-Jones, Morgan, & Schutter, 2010). Although the role of testosterone in explaining human aggressive behavior is not as strong as in non-human animals, testosterone levels have been found to correlate positively with aggressive behavior (Archer, 2006; van Honk et al., 2010), feelings of anger and selective attention to angry faces (van Honk, Tuiten, Verbaten, van den Hout, Koppeschaar, Thijssen, & de Haan, 1999). The association between

cortisol and aggressive behavior is in the opposite direction; low levels of cortisol have been associated with aggressive behavior (van Honk et al., 2010).

The above mentioned neurotransmitters and hormones were reviewed with respect to their effects on hostile or reactive forms of aggressive behavior. Although some studies have directly investigated the association between these neurotransmitters as well as hormones, and anger (e.g. Dougherty et al., 2006; Fava & Rosenbaum, 1998; Harmer, Shelley, Cowen, & Goodwin, 2004; Salzman et al., 1995), it is hypothesized that they have associations with anger also based on the fact that anger and aggressive behavior are so closely connected in hostile and reactive forms of aggressive behavior (Anderson & Bushman, 2002; Geen, 2001). Recent efforts to understand the biological etiology behind aggressive behavior include investigating the neuropeptides vasopressin and oxytocin, not least in hope of understanding the broader biological basis for these behaviors, but also in hope of finding more varied options for treatment of problematic aggressive behavior (Yanowitch & Coccaro, 2011). Whereas the effect of vasopressin on aggressive behavior is facilitative, the effects of oxytocin seem to be suppressive (Siegel et al., 2007; Siever, 2008; Yanowitch & Coccaro, 2011). Oxytocin and its associations with social and aggressive behavior will be described in section 1.9.

1.7 Genetic effects on aggressive behavior and anger

Besides neurobiological correlates of aggressive behavior, genes have been found to affect aggressive behavior. Using quantitative genetic twin modeling or adoption studies, a significant contribution of genetic effects on explaining variability between individuals in aggressive and antisocial behavior has been shown (e.g. reviews by Miles & Carey, 1997; Rhee & Waldman, 2002) (the reader is kindly advised to consult the method section for information about quantitative twin modeling techniques). A meta-analysis by Miles and Carey (1997) estimated genetic effects to account for up to 50% of the variance in aggressive behavior. A study of relational and direct aggressive behavior in children found genetic effects of similar magnitude, with heritability estimates being higher for relational (66%) than for direct aggressive behavior (53-60%) (Ligthart, Bartels, Hoekstra, Hudziak, & Boomsma, 2005). Another study (Yeh, Coccaro, & Jacobson, 2010) found aggressive behaviors to best be explained by two different factors, general and physical aggressive behavior, with heritability estimates around 50% for the former and around 40% for the latter. Genes were

found to explain approximately 70% of the variance between individuals in aggressive behavior in a sample partly overlapping with the population-based sample used in the present thesis (von der Pahlen et al., 2008).

The overall effect of genes on antisocial behavior was estimated to around 40% in a meta-analysis by Rhee and Waldman (2002). However, when differentiating between aggressive forms of antisocial behavior from nonaggressive ones, the amount of variance explained by genetic effects increases to around 60% regarding the aggressive forms (Burt, 2009; Eley, Lichtenstein, & Moffitt, 2003). This is consistent with the results of a large population study investigating familial aggregation of convictions for violent crimes in Sweden ($N > 12.5$ million) (Frisell, Lichtenstein, & Långström, 2011). The results showed a strong familial risk among first-degree relatives, with an odds ratio of 3.5 (95% CI lower bound 3.5, upper bound 3.6) for parent-child dyads, and an odds ratio of 4.3 (95% CI lower bound 4.2, upper bound 4.3) for siblings (Frisell et al., 2011). Although this *per se*, does not necessarily indicate the influence of genes since family members also share their environments to an extent, the patterns of familial risk across biological and adoptive relations indicated involvement of both genetic and environmental effects (Frisell et al., 2011). Several genes influencing aggressive behavior have been suggested among those the monoamine oxidase A (MAOA) gene, the catechol-O-methyl transferase (COMT) gene, and various subtypes of serotonin receptor genes (Craig & Halton, 2009).

Trait anger and anger control have not been as extensively studied as aggressive behavior also with regards to etiological factors. Rebollo and Boomsma (2006) found genetic effects to influence trait anger using quantitative genetic twin modeling. For men, interindividual variance in trait anger was explained by a combined genetic effect of 49%, with the rest of the variance being influenced by nonshared environmental effects. For women, the variance in trait anger was best explained by additive genetic effects (34%) and nonshared environmental effects (Rebollo & Boomsma, 2006). In an earlier study including only male twins, additive genetic effects on trait anger were estimated to 25% with the rest of the variance being explained by nonshared environmental effects (Sluyter, Keijser, Boomsma, van Doornen, van den Oord, & Sneider, 2000).

In a study that explored the magnitude of genetic effects on expression and control of anger, a separation was made between 1) anger expression towards other people and environments; 2) anger suppression; and 3) anger control (Wang, Trivedi, Treiber, & Snieder, 2005). Genetic

effects were found on anger control (34%), but not on anger suppression which was instead influenced by shared environmental (18%) as well as nonshared environmental effects (82%) (Wang et al., 2005). Outward anger expression had a significant familial component, but no distinction between the effects of genes and shared environment could be made (Wang et al., 2005). It should be noted, though, that the twin correlations were higher for dizygotic (DZ) twins than for monozygotic (MZ) twins for some of the variables, which is inconsistent with genetic theory, and the results should therefore be interpreted with caution. According to another study using a sample of 200 individuals, all anger control and expression variables were under significant influence of genes, with a heritability estimate of around 30% for the overall anger expression variable (Gleiberman, Greenwood, Luke, Delgado, & Weder, 2008). Fewer molecular genetic association studies have been conducted to elucidate control and expression of anger and trait anger compared to studies focusing on aggressive behavior, but some specific genes have been suggested in the literature. For example, the tryptophan hydroxylase gene (Baud et al., 2009; Manuck, 1999), the COMT gene (Rujescu, Giegling, Gietl, Hartmann, & Möller, 2003), and the serotonin receptor 2 A gene (Giegling, Hartmann, Möller, & Rujescu, 2006) have all been investigated in the context of anger. Many of these genes have been implicated in molecular genetic association studies on aggressive behavior as well (Craig & Halton, 2009).

1.8 Interactions between genes and environmental factors

Human behavior and traits are directly influenced by genetic and environmental effects, but in addition, there is interplay between genes and environmental factors (Moffitt et al., 2006; van der Sluis, Dolan, Neale, & Posthuma, 2008). There are several different mechanisms of interplay between genes and environmental factors (Moffitt et al., 2006), but the present thesis is focused on gene-environment interactions (G x E). G x E refers to the concept that individuals can react differently to the same environmental influences based on their genetic variants, that is, that differences in sensitivity to specific environmental features are influenced by genes (Dick, 2011; Rutter & Silberg, 2002; Moffitt et al., 2006). Since the 1990s, there has been renewed interest in examining G x Es (Dick, 2011; Rutter, Moffitt, & Caspi, 2006; Waldman, 2007). Moffitt and colleagues (2006) note that G x E may be much more common than previously thought, and van der Sluis et al. (2008) emphasize that such interactive effects need to be taken into account when trying to explain individual differences. The term gene-environment interaction has been used, sometimes incorrectly, to explain

somewhat different phenomena (Moffitt, et al., 2006). For example, a difference should be made between dissimilar heritability estimates in subpopulations, which involves a statistical interaction but is not the same as studies that address biological G x E by showing that individuals differ in their susceptibility to measured environmental effects by differences in identified genetic variants (Moffitt et al., 2006). If interactions between genes and family-wide environments play a role in explaining variability of a specific trait under study, failure to incorporate the interactions in an analysis would be seen in the interactive effects being captured in the additive genetic estimates when using a quantitative behavior genetic twin modeling approach (Rutter & Silberg, 2002).

Genes have been shown to interact with environmental factors in influencing aggression-related traits. In 2002, Caspi et al. showed that the effect of childhood maltreatment on antisocial behavior was moderated by the individual's genotype on an MAOA gene polymorphism. In addition, variants of the MAOA gene have been shown to moderate the effect of adverse psychosocial risk factors during adolescence on development of criminal behavior (Nilsson, et al., 2006). Another gene that has shown interactions with environmental variables in influencing aggressive behavior is the serotonin transporter gene (Edelyn et al., 2006; Reif et al., 2007).

There is strong evidence that not all individuals will become aggressive when alcohol intoxicated (e.g. Ito, et al., 1996). One explanation why this is the case, could be that individuals react differently to the effects of alcohol on aggressive behavior, based on their genotypes (G x E). Still, to our knowledge, only one study (Tikkanen et al., 2010) has found an interaction between a gene and alcohol consumption on aggressive behavior in humans and no study has investigated interactions between genes and alcohol on anger related traits. Tikkanen et al. (2009) explored the association between genetic variants of the MAOA-LPR polymorphism, alcohol consumption and recidivism in a sample of alcoholic violent offenders. The results suggested that while higher alcohol consumption was associated with increased risk for recidivism in carriers of the high activity genetic variant, the same was not true for carriers of the low activity variant (Tikkanen et al., 2009). The interaction was not, however, tested specifically in that study, but a later study showed that this interaction was indeed significant (Tikkanen et al., 2010). Subsequently, a research group comprising partly of the same researchers as in the Tikkanen et al. (2009) study found a stop codon (Q20) in the gene encoding the 5-HTR2B receptor to be more common in a sample of Finnish violent offenders of which a high percent were diagnosed with alcohol use disorder (97%) than in controls

(Bevilacqua et al., 2010). It is, however, unknown if these violent offenders with alcohol use disorder differ from violent offenders without alcohol use disorder with regards to genotype frequency of the stop codon. In 2010, Ray and colleagues showed in a sample of heavy drinkers that subjective responses to alcohol, for example, changes in vigor and mood, varied between individuals based on their genetic variants on the Asn40 polymorphism in the μ-opioid receptor (OPRM1) gene. This indicated that it is reasonable to assume that genetic variants can affect the way people react to the acute effects of alcohol. With regards to aggressive behavior under the influence of alcohol, genes other than the MAOA (Tikkanen et al., 2009) that have been suggested to be of importance include those related to serotonergic systems (Bevilacqua et al., 2010; Heinz et al., 2011) and systems involving the γ-Aminobutyric acid (GABA) (Heinz et al., 2011).

Animal models of aggressive behavior under the influence of alcohol are useful in many ways. Not only is it easier to control and manipulate environmental effects in studies using animals, but a wider range of experimental procedures can be used, relatively larger quantities of alcohol can be administered, and it is easier to study the underlying neurobiological changes and mechanisms (Higley, 2001). Like humans, animals display individual variation in how they react to alcohol (Chiavegatto, Quadros, Ambar, & Miczek, 2010; Higley, 2001). About one third of mice and rats can be characterized as alcohol-heightened aggressors (AHA; Chiavegatto et al., 2010). Chiavegatto et al. (2010) compared such male mice against mice that did not react to alcohol with increases in aggressive behavior (alcohol non-heightened aggressors, ANA) and found lower expression patterns of all 5-HT receptor subtypes except for 5-HT_3 in the PFC of AHA mice, as well as higher expression patterns of the 5-HT_{1B} in the amygdala and hypothalamus of AHA mice compared to ANA mice. According to the authors, these differences most likely originate from differences in expression of the corresponding gene, but note that it cannot not be concluded whether the differences are the cause for or effect of alcohol related aggressive behavior, but hypothesize that interactions between genetic and environmental effects might explain these findings (Chiavegatto et al., 2010).

1.9 Oxytocin and polymorphisms in the oxytocin receptor gene

Another candidate for interactive effects with alcohol on aggressive behaviors and anger related traits is the neuropeptide oxytocin (OXT) and genes related to it. OXT is known for its peripheral effects in mammalian species (e.g. uterine contractions during parturition), but it has also been associated with numerous socially important traits as well as aggressive

behaviors both in animal and human studies (e.g. see reviews by MacDonald & MacDonald, 2010; Lee, Macbeth, Pagani, & Young 3rd, 2009, and the study in humans by Lee, Ferris, Van de Kar, & Coccaro, 2009). OXT is primarily produced in hypothalamic structures in the brain, and besides having effects in the brain as a neurotransmitter, it is also released into the bloodstream where it functions as a hormone (Veening, de Jong, & Barendregt, 2010; Insel, 2010). Receptors for OXT are found in peripheral tissues as well as in several areas of the brain (Gimpl & Fahrenholz, 2001; Lee, Macbeth et al., 2009).

In rodents, OXT has been related to several types of aggressive behaviors (DeVries, Young 3rd, & Nelson, 1997; Harmon et al., 2002; Ferris et al., 1992; Lubin, Elliott, Black, & Johns, 2003; Ragnauth et al., 2005; Sala et al., 2011; Takayanagi et al., 2005; Winslow & Insel, 2002). Animal studies show effects in different directions, both increasing and decreasing aggressive behavior, partly depending on the species studied (Lee, Macbeth, et al., 2009; Winslow & Insel, 2002). In humans, the majority of studies indicate an inverse relationship between OXT and aggressive behavior. For example, Lee, Ferris, et al. (2009), explored associations between levels of OXT in the cerebrospinal fluid (CSF) and life history of aggression, and found that high levels of OXT in the CSF were correlated with lower levels of aggressive behavior. Likewise, another study showed a tendency for CSF OXT levels to be negatively related to lifetime violent behavior (Jokinen et al., 2012). In addition, higher levels of autoantibodies reactive for OXT were found both for prisoners and participants with conduct disorder than for controls (Fetissov et al., 2006). Although the relationship between autoantibodies reactive for OXT and OXT levels in the brain is not clear, a possibility is that the autoantibodies would interfere with neural circuits and thus reduce levels of OXT (Fetissov et al., 2006). Intranasally administered OXT has been suggested as a possible therapeutic tool for individuals with Prader-Willi syndrome (Tauber et al., 2011). Individuals with Prader-Willi syndrome show an inability to control emotion with frequent temper outbursts and disruptive behavior as a consequence, which has been hypothesized to be related to deficits in OXT producing neurons in the hypothalamic paraventricular nucleus found in these individuals (Tauber et al., 2011). Intranasally administered OXT reduced such disruptive behaviors when measured two days after the administration of OXT (Tauber et al., 2011). On the other hand, intranasally administered OXT increased noncooperation with competing out-group participants – a form of defensive aggressive behavior according to De Dreu et al. (2010). It should be noted, though, that defensive aggressive behaviors are distinct from other forms of aggressive behavior which could partly explain the, at first sight,

discrepant result. This was also indicated in the De Dreu et al. (2010) study since OXT did not affect offensive aggressive behavior (De Dreu et al., 2010). Offensive aggression was defined in the DeDreu et al. (2010) study as noncooperation with the out-group motivated by greed.

Furthermore, a study by Kirsch et al. (2005) showed that intranasally administered OXT reduced neural activation in amygdala especially as a response to angry and fearful faces for men. There are somewhat discrepant results related to the effect of OXT on amygdala activation as a response to happy faces. Domes et al. (2007a) showed that amygdala activation was attenuated also as a response to happy facial expressions, whereas Gamer, Zurowski and Büchel (2010) found that OXT decreased amygdala activity after seeing fearful faces but increased amygdala activity after seeing happy faces. For women, no effect of OXT administration on amygdala responses as a response to angry facial images was seen (Domes et al., 2010). These results are interesting particularly in light of studies showing that participants with high levels of aggressive behavior (or high levels of traits related to aggressive behavior) have increased amygdala reactions to angry faces in comparison to controls or individuals with lower levels of aggression-related traits (Beaver, Lawrence, Passamonti, & Calder., 2008; Carré, Murphy, & Hariri, in press; Coccaro et al., 2007).

Besides associations with phenotypes directly related to aggressive behavior, increased OXT levels have been associated with socially important skills and traits such as improved recognition of faces seen before (Rimmele et al., 2009), as well as an enhanced ability to correctly recognize the emotions of others from facial expressions (Di Simplicio et al., 2009; Domes et al., 2007b; Marsh, Yu, Pine, & Blair, 2010; Schulze et al., 2011; Van IJzendoorn & Bakermans-Kranenburg, 2012). Theories about the effects of alcohol on aggressive behavior stipulate that alcohol intoxicated individuals have more difficulties in interpreting socially ambiguous situations than sober individuals because of the disruptive effects alcohol have on cognitive functions (Giancola, 2000; Lange, 2002). Accurate recognition of the emotions of others is an important feature of trying to understand the motives of others in socially ambiguous situations, and therefore these traits are of interest when exploring the link between alcohol and aggressive behavior. It could thus be hypothesized that alcohol would have a larger effect on aggressive behavior for individuals who have more difficulties with such abilities, due to their levels of OXT or the responsiveness of their oxytocin receptors (OXTR).

Although evidence suggests that OXT is involved in aggressive behaviors as well as functions associated with regulation of these, to our knowledge, no study had, until recently, investigated if aggressive behavior is associated with oxytonergic genes in humans. A recent study showed associations between two *OXTR* polymorphisms and childhood-onset aggressive behavior (Malik, Zai, Abu, Nowrouzi, & Beitchman, in press). In mice, knock-out of the oxytocin receptor gene (*OXTR*) results in heightened levels of aggressive behavior (Takayanagi et al., 2005). In humans, polymorphisms in the *OXTR* have also been associated with, for example, autism spectrum disorders (Insel, 2010; Jacob et al., 2007; Lerer et al., 2008; Wu et al., 2005; Yrigollen et al., 2008), callous-unemotional traits in children displaying aggressive behavior (Beitchman et al., in press), empathy (Wu, Li, & Su, in press), the ability to correctly infer the emotions of others as facially expressed (Rodrigues et al., 2009), adult attachment style among individuals with unipolar depression (Costa et al., 2009) as well as pro-social behavior (Israel et al., 2009; Tost et al., 2010). A study by Apicella et al. (2010) did not, however, replicate the effects of *OXTR* polymorphisms on pro-social behavior. Furthermore, individuals with a specific variant of an *OXTR* polymorphism rated subjects who had committed harm accidentally as more blameworthy than non-carriers of the genetic variant (Walter et al., 2012). This result is interesting with regards to aggressive behavior and anger, since interpretation of the situation and the intentions of the opponent are thought to influence the likelihood of responding with anger and aggressive behavior (Giancola, 2000). Although the functionality of *OXTR* polymorphisms with regards to OXT levels and amount of OXTRs in still unclear, a recent study indicated that two *OXTR* polymorphisms were related to plasma levels of OXT (Feldman et al., in press), and unpublished results from a research group indicate that a polymorphism in the *OXTR* is associated with mRNA expression and might thus influence the amount of OXTR receptors (Walter et al., 2012).

Furthermore, studies suggest that alcohol decreases the levels of OXT. Animal studies have shown that alcohol decreases the levels of OXT in rat dams (McMurray et al., 2008), and suppresses the release of OXT (Hashimoto et al., 1985; Knott et al., 2000). In humans, alcohol decreases the levels of OXT at least in nulliparous and lactating women (Menella, Pepino, & Teff, 2005; Menella & Pepino, 2006) as well as during labor (Gibbens & Chard, 1976). OXT can stimulate its own release through its receptor (Neumann, Douglas, Pittman, Russell, & Landgraf, 1996), and therefore, another hypothesis could be that alcohol would affect the change in OXT levels differently depending on the genotype of the individual on *OXTR* polymorphisms.

2 AIMS AND RESEARCH QUESTIONS

The general aim of the present thesis was to investigate the effects of alcohol on anger related phenotypes as well as aggressive behavior, with specific focus on interactive effects between genes and alcohol. The oxytocin receptor gene (*OXTR*) was tested as a candidate gene for the moderation of the effects of alcohol on aggressive behavior and anger. For the genotypic analyses, both quantitative and molecular genetic approaches were used. Both self-report and laboratory measures were used to collect data.

In **Study I**, the aim was to investigate if levels of anger control would be lower in self-reported intoxicated than sober states, and if this effect of state would be moderated by trait anger or alcohol consumption. Usually, questionnaires do not separate between behavior conducted and feelings felt while being sober or intoxicated. Thus, in Study I, we wanted to explore if different associations could be detected when separating between recalled usual levels of anger control of the participants when they are sober and intoxicated.

In **Study II,** the aim was to test how much of the inter-individual variation in anger control both regarding self-reported sober and intoxicated states would be explained by genetic and environmental factors. One aim was also to test if the genetic and environmental effects influencing to what degree a person controls his or her anger when sober compared to when intoxicated would be common (i.e. if the genetic and environmental effects on anger control both when sober and when intoxicated are the same). In addition, it was explored if genes would influence the difference in usual levels of anger control between sober and intoxicated states, which could suggest interactive effects between alcohol and genes on anger control. No hypotheses were made regarding the magnitude of the effects.

In **Study III**, the aim was to explore genetic effects of *OXTR* polymorphisms on aggressive behavior exclusively in men, and more specifically, to test if the effect of alcohol on aggressive behavior would be moderated by these polymorphisms. The focus of the study was on interactions between alcohol and the *OXTR* polymorphisms on aggressive behavior, however, no hypotheses were made regarding specific polymorphisms. An experimental approach was used to test acute effects of alcohol intoxication as well as to ensure causality of the effect of alcohol. Only men were tested in this first study since they tend to show higher levels of aggressive behavior than women, and previous studies suggest that the effect of alcohol on aggressive behavior could be more pronounced for men compared to women (e.g.

Giancola et al., 2009). Furthermore, OXT could have different effects for men and women based on earlier studies (e.g. Domes et al., 2010; Kirsch et al., 2005; MacDonald & MacDonald, 2010), suggesting that the effects of OXT should be analyzed separately for men and women. Since the sample sizes that can be obtained in experimental studies often are relatively small in comparison to questionnaire studies, the decision was made to focus on men in the study in question.

In **Study IV,** the aim was twofold. The first aim was to replicate the results of Study III in a population-based sample of both men and women, using self-reports of aggressive behavior. The second aim was to explore if the SNPs[1] that were found to have at least nominal effects on aggressive behavior in Study III, would also affect anger control and trait anger in a similar manner, since they are associated with aggressive behavior. Additionally, it was tested if these SNPs would have an effect on the difference in anger control between self-reported sober and intoxicated states.

The following specific hypotheses were made:

Study I

1) Anger control will be significantly lower in self-reported alcohol intoxicated than sober states.
2) Trait anger will be negatively associated with anger control, regardless of self-reported prior sober or intoxicated states.
3) The difference in anger control between the self-reported sober and intoxicated state will be larger for those with high levels of alcohol consumption than for those with low levels.
4) The difference in anger control between the self-reported sober and intoxicated state will be larger for those with high levels of trait anger than for those with low levels.
5) Individuals with high levels of trait anger and alcohol consumption will have the lowest levels of anger control in the self-reported alcohol intoxicated state.

[1] rs4564970, rs1488467 and rs1042778

Study II
6) Genes will significantly explain some of the inter-individual variance in anger control regarding sober states.
7) Genes will significantly explain some of the inter-individual variance in anger control regarding intoxicated states.
8) Genes will significantly explain some of the inter-individual variance in anger control regarding intoxicated states.
9) There will be genetic effects on the difference in anger control between sober and alcohol intoxicated states.

Study III
- No specific hypotheses were made.

Study IV
10) The rs4564970 and the rs1488467 polymorphisms will both separately moderate the effect of alcohol consumption on aggressive behavior and trait anger.[2]
11) The rs4564970 and the rs1488467 polymorphisms will show main effects on the difference in anger control between the self-reported sober and intoxicated states.[3]
12) The rs1042778 polymorphism will show main effects on aggressive behavior, trait anger and anger control.[4]

[2] The hypothesis was that the positive association between alcohol consumption and both aggressive behavior and trait anger would be more pronounced for carriers of at least one cytosine (C) allele than for participants with two guanine (G) alleles.
[3] The hypothesis was that the difference in anger control between sober and intoxicated states would be larger for individuals carrying at least one C allele compared to individuals with two G alleles.
[4] The hypothesis was that individuals with at least one G allele would show higher levels of aggressive behavior and trait anger and lower levels of anger control than individuals with two thymine (T) alleles.

3 METHODS AND MATERIALS

3.1 Participants

The results of the present thesis were based on two different projects. Studies I, II and IV were part of the "Genetics of Sexuality and Aggression" study, a project aimed at investigating genetic effects using questionnaire data from a population-based sample of male and female twins and their siblings. Study III was experimental in its nature and the sample consisted of male students recruited from universities. All participants were Finnish. All studies were conducted at the Department of Psychology and Logopedics at the Abo Akademi University in Turku, Finland.

3.1.1 The Genetics of Sexuality and Aggression Sample (studies I, II, IV)

The Genetics of Sexuality and Aggression (GSA) sample is based on two data collections. The first data collection was carried out in 2005 and targeted 33-43-year-old twins. The second data collection was carried out in 2006 and was aimed at 18-33-year-old twins and their siblings aged 18 or above registered as Finnish citizens with Finnish as their mother tongue. There was no overlap between the data collections. Only data from the second data collection was used in the present thesis, and is therefore described in further detail. In the second data collection, a total of 23,577 individuals were contacted by postal mail and asked if they were interested in filling out a sexuality and aggression related questionnaire. The participants could also indicate whether they in addition to completing the questionnaire wanted to give a sample of saliva for DNA and hormone analyses. The addresses were obtained from the Finnish population registry in December 2005. Those willing to participate were given the option of completing the questionnaire by mail or through a secure internet web page. One reminder letter was sent. A total of 3923 men (32.9%) and 6601 women (56.6%) responded. In all, 4278 (66.0%) of the participants who had indicated willingness to give a saliva sample for DNA analyses returned the DNA-kits. The questionnaires covered a wide range of, for example, sexual behaviors and attitudes, aggressive behaviors, anger, childhood experiences and alcohol use. The purpose of the study was clearly described and the voluntary and anonymous nature of participation emphasized. The research plan was approved by the Ethics Committee of the Abo Akademi University in accordance with the

1964 Declaration of Helsinki. Differences in the numbers of participants used in studies I, II, and IV are briefly outlined below.

In Study I, one person per family was randomly selected for the analyses in order to account for intra-family dependence of observations in order to be able to analyze the effects of alcohol consumption and trait anger on anger control which was measured repeatedly. In addition, only participants with responses to at least one third of the items of each of the instruments used in the study, except for anger control when intoxicated, were included. In studies II and IV, statistical methods able to take into account the dependent structure of family data were used, and therefore all participants in a specific family could be included in these studies. Similarly to Study I, only participants with responses to at least one third of the anger control items regarding the sober state and 1/3 of the items on alcohol consumption were included in the sample of Study II. Participants not drinking alcohol did not respond to questions regarding the intoxicated states. In order for such participants to be included in the analyses regarding the sober states, number of responses to the items regarding the intoxicated states was not used as inclusion criteria in studies I and II. In Study IV, participants with responses to a minimum of one third of the items for at least one of the measures used were included in the sample. In addition, abstainers were excluded from the sample. The sample for Study IV was selected based on the criteria outlined above from the 4278 participants who had returned a DNA sample. Additional information can be seen in tables 2 and 3.

3.1.2 The Experimental Sample (Study III)

Altogether, 116 men aged between 18 and 30 years were included in Study III. The participants were recruited from universities in Turku using university mailing lists and posters or personal referral. The participants were randomly assigned to either a group receiving alcohol, or a group receiving placebo. The alcohol group consisted of 63 individuals, and the placebo group of 53 individuals. Exclusion criteria used included the following: previous adverse reactions to alcohol, drug-related problems, poor general health, a body mass index (BMI) exceeding 30, excessive use of alcohol, medication contraindicating alcohol consumption, diabetes and/or tinnitus. Written consent was obtained from all participants and it was emphasized that they could discontinue the experiment at any time. A cover story was used to conceal that the true purpose of the experiment was to measure aggressive behavior, stating that the aim of the study was to investigate the effects of alcohol

on reaction time, interpersonal communication and temperament. The research plan was approved by The Ethics Committee of the Abo Akademi University in accordance with the 1964 Declaration of Helsinki.

Table 2
Characteristics of the Samples Used in the Four Original Studies as well as an Overview of Research Questions and Main Measures Used in the Studies

Study	Study queries	Sample	Participants (*N*)	Age range in years	Main instruments	Methods
I	Phenotypic associations between trait anger, alcohol use and anger control	GSA: Population-based	4852 1654 men 3198 women	18-47	AUDIT, STAXI-2	Survey data
II	Genetic effects on anger control (sober and intoxicated) Genetic effects on the difference in anger control between these states	GSA: Population-based	8964 3072 men 5892 women	18-49	STAXI-2	Survey data Quantitative genetic twin modeling
III	Interactive effects between *OXTR* SNPs and alcohol on aggressive behavior	University students	116 men	18-30	RCAP	Experimental Molecular genetic association study
IV	Interactive effects between *OXTR* SNPs and alcohol on aggressive behavior, trait anger and anger control	GSA: Population-based	3577 1498 men 2079 women	18-49	AUDIT, STAXI-2, AQ	Survey data Molecular genetic association study

Notes. GSA = Genetics of Sexuality and Aggression. SNP = Single nucleotide polymorphism. *OXTR* = Oxytocin receptor gene, AUDIT = The Alcohol Use Disorders Identification Test (Saunders, Aasland, Babor, de la Fuente & Grant, 1993), STAXI-2 = The second version of the State-Trait Anger Expression Inventory (Spielberger, 1999), RCAP = the Response Choice Aggression Paradigm (Zeichner, Frey, Parrot & Butryn., 1999), AQ = the Aggression Questionnaire (Buss & Perry, 1992). All participants from the GSA project were from the second data collection.

Table 3

Relations between, as well as Inclusion Criteria Used in the Subsamples of the Genetics of Sexuality and Aggression Sample in Studies I, II, and IV

Study	Inclusion criteria 1	Inclusion criteria 2	Inclusion criteria 3	Relation to other samples
I	1 randomly selected person per family	Responses to at least 1/3 of the items of anger control sober, trait anger and alcohol consumption		
II	Responses to at least 1/3 of the items measuring anger control regarding the sober state and alcohol consumption			All participants in Study I were included in Study II
IV	Returned DNA sample which was successfully genotyped	Responses to a minimum of 1/3 of the items for at least one of the following traits: anger control sober, anger control intoxicated, trait anger, aggressive behavior, alcohol use	Response other than "*never*" to the item "*How often do you have a drink containing alcohol?*"	A majority of the participants (n =3539) in Study IV were included in studies I and II. Participants not (n = 38) included in earlier studies had missing data for anger control but not for aggression.

3.2 Measures

The main measures used in the four original studies will be briefly described below. For more thorough descriptions of the measures, the reader is advised to consult the original studies.

3.2.1 Measurement of alcohol consumption and intoxication

In the present thesis, both self-report survey data on alcohol consumption and as well as a measure of the acute level of intoxication following consumed alcoholic beverages were used to measure the effects of alcohol. Below, the instruments used to measure alcohol consumption and alcohol intoxication are described.

3.2.1.1 Self-reports of alcohol consumption (studies I, II, III, and IV). Self-reports of alcohol consumption were used in some form in all original studies. The three first items, also

known as the AUDIT alcohol consumption questions (AUDIT-C; e.g. Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998) or the hazardous alcohol use domain (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001), from the Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente & Grant, 1993) were used to measure alcohol consumption in the present thesis. The items read as follows: 1. "*How often do you have a drink containing alcohol?";* 2. "*How many drinks containing alcohol do you have on a typical day when you are drinking?"*; and 3. "*How often do you have six or more drinks on one occasion?".* Five Likert-type response alternatives were given for each item, coded from 0 to 4 points each. For question 1, the response alternatives were: *"never", "monthly or less", "2-4 times a month", "2-3 times a week",* and *"4 or more times a week*". Response alternatives for the second item were: "*1-2", "3-4", "5-6", "7-9"* and *"10 or more"*. For the third item, the response alternatives were the following: "*never", "less than monthly", "monthly", "weekly",* and *"daily or almost daily"*. A composite variable for alcohol consumption was computed by summing the scores of the items according to the AUDIT guidelines (Babor et al., 2001). The internal consistency of the items was considered acceptable (Cronbachs αs ranged between .51 and .62) taking into account the low number of items.

The AUDIT was developed by the World Health Organization as a screening tool for excessive alcohol use (Babor et al., 2001). It is one of the most widely used self-report measures of alcohol use (Allen, Litten, Fertig, & Babor, 1997), and has been translated into various languages (Babor et al., 2001). According to a review by Fiellin et al. (2000), sensitivity of the items ranged between 54% and 98%, and specificity between 57% and 93% for different definitions of heavy drinking.

3.2.1.2 Measurement of acute alcohol intoxication (Study III). Participants randomly assigned to the alcohol manipulation group in Study III, were given alcoholic drinks leading to a moderate level of intoxication. Their levels of acute alcohol intoxication were measured using the Mark X Electrochemical Breath Alcohol Analyzer (Alcovisor®, C4 Development Ltd., Kownloon, Hong Kong). Levels of intoxication were reported using a measure of Blood Alcohol Concentration (BAC) (1cg alcohol per mL blood).

3.2.2 Measurement of anger related phenotypes

Anger related traits were measured using self-report survey data. Two features of anger were analyzed: trait anger and anger control. The questionnaires used to measure the anger related traits are described briefly below.

3.2.2.1 Measurement of trait anger (studies I and IV). Trait anger was measured using the Trait Anger-scale of the second version of the State-Trait Anger Expression Inventory (STAXI-2; Spielberger, 1999), a self-report measure. The scale consists of 10 items with response options on a four-point Likert-type scale ranging from 1 ("*almost never"*) to 4 ("*almost always"*) to describe how they generally feel or react. The items were subjected to a factor analysis (Study I), which showed that a one-factor solution suited the data best. Subsequently, a composite variable measuring trait anger was computed by multiplying the factor score coefficients with the item scores and then summing the products. One randomly selected person per family was used in the factor analyses and extraction of the factor score coefficients in order to account for intra-family correlation. Higher values on the composite score indicated higher levels of trait anger. In Study IV, only 8 of the 10 items were included in the composite variable measuring trait anger. This was done since the aim of the study was to investigate interactions between alcohol consumption and three polymorphisms on trait anger, and two of the trait anger items most likely are not related to feelings of anger when alcohol intoxicated since they specifically measure anger in work situations where most individuals will not have been intoxicated ("*I am not given recognition for doing good work*" and "*I feel infuriated when I do a good job and get poor evaluation*"). Internal consistency of the trait anger items was good (Cronbachs α-values between .79 and .83).

In previous studies as well, the scale has been shown to have good reliability with Cronbach's α coefficients ranging between .78 and .89 (Spielberger, 1999). In addition, a study by Deffenbacher et al. (1996) showed that the trait anger scale both had good convergent as well as discriminant validity in that it predicted the frequency and intensity of angry feelings and showed higher correlation with anger related constructs than with other traits or behaviors.

3.2.2.2 Measurement of anger control (studies I, II and IV). Anger control was measured using the anger expression and control items of the STAXI-2 (Spielberger, 1999). The part

consists of 32 statements that the participant is to rate on a four-point Likert-type scale from 1 ("*almost never"*) to 4 ("*almost always"*) according to how well the statement describes how the participant generally reacts when angry. Differing from the original scale, participants were asked how they usually react both when they are sober and intoxicated (hereafter referred to as anger control regarding sober and alcohol intoxicated states). Twenty-five of the 32 items were included in the composite variables measuring anger control in the two states based on the results of a factor analysis indicating that a one-factor solution fitted the data best (kindly see Study I for additional information regarding the factor analysis). Items with factor loadings exceeding .30 were included in the composite variable. The composite variable measuring anger control regarding the sober state was computed for each individual by multiplying the scores of the items with their factor score coefficients, and then summing the products. Factor score coefficients regarding the sober state were used to calculate a composite variable for anger control regarding the intoxicated state in a similar manner as for the sober one. Factor score coefficients were calculated based on analyses of one randomly selected individual per family. Higher values on the composite scores indicated higher anger control and lower anger expression. The internal consistency of the variables was good, both regarding the sober and intoxicated states (Cronbach's αs ranged between .77 and .79).

STAXI-2 and its predecessors have been shown to have good psychometric properties, and have been considered the preferred instrument for assessing expression and control of anger (Kroner and Reddon, 1992; Martin and Dahlen, 2007; Spielberger, 1999). Spielberger (1999) reported Cronbach's α coefficients ranging between .67 and .94 for women and between .55 and .93 for men for the STAXI-2 anger expression and control factors.

3.2.3 Measurements of aggressive behavior

Aggressive behavior was measured in studies III and IV. In Study III, aggressive behavior was measured using a laboratory paradigm and in Study IV using self-report survey data. Both measures are described in brief below.

3.2.3.1 Self-reports of aggressive behavior (Study IV). Aggressive behavior, as self-reported, was measured in Study IV using the verbal and physical aggression scales of the Buss and Perry (1992) Aggression Questionnaire (AQ). The scales consist of altogether 14

items with response alternatives given on a five-point Likert-type scale ranging from 1 ("*extremely uncharacteristic of me"*) to 5 ("*extremely characteristic of me"*). The items were subjected to a factor analysis in a study by von der Pahlen et al., (2008) using a sample that partly overlaps with the one used in Study IV of the present thesis. The results of the factor analysis indicated that a one-factor solution suited the data best, excluding two items that did not show sufficient loadings on the factor. Therefore, a composite score of aggressive behavior was calculated by summing the scores of the remaining twelve items in accordance with von der Pahlen et al., (2008). On item with a negative factor loading was reversed prior to calculation of the composite score. Higher values on the composite score indicated higher levels of aggressive behavior. The AQ has shown good reliability, both for internal consistency and test–retest correlations, as well as convergent validity with other self-report measures of aggressive behavior (Harris, 1997). Cronbach's α coefficients for the aggressive behavior measure ranged between .71 for men and .74 for women.

3.2.3.2 Laboratory measurement of aggressive behavior (Study III). A version of the Response Choice Aggression Paradigm (RCAP; Zeichner, Frey, Parrot, & Butryn., 1999) was used to measure aggressive behavior in laboratory conditions in Study III. The RCAP is in turn an adaptation of the Taylor Aggression Paradigm (Taylor, 1967), which is together with its modified versions a widely used laboratory measure of aggressive behavior (Hoaken & Pihl, 2000). A difference between the TAP and the RCAP is that in the latter paradigm, the participants have a choice to refrain from responding aggressively, a modification that increases its ecological validity (Zeichner, Parrott, & Frey, 2003). Using the RCAP, the participants were made to believe that they were going to take part in a reaction-time task against a male opponent, sitting in an adjacent room and undergoing the same procedure as the participant himself. The participants were told that a form of punishment could be received from, and administered to the opponent throughout the task. In fact, there was no such opponent; instead the participants were playing against a computer with a pre-determined schedule to administer punishments to the participant as provocation. Punishments were administered in the form of aversive noise delivered through headphones (previously done e.g. by Bond & Lader, 1986; Cheong & Nagoshi, 1999; Krämer, Büttner, Roth, & Münte, 2008). In total 30 reaction time trials were administered, of which 14 trials were pre-programmed so that the participants lost against their opponent and 16 trials so that they won. The order of the trials was identical to the participants. Upon each trial, the participants had

the opportunity to deliver an aversive sound to their fictive opponent by choosing the desired level of sound to be administered to the opponent on a scale from 1 to 10 with higher values indicating louder noise. This is also a difference to the TAP, in which participants only administer aversive stimuli after trials that are won (Zeichner et al., 2003). If the participants chose not to administer any noise to the opponent, this was coded as zero. The first sound-provocation by the fictive opponent to the participant occurred on the sixth trial, and the participant was altogether provoked 15 times at 81.25% to 100% of their personal maximum sound tolerance. Each provocation lasted 200 milliseconds. Aggressive behavior was operationalized as the level of aversive noise administered by the participant to the fictive opponent. The RCAP has shown acceptable internal consistency (Zeichner et al., 1999) and both the RCAP and TAP have been shown to correlate with self-reports of aggressive behavior (e.g. Giancola & Parrott, 2008, Zeichner et al., 1999; Zeichner et al., 2003).

3.3 Zygosity determination (studies I, II, and IV)

Zygosity of the twins from the GSA sample used in studies I, II, and IV was determined using two questionnaire items inquiring about physical resemblance (Sarna, Kaprio, Sistonen, & Koskenvuo, 1978). The questions read as follows: 1) "*During childhood, were you and your twin partner as like as "two peas in a pod" or were you not more alike than siblings in general?"*; and 2) *"Were you and your twin partner so similar in appearance at school age that people had difficulty in telling you apart?"*. The response alternatives for the first question were: *"like two peas in a pod"*, *"of ordinary family likeness"*, and *"don't know"*. The second question's response alternatives read as follows: *"no"*, *"yes"*, and *"don't remember"*. Twins were classified as MZ if both twins in a pair answered "*as two peas in a pod*" to the first question and "*yes*" to the second question and as DZ if they responded *"of ordinary family likeness"* to the first question and *"no"* to the second (for more detailed information, the reader is advised to Sarna et al., 1978).

Questionnaire-based procedures to determine zygosity of twins show acceptable reliability (Christiansen et al., 2003; Eisen, Neuman, Goldberg, Rice, & True, 1989; Sarna et al., 1978). When comparing questionnaire-based zygosity determination with blood typing analyses, the misclassification rate has been estimated to about 5% (Eisen et al., 1989; Lembo, Zaman, Jones, & Talley, 2007) or less (Sarna et al., 1978). Comparisons with genetic marker analyses have also yielded high rates of accuracy (Christiansen et al., 2003; Lichtenstein, De Faire,

Floderus, Svartengren, Svedberg, & Pedersen, 2002). There are somewhat discrepant results of whether it is more common that MZ-twins would be misclassified as DZ twins (Christiansen et al., 2003; Forsberg, Goldberg, Sporleder, & Smith, 2010) or the reverse (Chen et al., 1999); however, both would result in somewhat inflated estimates of heritability in quantitative genetic twin-studies (Strachan & Read, 1999).

3.4 Genotyping (studies III and IV)

DNA was extracted from samples of saliva in studies III and IV. Oragene ™ DNA self-collection kits (DNA Genotek, Inc.) were used when collecting saliva samples from participants. Genotyping of the single nucleotide polymorphisms (SNPs) was made by the KBioscience laboratory in the UK (http://www.kbioscience.co.uk) using the KASPar chemistry - a competitive allele specific PCR SNP genotyping system performed with FRET quencher cassette oligos (http://www.kbioscience.co.uk/genotyping/genotyping-chemistry.htm). In Study III, twelve *OXTR* single nucleotide polymorphisms (SNP) were analyzed (Table 7, Figure 2). These SNPs were chosen based on reported associations between them and different traits in human studies. The functionality of polymorphisms in the *OXTR* gene is unclear, however, by choosing SNPs with known associations to traits or behavioral variables, we wanted to increase the likelihood of these SNPs being functional. Furthermore, recent studies indicate functionality of some of the *OXTR* SNPs by showing associations between them and plasma levels of OXT (Feldman et al., in press), or mRNA expression (unpublished data cited in Walter et al., 2012). In Study IV, three *OXTR* SNPs, that were found to have at least nominally significant effects in Study III, were analyzed.

3.5 Statistical analyses and study designs

In **Study I**, the effects of trait anger and alcohol consumption on anger control were analyzed. Exploratory factor analyses were conducted using SPSS 15.0. Loading invariance between men and women for the trait anger as well as anger control variables were examined separately with confirmatory factor analytic methods using AMOS Graphics 7.0. Anger control was measured as a within-subjects variable since participants answered questions regarding their anger control both regarding sober and intoxicated states, whereas trait anger and alcohol consumption were between-subjects variables. The repeated measures general linear model of the statistical package SPSS 15.0 was used to test if anger control differed

between the sober and intoxicated states, as well as to analyze the effects of alcohol consumption and trait anger on anger control. The higher-order interaction between state (anger control as sober or intoxicated), alcohol consumption and trait anger was analyzed further by conducting univariate analyses of covariance tests separately for anger control regarding the self-reported sober and intoxicated states. In order to avoid dependence between family members, one randomly selected person per family was used in Study I.

In **Study II**, genetic effects on anger control as well as on the difference in anger control between the sober and the intoxicated state were examined using quantitative genetic twin model fitting techniques. The quantitative genetic twin model fitting analyses were conducted using the Mx statistical package (Neale et al., 2003), designed for twin and sibling analyses. The Mx- package was also used to test for differences in means and variances between monozygotic (MZ) twins, dizygotic (DZ) twins and siblings as well as to calculate twin (phenotypic) correlations. The twin design can be used to separate genetic and environmental influences because genetic resemblance varies as a function of zygosity, whereas the assumption is that familial resemblance due to shared environmental influences does not. Specifically, the DNA of MZ twins is virtually identical, whereas DZ twins on average share 50% of their genes. In contrast, environmental influences that contribute to familial resemblance (i.e. makes the twins more alike) are assumed to affect MZ and DZ twins equally (Jinks and Fulker, 1970). These environmental influences are referred to as shared environmental influences (Plomin, DeFries, McClearn, & McGuffin, 2001). Nonshared environmental influences, on the other hand, are those that are not shared by the twins and contribute to making them more distinct from each other (Plomin et al., 2001). The twin model is based on the understanding that the observed (phenotypic) variance (*Vp*) in a trait is a linear function of additive genetic influences (*A*), non-additive genetic influences (*D*), shared environmental influences (*C*), and nonshared environmental influences (*E*) (i.e., $Vp = A + D + C + E$). However, dominant genetic effects and shared environmental effects cannot be estimated simultaneously with twin data only. Phenotypic correlations between the MZ and the DZ twins are used to suggest which of the models (*ACE* vs. *ADE*) is more suitable. Usually, an *ACE* model is applied when DZ correlations are half the MZ correlations or higher, whereas an *ADE* model is estimated when the DZ correlations are less than half the MZ correlations (e.g. Carey, 2003). When estimating these components, measurement error is subsumed under the nonshared environmental source of variance. The question of genetic effects refer to effect size, that is, how much of the interindividual variance of a specific trait

in a population can be explained by genes. Thus, genetic effects measured in this manner do not refer to a specific individual, but instead to the entire population (Plomin et al., 2001).

Model-fitting was conducted using full information maximum likelihood estimation. This method allows inclusion of singletons, that is, when only information from one twin of a twin pair is available, as well as the siblings of twins. Based on the phenotypic twin correlations, three types of genetic models were fitted: a model where *A, C*, and *E* were fitted for both genders, a model where *A*, *D* and *E*, were fitted for both genders, as well as a hybrid model where an *ADE* model was fitted for women and an *ACE* model for men. The best fitting full genetic model was determined by comparing the Akaike Information Criterion (AIC; Akaike, 1987) value as well as the Bayesian Information Criterion (BIC; Schwarz, 1978) value adjusted for sample size. Models having lower AIC and BIC values were preferred. In addition, the full genetic models were compared to a phenotypic constrained saturated script in which no genetic or environmental effects were estimated, by taking the fit function (–2 * Log-likelihood of data) and subtracting it from the fit function and degrees of freedom of the different genetic models. The subtraction gives a χ^2-value and associated degrees of freedom which can be tested for significance. Quantitative sex differences between the genders were tested for in the same manner. After the best full genetic model was chosen, a bivariate model was fitted to the data in order to investigate genetic and environmental influences on the covariance between anger control in the sober and intoxicated states. The impact of a specific parameter (e.g. *A*, *C*, or *D*) was determined using the bivariate scripts by again, testing for significant decreases in the -2* Log-likelihood of the data and by considering the AIC and BIC values in the similar manner as when choosing the best full genetic model. If the difference in the -2* Log-likelihood of the data was not significant, the more parsimonious model was chosen.

In addition, genetic and environmental influences on the difference in anger control between the sober and intoxicated state were explored. Genetic effects on this difference could indicate that genes affect the change in anger control as a function of alcohol, that is, interactions between alcohol and genetic effects.

In **Study III**, both between-subjects variables as well as within-subjects variables were used, and therefore, a mixed models design was warranted. Generalized estimating equations (GEE) of SPSS 17.0 with the robust variance estimator was used to analyze the effects of the polymorphisms on aggressive behavior. A measure of aggressive behavior was received for

each reaction time trial, and the GEE can take into account the dependency of these repeated measures. The effects of the polymorphisms (analyzed separately for each polymorphism), the effect of alcohol manipulation as well as their interaction were added as predictors, and the level of provocation and the general level of alcohol consumption as covariates. The experiment wide significance threshold required to keep Type 1 error rate at 5% was calculated using the effective number of independent variables (which in the current analysis was 10 according to the procedure suggested by equation 5 of Li & Ji, 2005) in an approach utilizing a linkage disequilibrium (LD) correlation measure (Nyholt, 2004). This resulted in a corrected α-level of .0051. One-tailed significance tests were used to test the hypothesized effects of alcohol and provocation on increasing aggressive behavior.

In **Study IV**, the GEE module was again used, this time using version 19.0 of SPSS. The GEE was used since the method takes into account the dependent structure inherent in the sample consisting of twins and their siblings. In Study IV, effects of three polymorphisms on aggressive behavior and trait anger were assessed, as well as if their effects would be moderated by alcohol consumption. In addition, effects of the polymorphisms on anger control regarding the sober and the intoxicated state, as well as on the difference in anger control between the self-reported sober and intoxicated states were explored. For information regarding covariates used in the analyses, the reader is kindly advised to consult the original study. The significance threshold was set at .05.

Missing values were imputed in **studies I, II, and IV** using the Expectation Maximization method of SPSS. Missing values were replaced for a specific scale if the participant had responded to over 1/3 of the items of that scale. In addition to data used in the original study, responses to additional instruments included in the GSA questionnaire were used. Overall, the numbers of imputed responses were low (for detailed information, kindly see original studies). For significant results that are not reported in a table, the *p*-value will be reported, together with *M* and *SE* in cases where it is applicable (i.e. group comparisons). For more detailed description of the results, the reader is advised to the original studies. Effect sizes are reported both in eta-squared (η^2) and partial eta-squared ($\eta^2_{partial}$) estimates. Whereas η^2 is defined as the proportion of total variation in the dependent variable that is attributable to the independent variable, $\eta^2_{partial}$ is the proportion of total variation attributable to the independent variable when the nonerror variation due to other variables is excluded (Pierce, Block, & Aguinis, 2004). Eta-squared is more easily interpreted than $\eta^2_{partial}$, but the strength of the latter effect size measure lies in the fact that it is not dependable on the number and

significance of other independent variables measured as is the case with the former estimate (Tabachnick & Fidell, 2001). R^2 was originally used in Study II, however, it is in this case comparable to the η^2 estimate (Tabachnick & Fiedell, 2001). The GEE-method used in studies III and IV, does not provide estimates of effect size. In order to get an approximate estimate of the effect sizes, univariate general linear analyses (specifically univariate analyses of covariance; ANCOVA) were computed. For Study IV, one randomly selected individual per family was included in the ANCOVA.

4 RESULTS

4.1 Descriptive statistics of phenotypic data as well as gender differences

Means and standard deviations for the different variables used in **studies I, II and IV** can be seen in Table 4. The participants in studies I, II and IV were all part of the population-based GSA sample. The samples of the three studies were all to some extent overlapping, but none of the original studies included all of the participants (see Table 3 for more information about overlap between the samples). Therefore, descriptive statistics were calculated specifically for this overview of the original studies for the maximum number of participants available for each of the variables based on the inclusion criteria of at least one third of the items per scale having been responded to (Table 4). This was done in order for the reader to get an overall picture of the sample. Gender differences in the sample can also be seen in Table 4.Women showed significantly lower levels of alcohol consumption and self-reported aggressive behavior than men. On the other hand, women showed higher levels of trait anger and lower levels of anger control both regarding the self-reported sober and intoxicated states. In addition, the difference in anger control between the sober and intoxicated states was larger for women than for men.

In **Study III**, a sample of male university students was used. The self-reported levels of alcohol consumption were somewhat higher in this sample (M = 7.10, SD = 2.10) than in the population-based samples. It should, however, be remembered that a cut-off score for alcohol consumption was used (for more details, the reader is advised to consult Study I), and that potential participants showing the highest levels of alcohol consumption were thereby excluded from the study. Abstainers could also not participate in Study III. Aggressive behavior was measured with a version of the RCAP laboratory paradigm. Eleven participants (five from the placebo group and six from the alcohol group) did not show any aggressive behavior during the test. For those who responded aggressively at least once, the mean percent of trials responded aggressively to was 55.26% (SD = 24.83, range 3.00% – 100.00%) with the mean level of noise administered to the fictive opponent being 3.17 (SD = 2.03, scale range per trial 0-10, range of individuals' means over all trials .03 - 8.30). Six participants showed aggressive behavior on each trial, with five of them having received alcohol, and one having received placebo. Participants in the alcohol group had a mean BAC of 0.062% (SD = 0.012) just before the task and 0.055% (SD = 0.009) after the task.

Table 4

Means and Standard Deviations for Anger Control, Trait Anger, Aggressive Behavior, and Alcohol Consumption for the Genetics of Sexuality and Aggression Sample

		Potential range		Men		Women		*df*	Wald χ^2	*p*	$\eta^2_{partial}$
Variable	*n*	Min.	Max.	*M*	*SD*	*M*	*SD*				
Anger control sober	8984	1	4	3.26	0.39	3.07	0.43	1	425.200	<.001	.045
Anger control intoxicated	7870	1	4	3.01	0.45	2.84	0.49	1	240.426	<.001	.024
Difference in anger control	7867	-3	3	0.26	0.33	0.24	0.33	1	7.005	.008	.003
Trait anger	9066	1	4	1.70	0.41	1.90	0.47	1	410.695	<.001	.045
Aggressive behavior	9042	1	5	1.90	0.57	1.73	0.55	1	171.631	<.001	.020
Alcohol consumption	9142	0	4	1.86	0.92	1.30	0.79	1	756.338	<.001	.101

Notes. These descriptive statistics were computed in order for the reader to get an overall picture of the descriptive statistics for the sample of which the original studies I, II and IV used subsamples from. Composite variables were computed for these statistics as the mean of the items measuring each trait with items loading negatively being reversed. Raw scores were used. Higher values indicate higher levels of aggressive behavior, trait anger, alcohol consumption and anger control. The difference in anger control variable was calculated as anger control in the sober state minus anger control in the intoxicated states. For each trait, the number of participants who had responded to at least 1/3 of the items measuring the respective scale is shown. Discrepancies in values with Study I and II are due to errors in the original studies. Gender differences were calculated using the Generalized Estimating Equations procedure. [a]Approximate effect sizes were estimated with univariate analyses of variance using one person per family to account for correlation between family members. $\eta^2_{partial}$ is equivalent to η^2 when only one independent variable is used.

4.2 Correlations between anger control, trait anger, aggressive behavior and alcohol consumption (Study IV)

As shown in **Study IV**, aggressive behavior, trait anger and anger control both regarding the sober and the intoxicated states were all correlated (Table 5). The highest correlations, positive in their nature, were seen between anger control regarding the sober and the intoxicated states. Trait anger showed moderate negative correlations with anger control regarding both states, indicating that individuals higher in trait anger show lower levels of anger control. Aggressive behavior correlated moderately with both trait anger and anger control. The correlations showed that individuals with high levels of aggressive behavior show higher levels of trait anger, as well as lower levels of anger control. The correlation between aggressive behavior and anger control was somewhat higher in magnitude regarding anger control in the intoxicated state than the sober. Alcohol consumption showed a positive and significant correlation with aggressive behavior and a somewhat smaller positive correlation with trait anger for both genders. Whereas the negative correlations between alcohol consumption and anger control regarding the sober state were small (and not significant for women), they were moderate for anger control regarding the intoxicated states. Bivariate correlations between anger control, trait anger, aggressive behavior and alcohol consumption are depicted in Table 5.

Table 5
Correlations between the Variables for Men above and for Women below the Diagonal (Study IV)

	Alcohol consumption	Aggressive behavior	Anger control sober	Anger control intoxicated	Trait anger
Alcohol consumption	-	.29***	-.06	-.20***	.15***
Aggressive behavior	.20***	-	-.36***	-.51***	.52***
Anger control sober	-.11**	-.40***	-	.72***	-.44***
Anger control intoxicated	-.28***	-.45***	.74***	-	-.42***
Trait anger	.14***	.54***	-.50***	-.46***	-

Notes. Correlations were calculated based on one randomly selected person per family in order to exclude dependence between family-members (*n* =808 men and 887 women). ** $p < .01$, *** $p < .001$. Higher values indicated higher levels on all variables.

4.3 Associations between anger control, trait anger and alcohol consumption (Study I)

In Study I, self-reports of the participants' levels of anger control regarding both sober and intoxicated states were used. As hypothesized, participants reported lower levels of anger control regarding the intoxicated state than the sober ($p < .001$, sober: $M = 3.23$, $SE = .02$, intoxicated: $M = 3.08$, $SE = .01$, $\eta^2_{partial} = .242$, $\eta^2 = .236$). Further, we wanted to explore if trait anger and alcohol consumption would moderate this effect as well as to investigate if they would affect anger control overall without differentiating between anger control in sober and intoxicated states. Both trait anger ($p < .001$, $\eta^2_{partial} = .158$, $\eta^2 = .156$) and alcohol consumption ($p < .001$, $\eta^2_{partial} = .008$, $\eta^2 = .007$) showed significant main effects on anger control so that participants consuming more alcohol and reporting higher levels of trait anger had lower levels of anger control. Alcohol consumption interacted significantly with state (i.e. sober or intoxicated) ($p < .001$, $\eta^2_{partial} = .029$, $\eta^2 = .022$), so that the difference in anger control between the two states was larger for those consuming more alcohol. Furthermore, trait anger interacted with state ($p = .013$, $\eta^2_{partial} = .001$, $\eta^2 = .001$). The difference in anger

control between the sober and intoxicated states was larger for individuals high in trait anger than for those with lower levels of trait anger.

In addition a significant three-way interaction between trait anger, alcohol consumption and state was seen (p = .024 approximate $\eta^2_{partial}$ = .001, η^2 = .001). The interaction is depicted in Figure 1 (a figure illustrating the interaction using regression lines can be seen in the original study). In order to analyze the interaction further, the interactions between alcohol consumption and trait anger were separately analyzed for anger control regarding the sober and the intoxicated states. Whereas there was no interaction between alcohol consumption and trait anger for anger control regarding the sober state (p = .638, $\eta^2_{partial}$ < .001, η^2 < .001), there was such an interaction for anger control regarding the intoxicated state (p = .034, $\eta^2_{partial}$ = .001, η^2 = .001). This indicated that the difference in anger control between those with high and low levels of alcohol consumption was greater for individuals high in trait anger. In conclusion, the lowest levels of anger control were seen in participants with high levels of alcohol consumption and trait anger, regarding the intoxicated state. The associations between anger control, trait anger and alcohol consumption were the same for men and women.

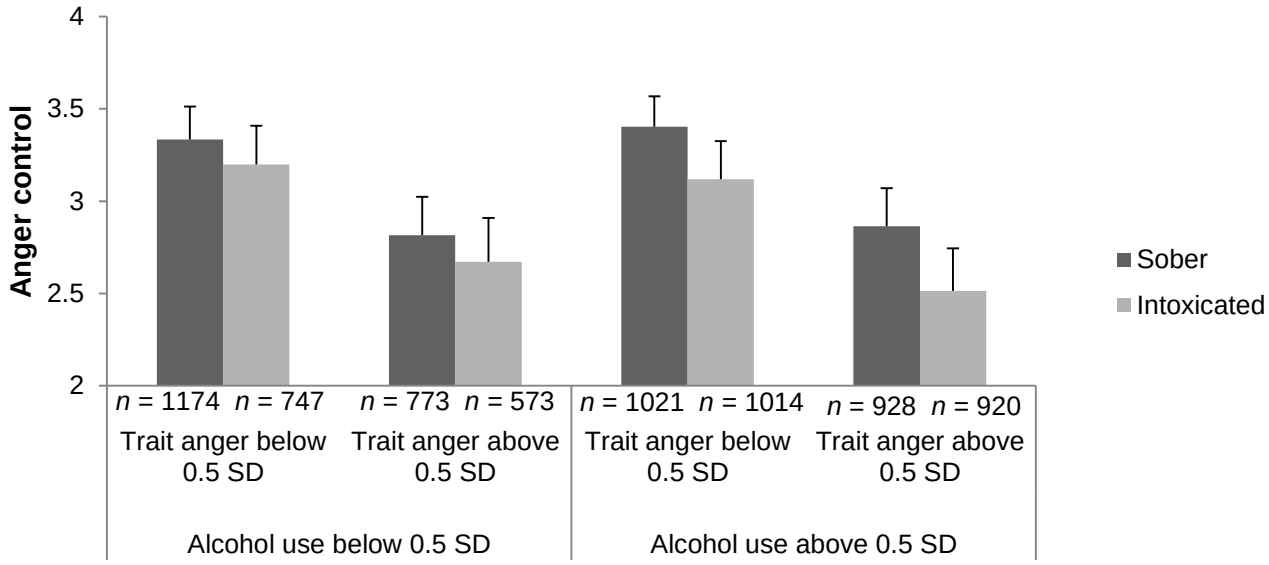

Figure 1. This figure is to depict the interaction between state (sober or intoxicated as self-reported), trait anger and alcohol use on anger control (Study I). Levels of anger control are depicted separately for participants with alcohol consumption habits 0.5 standard deviations (*SD*) below and above the mean, and with levels of trait anger 0.5 *SD* below and above the mean. Anger control levels are depicted separately for the self-reported sober and intoxicated states. Higher values indicate higher anger control (range 1-4). The bars representing standard deviations were divided by two for illustrative purposes. Anger control was calculated for the figure as the mean of the items measuring anger control with items loading negatively being reversed.

4.4 Genetic effects on anger control as well as on the difference in anger control between the sober and intoxicated states (Study II)

In order to explore the influence of genes and environmental effects on anger control, a twin model fitting approach was used in Study II. Based on the phenotypic twin correlations and a comparison of different genetic models, full genetic models which estimated *A, C* and *E* components for men at the same time as estimating *A, D,* and *E* components for women were chosen as these fitted the data best. The results showed that anger control was influenced both by genetic and nonshared environmental effects (Table 6). No effects of shared environment were detected. This was true for anger control both regarding the self-reported sober and intoxicated states. There was a difference between men and women; for men, the genetic effects were additive in nature, whereas they were found to consist mostly of dominant genetic effects for women. A test of quantitative sex differences showed that the magnitude of overall genetic effects was the same for men and women. The magnitudes of genetic and environmental effects were similar regarding the sober and intoxicated states (Table 6), however, the bivariate analyses showed that the genes affecting anger control were not entirely common for the sober and intoxicated states (additive genetic correlation of .77 for men, additive genetic correlation of .85 and a dominant genetic correlation of .78 for women). Although the nonshared environmental correlations (for men .73 and for women .74) showed that largely the same environmental factors influenced anger control both regarding the sober and intoxicated states, they also showed that differences exist.

Table 6

Estimates of Genetic and Environmental Effects on Anger Control in the Self-Reported Sober and Intoxicated State with 95% Confidence Intervals

Model	*A (95% CI)*	*C♂/D♀ (95% CI)*	*E (95% CI)*
Bivariate hybrid[a]			
Men			
Anger control sober	.27 (.12, .40)	.03 (.00, .14)	.70 (.60, .80)
Anger control intoxicated	.29 (.15, .40)	.01 (.00, .12)	.70 (.60, .80)
Women			
Anger control sober	.10 (.02, .22)	.24 (.09, .35)	.66 (.60, .73)
Anger control intoxicated	.16 (.07, .30)	.21 (.05, .34)	.62 (.56, .70)

Notes. [a] *ACE* for men and *ADE* for women. *A* = additive genetic effects, *D* = dominant genetic effects, *C* = shared environmental effects, *E* = nonshared environmental effects including measurement error.

In order to explore the possibility of genes influencing the difference in anger control between sober and intoxicated states, three genetic models were fitted to the data. Again, the best full genetic model estimated *A*, *C*, and *E* components for men and *A*, *D*, and *E* components for women. The results indicated that genes had a significant effect on the difference in anger control between the states, with the magnitude of this effect being comparable between men and women. In the full genetic model, the genetic effects were estimated to be additive in nature and influence 26% (95% CI .04, .42) of the variation for men. For women, the full genetic model suggested that the genetic effects would mostly consist of dominant genetic effects, with the overall genetic effect explaining 29% (*A* component .08 95% CI .01, .28, *D* component .21 95% CI .00, .33) of the variance. For both men and women, the best fitting and most parsimonious model was one in which only additive genetic and nonshared environmental effects were estimated. Using an *AE*-model, the additive genetic component was estimated to .32 (95% CI .20, .42) for men and .25 for women (95% CI .17, .33). One way to interpret genetic effects on the difference in anger control between the sober and alcohol intoxicated states is that individuals would differ in the effects of alcohol on anger control, based on their genetic variants.

4.5 Descriptive statistics of genetic data (studies III and IV)

Genetic data extracted from DNA samples of saliva were analyzed in **studies III and IV**. In Study III, twelve *OXTR* SNPs were genotyped and analyzed, whereas in Study IV, the effects of three SNPs were analyzed based on indicated effects in Study III. The SNPs, their nucleotide compositions and minor allele frequencies in both samples are shown in Table 7. The distribution of genotypes did not significantly differ from what would be expected if the population was in Hardy–Weinberg equilibrium for any of the SNPs. A schematic representation of the *OXTR* gene and a linkage disequilibrium (LD) map based on the sample in Study III can be seen in Figure 2. The LD measures between the SNPs analyzed in Study IV were similar to the ones seen in Study III with high LD between the rs1488467 and the rs1488467 SNPs and low between them and the rs1042778 SNP.

Table 7

Analyzed Oxytocin Receptor Gene (OXTR) Single Nucleotide Polymorphisms, Their Nucleotide Compositions and Minor Allele Frequencies in Studies III and IV

RS number	Nucleotide composition	Minor allele frequency in Study III sample (%)	Minor allele frequency in Study IV sample (%)
rs75775	G/T	T: 19.74 [a]	
rs1488467	G/C	C: 7.26	C: 3.84 [a]
rs4564970	G/C	C: 10.05	C: 4.64 [a]
rs4686302	C/T	T: 11.97 [a]	
rs237897	A/G	A: 47.41	
rs53576	G/A	A: 39.74	
rs2254298	G/A	A: 13.04 [a]	
rs2268493	T/C	C: 42.17	
rs237887	A/G	G: 43.91	
rs1042778	G/T	T: 38.26	T: 39.23
rs7632287	G/A	A: 28.21	
rs11720238	G/T	T: 14.66 [a]	

Notes. SNP = Single nucleotide polymorphism. A = adenine, G = guanine, T = thymine, C = cytosine. [a] The rare homozygotes were grouped together with the heterozygotes for analyses.

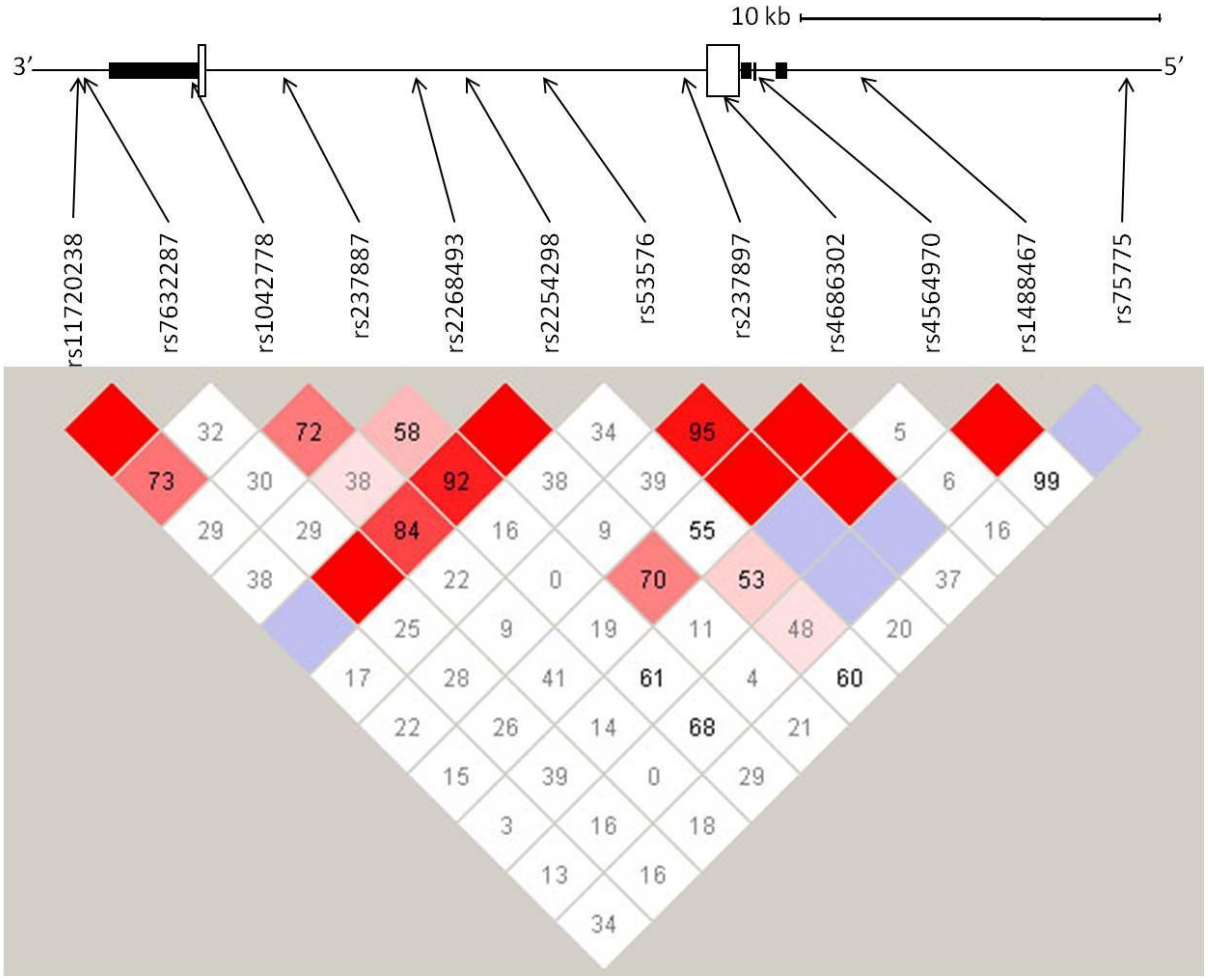

Figure 2. Schematic representation of the oxytocin receptor gene (*OXTR*) with the location of the twelve analyzed single-nucleotide polymorphisms (SNPs) and linkage disequilibrium (LD) plot for the sample (Study III). Disequilibrium coefficient (D') measures are shown in the boxes. The LD plot was generated using the Haploview 4.2 software (Barrett et al., 2005) with the standard color scheme. Pairwise LD levels between the SNPs are represented by the color of the squares, which increase from white to blue to red (white, D' < 1 and LOD score < 2; blue, D' = 1 and LOD score < 2; pink or light red, D' < 1 and LOD score ≥ 2; bright red, D' = 1 and LOD score ≥ 2).

4.6 Interactions between oxytocin receptor gene polymorphisms and alcohol on aggression: An experimental study (Study III)

The results of Study III indicated a trend for alcohol to increase aggressive behavior so that participants receiving alcohol showed higher levels of aggressive behavior (*M* = 3.15, *SE* = 0.30) than those receiving placebo (*M* = 2.51, *SE* = 0.28) (one-tailed *p* = .063, approximate $\eta^2_{partial}$ = .022, η^2 = .022).

In addition, the effects of twelve *OXTR* SNPs on aggressive behavior were explored experimentally. Both main effects and interactive effects between the SNPs and alcohol on aggressive behavior were tested. One main effect was nominally significant (i.e. when α was set at .05). Participants with two G alleles on the rs1042778 (*M* = 3.01, *SE* = 0.36) as well as participants with the T:G genotype (*M* = 2.97, *SE* = 0.28), showed higher levels of aggressive behavior than those who were homozygous for the T allele (*M* = 2.02, *SE* = 0.28) (*p* = .027, approximate $\eta^2_{partial}$ = .018, η^2 = .018). When the α-level was corrected to account for multiple testing (α = .0051), the main effect of the rs1042778 SNP did not, however, remain statistically significant. Two SNPs, the rs1488467 and the rs4564970, showed nominally significant interactions with alcohol manipulation. The moderation of the effect of alcohol on aggressive behavior by the two SNPs is depicted in Figure 3. As seen in the figure, alcohol increased aggressive behavior for individuals with a C:G genotype on the SNPs in question, whereas it did not have such an effect for those homozygous for the G allele. The interaction between the rs4564970 and alcohol (*p* = .004, approximate $\eta^2_{partial}$ = .051, η^2 = .049, C:G; placebo *M* = 1.57, *SE* = 0.30, alcohol *M* = 4.34, *SE* = 0.69, G:G; placebo *M* = 2.65, *SE* = 0.33, alcohol *M* = 2.94, *SE* = 0.32) remained significant after taking multiple tests into account by setting the α-level at .0051, whereas the interaction between the rs1488467 and alcohol did not (*p* = .006 approximate $\eta^2_{partial}$ = .042, η^2 = .041).

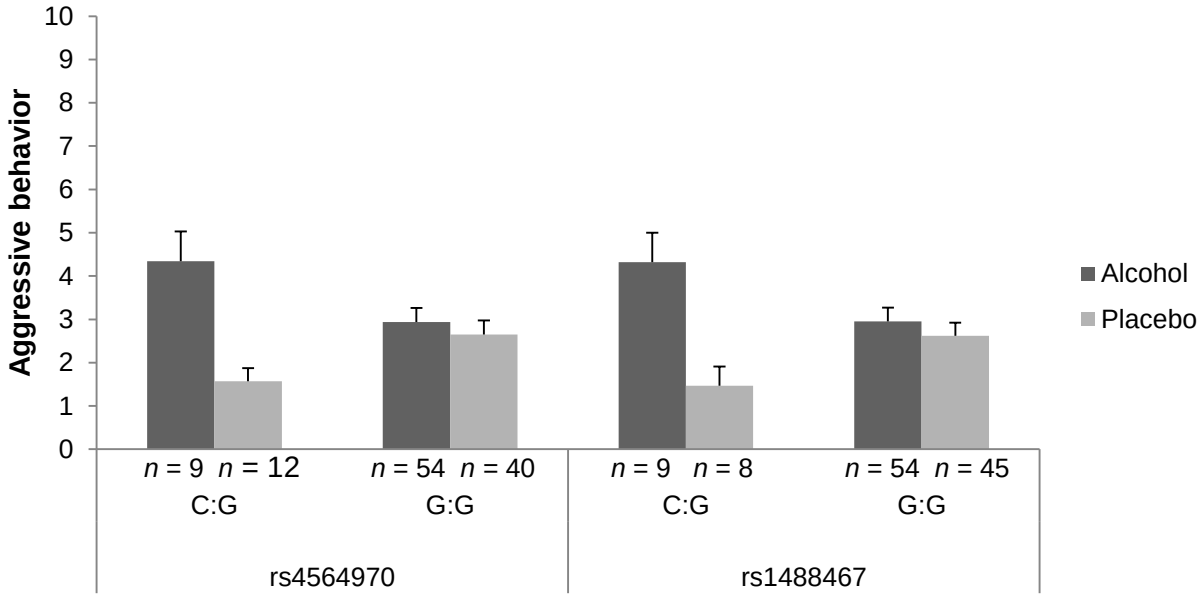

Figure 3. Interactive effects between the rs4564970 and alcohol as well as between the rs1488467 and alcohol on aggressive behavior (Study III). The levels of aggressive behavior with standard errors are depicted separately for the C:G and the G:G genotypes in the alcohol and placebo groups. Note that there were no individuals homozygous for the C allele in the present sample. G = guanine, C = cytosine.

4.7 Interactions between oxytocin receptor gene polymorphisms and alcohol on aggressive behavior, anger control and trait anger: A survey study (Study IV)

In **Study IV**, one of the aims was to replicate the above mentioned results in a population-based sample using self-reports of alcohol consumption and aggressive behavior. Based on the results of Study III, we expected to find that the effect of the rs4564970 and the rs1488467 SNPs on self-reported aggressive behavior would be moderated by alcohol consumption. The results showed that this was true regarding the interaction between rs4564970 and alcohol consumption (p = .044, approximate $\eta^2_{partial} < .001$, $\eta^2 < .001$), whereas there only was a trend towards an interaction between rs1488467 and alcohol consumption (p = .072, approximate $\eta^2_{partial} = .001$, $\eta^2 = .001$). Since alcohol increased aggressive behavior only for carriers of a C allele in Study III, we hypothesized that self-reports of aggressive behavior would be more closely related to alcohol consumption for participants with at least one C allele in comparison to those with two G alleles. As shown in Figure 4, this was indeed true.

Based on the fact that aggressive behavior is related to both trait anger and anger control, similar hypotheses were tested regarding these phenotypes. Regarding trait anger, the effect of

alcohol consumption was moderated by both the rs4564970 (p = .044, $\eta^2_{partial}$ = .001, η^2 = .001) and the rs1488467 SNPs (p = .021, $\eta^2_{partial}$ = .002, η^2 = .002). Similarly to aggressive behavior, the association between alcohol consumption and trait anger was more pronounced for carriers of at least one C allele compared to participants with two G alleles on both the rs4564970 (Figure 5) and the rs1488467 SNPs (Figure 6). Again, there was no main effect of the rs1042778 SNP. There were no main effects of the SNPs on anger control regarding the sober or alcohol intoxicated states either, nor were there any effects on the difference in anger control between these two states.

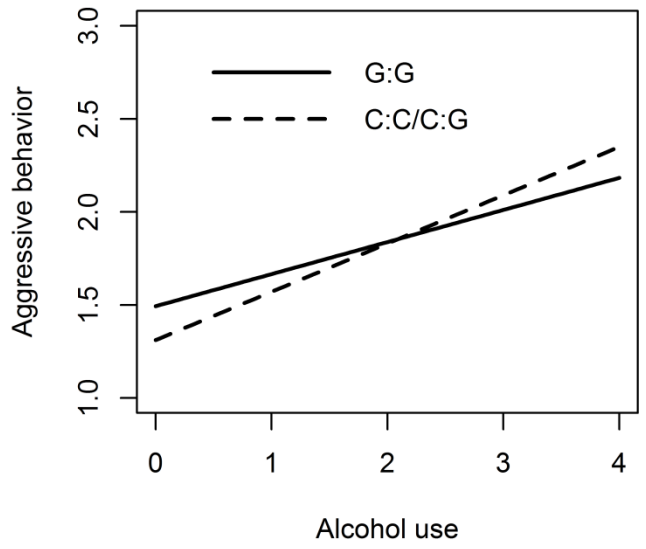

Figure 4. Interactive effect between the rs4564970 polymorphism and alcohol use on self-reports of aggressive behavior (Study IV). For the sake of interpretability, aggressive behavior and alcohol use were depicted as the mean of the items with negatively loading items being reversed (aggressive behavior scale 1-5, alcohol use scale 0-4 with higher numbers indicating higher levels of aggressive behavior and alcohol use). Slopes were calculated without covariates. C = cytosine, G = guanine.

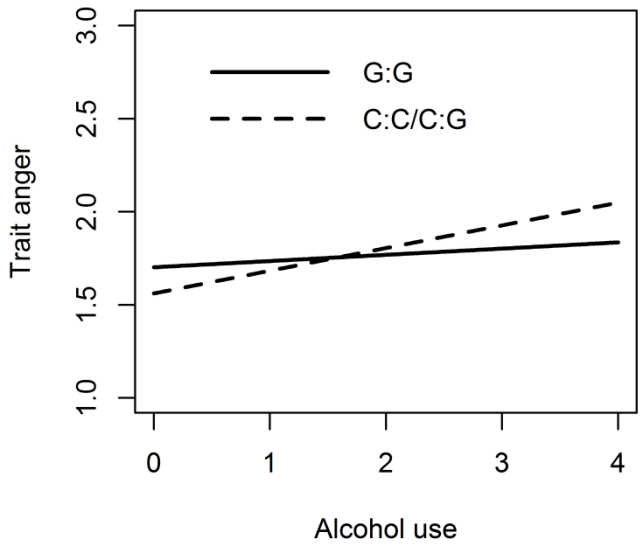

Figure 5. Interactive effect between the rs4564970 polymorphism and alcohol use on self-reports of trait anger (Study IV). For the sake of interpretability, trait anger and alcohol use were depicted as the mean of the items (scale range 1-4 for trait anger and 0-4 for alcohol use, with higher numbers indicating higher levels of trait anger and alcohol use). Slopes were calculated without covariates. C = cytosine, G = guanine.

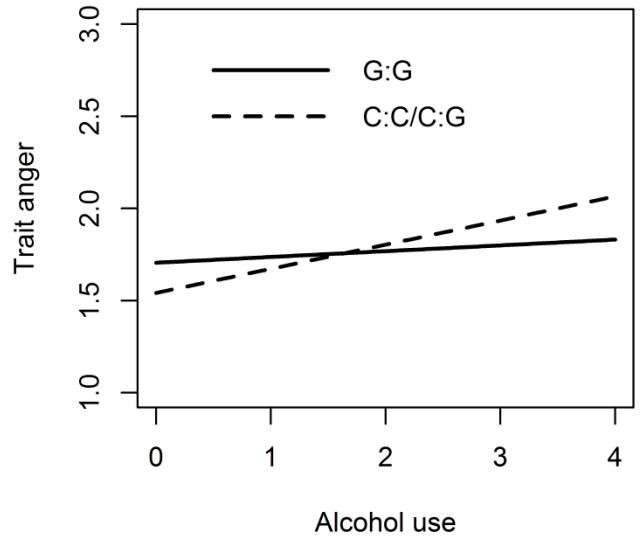

Figure 6. Interactive effect between the rs1488467 polymorphism and alcohol use on self-reports of trait anger (Study IV). For the sake of interpretability, trait anger and alcohol use were depicted as the mean of the items (scale range 1-4 for trait anger and 0-4 for alcohol use, with higher numbers indicating higher levels of trait anger and alcohol use). Slopes were calculated without covariates. C = cytosine, G = guanine.

5 DISCUSSION

The aim of the present thesis was to examine associations between anger related traits as well as aggressive behavior and alcohol consumption, with a specific focus on possible interactions between genes and alcohol on anger and aggressive behavior. The results showed a significant interaction between one of the analyzed *OXTR* polymorphisms and alcohol on aggressive behavior, which was also replicated in a second sample. Furthermore, interactions were found between two *OXTR* polymorphisms and alcohol consumption on trait anger. *OXTR* polymorphisms did not affect the difference in anger control between self-reported sober and alcohol intoxicated states, but results from a quantitative genetic analysis suggested that interactions between alcohol and genes could be possible. To our knowledge, the set of studies were the first to investigate interactions between alcohol and genes on anger related traits as well as to experimentally examine interactions between measured polymorphisms and acute alcohol intoxication on aggressive behavior in humans.

5.1 Correlations between anger control, trait anger, aggressive behavior and alcohol consumption

Anger control (both regarding the sober and intoxicated states) was negatively associated with trait anger, with the magnitude of these negative correlations being very similar to that found by Parrott and Giancola (2004). High levels of trait anger and low levels of anger control were associated with high levels of aggressive behavior, also in line with previous studies (e.g. Deffenbacher et al., 1996; Parrott & Giancola, 2004), with the association between anger control in the intoxicated state and aggressive behavior being stronger than for anger control in the sober state. Alcohol consumption was positively associated with aggressive behavior, as has also been shown by previous studies (e.g. Bácskai et al., 2008; Wells et al., 2000). Confirming previous reports, trait anger was positively associated with alcohol consumption (Deffenbacher et al., 1996; Nichols, Mahadeo, Bryant, & Botvin, 2008). Alcohol consumption did not correlate with anger control in the sober state for women, and showed only a relatively small negative correlation for men. For anger control in the intoxicated state, however, there was a negative correlation of moderate size with alcohol consumption. If chronic heavy alcohol use would affect anger control, one would expect alcohol consumption to correlate with anger control also in the sober state. The finding that the correlation between alcohol

consumption and anger control was more pronounced for the intoxicated state suggests that acute effects of alcohol have a stronger effect on anger control than chronic ones.

5.2 Associations between anger control, trait anger and alcohol consumption

Participants reported lower levels of anger control regarding intoxicated states than sober ones. Previous studies have found that alcohol decreases inhibitory control (e.g. Fillmore, Ostling, Martin, & Kelly, 2009; Loeber & Duka, 2009; Weafer & Fillmore, 2008), in line with alcohol-aggression theories postulating that the effects of alcohol on aggressive behavior are mediated by impaired behavioral control (e.g. Bushman and Cooper, 1990; Chermack and Giancola, 1997). Such studies often concentrate on behavioral control that is relatively instant and does not involve high levels of deliberate thought. Control of one's angry feelings can at least in some instances involve more conscious cognitive processes, and nowadays, many theorists believe that the effects of alcohol are mediated by impairments in cognitive functions. According to the theory proposed by Giancola (2000), acute alcohol intoxication disturbs executive functions including attentional control, strategic goal planning, and information appraisal. Thus, alcohol could affect anger control by impairing reflective processes, such as the individual's capability to weigh pros and cons in the process of deciding whether to express or control his/her feelings, and instead give more room to impulsive automatic processes in accordance with dual-process models (Wiers et al., 2009; Wilkowski & Robinson, 2008).

Individuals with high trait anger scores showed a larger difference in anger control between the sober and intoxicated states compared to individuals with lower trait anger scores. Studies have shown that individuals high in trait anger are more likely than those with low levels of trait anger to react aggressively when intoxicated (Eckhardt, 2007; Giancola, 2002; Giancola et al.,2003; Parrott & Zeichner, 2002). Individuals who tend to react to situations with elevated levels of anger show a bias towards anger-related stimuli or hostile cues (e.g. van Honk, Tuiten, de Haan, van den Hout, & Stam, 2001; Parrott, Zeichner, & Evces, 2005) as well as biased hostile interpretations of ambiguous situations compared to individuals with low levels of trait anger (for a review see Wilkowski & Robinson, 2008). According to dual-process models of anger, this is because individuals with high trait anger rely to a higher degree on automatic impulsive processes than individuals low in trait anger (Wilkowski &

Robinson, 2008). Reflective processes such as effortful, deliberate control are dependent on cognitive functions (Wilkowski & Robinson, 2008), which are impaired by alcohol intoxication (Giancola, 2000). Thus, alcohol intoxicated individuals are also more prone to impulsive processes, such as hostile interpretation bias (Wiers et al., 2009). Indeed, alcohol intoxicated individuals seem to mistake ambiguous facial expressions as angry more often than sober individuals (Attwood et al., 2009). Based on the premises outlined above, the attention and interpretation biases of individuals with high trait anger could be further enhanced when alcohol intoxicated, which could explain the finding that alcohol seems to have a larger effect on anger control for individuals with high levels of trait anger.

Moreover, individuals with higher alcohol consumption had larger differences in anger control between the sober and intoxicated states than individuals with low alcohol consumption. Higher levels of intoxication are associated with higher levels of aggressive behavior (Bushman & Cooper, 1990; Ito et al., 1996). The same could be true for the effects of alcohol on anger control, which would explain the above-mentioned finding. It should be kept in mind though, that acute and long-term effects of alcohol on anger control could not be distinguished with the data available for the present group of studies. A three-way interaction between trait anger, alcohol consumption and state (sober vs. intoxicated) described the data further. While there was no interaction between alcohol consumption and trait anger in predicting anger control in the sober state, an interaction was found in the intoxicated state. High trait anger was associated with less anger control when intoxicated in participants with high overall alcohol consumption levels compared to individuals with low overall alcohol consumption levels. In other words, participants with high levels of both alcohol consumption and trait anger reported the lowest levels of anger control when intoxicated. It may be that individuals prone to anger are more susceptible to the hypothesized effect of rising levels of intoxication on decreasing anger control because of their proneness to attention and interpretation biases. When interpreting the results, it should be kept in mind that the effect sizes for the interactions were small (all $\eta^2_{partial} < .029$, all $\eta^2 < .022$), with the effect size for the three-way interaction being merely $\eta^2_{partial} = .001$ ($\eta^2 = .001$).

Most questionnaires that measure aggressive behavior and aggression-related traits (such as anger) measure overall levels of the trait without distinguishing between sober and intoxicated states. This is somewhat surprising since it is known that levels of aggressive behavior are higher in intoxicated states (Bushman & Cooper, 1990; Chermack & Giancola, 1997; Exum, 2006; Ito, Miller & Pollock, 1996). Likewise, based on our results and previous studies,

alcohol seems to affect anger related traits (Parrott et al., 2003; Zeichner et al., 1994). Without specifying if the participant should respond to the questions with sober or intoxicated behavior in mind, it is evident that the researcher cannot know for sure if the responses relate to sober or alcohol intoxicated behavior or feelings or both. For traits that are not associated with alcohol consumption, this should not be an issue. The instructions on questionnaires should help the participants to activate the right frame of reference with regards to the trait of interest. Questionnaires are probably the easiest way (although not without their own limitations) for a researcher to try and measure internal states such as anger or anger control. However, as noted in the introduction, anger is often accompanied by facial expressions (Eckhardt et al., 2004; Novaco, 1994), which can be used to measure internal feelings of anger (Parrott et al., 2003). Anger control is arguably more difficult to measure using other methods than questionnaires, however, verbally expressed thoughts of anger control have been used (Eckhardt, Barbour, & Davison, 1998). Anger control could conceivably be operationalized in an array of fashions, each capturing different potentially important dimensions of the trait. For example, is successful control of one's angry feelings defined by the fact that anger is not expressed outwards, or could the way anger is expressed (e.g. calmly confronting the instigator without behaving aggressively versus reacting with physically aggressive behavior) or the time it takes before an individual expresses the feelings be taken into account as well? Moreover, a distinction has been proposed to separate between deliberate and automatic emotion regulation, increasing the complexity of anger control (Mauss, Cook, & Gross, 2007).

5.3 Gender differences

The results showed gender differences in the levels of alcohol consumption, anger control, trait anger and aggressive behavior. Higher overall alcohol consumption in men was expected based on previous studies (see review by Wilsnack, Vogeltanz, Wilsnack, & Harris, 2000). Women showed higher levels of trait anger as well as lower levels of anger control than men. Previous results have been somewhat contradictory with regards to control and expression of anger, with some studies showing lower levels of control in women (Maxwell et al., 2009), some suggesting that women control angry feelings more (Spielberger, 1999), and yet others that show no differences (Bartz, Blume, & Rose, 1996; Spielberger, 1999). In contradiction to our results (i.e. that women were more prone than men to react to situations with elevated levels of anger), men showed higher levels of trait anger than women in the study by

Spielberger (1999). A meta-analytic review, however, suggests that there are no differences in levels of anger between men and women (Archer, 2004). Men reported higher levels of aggressive behavior than women in Study IV. The aggressive behavior variable that was used measured both verbal and physical aggressive behaviors. Most studies indicate that men are both physically and verbally more aggressive than women (Archer, 2004). This is not, however, necessarily true regarding some forms of physically aggressive behaviors in intimate relationships (Archer, 2002). If women are more prone to react to situations with anger, and control their anger to a lesser degree than men, why did men then still show higher levels of aggressive behavior? One possible explanation is that women express their angry feelings in ways other than verbal or physical aggressive behaviors. Such a way could, for example, be indirect aggressive behavior (e.g. spreading rumors) which has in some studies been indicated to be more common among women than men (Archer, 2004). The take home message is, however, that even if there were differences in anger between men and women, studies indicate that they are likely to be small (Bartz et al., 1996). Indeed, the effect sizes for the gender differences were modest (below $\eta^2_{partial}/\eta^2 = .045$ for all described traits except for alcohol consumption which was around $\eta^2_{partial}/\eta^2 = .101$).

5.4 Genetic effects on anger control

In prior studies concerning anger control that have relied on self-reports, no separation between anger control in sober and intoxicated states has been made. The results of Wang et al. (2005) suggested anger control to be under the influence of genes, with a heritability estimate for the anger control factor of 34%. The results of another study were comparable with a heritability estimate around 30% (Gleiberman et al., 2008). Whereas Gleiberman et al. (2008) also used a measure of overall anger control, Wang et al. (2005) separated between three anger control and expression factors. Our results suggest that at least in our population-based sample, such a division might not be the most adequate since the factors produced might not measure multiple constructs but rather be affected by the wordings of the items. Our results are consistent with these earlier findings in that significant genetic effects were found both for anger control regarding the sober and the intoxicated states. The study was the first to show that genes explained a substantial amount of the variance in individuals' levels of anger control also regarding self-reported intoxicated states. The magnitudes of the heritability estimates were similar to prior studies, with slightly higher genetic effects regarding the intoxicated states. Genetic effects for women were divided in additive and

dominant effects, whereas the effects were exclusively additive in nature for men. The rest of the variances were explained by nonshared environmental effects, highlighting situational effects such as provocation.

The genetic correlations between anger control in the self-reported sober and intoxicated states were high and ranged between .77 and .85, showing that although the genetic effects to a high degree were common for anger control in both states, there might be genetic effects that are specific for the intoxicated state, also after accounting for the variance explained by alcohol consumption habits. The detrimental effect of alcohol on higher order cognitive functioning (Godlaski & Giancola, 2009; Hoaken, Giancola & Pihl, 1998; Peterson, Rothfleisch, Zelazo & Pihl, 1990), might give room for other traits (specifically genes affecting such traits) to influence anger control when intoxicated. For example, when intoxicated, an individual might be more dependent on automatic reactions to control or express angry feelings due to cognitive impairments making deliberate efforts more strenuous (see dual-process models e.g. Wiers et al., 2009). A more likely explanation perhaps is, however, that an interaction between genes and alcohol on anger control when alcohol intoxicated is misattributed to additive genetic effects specific for the intoxicated state since the interaction is not incorporated into the model (Rutter & Silberg, 2002).

5.5 Genetic effects on the difference in anger control between the self-reported sober and intoxicated states

Genes were found to influence the difference in anger control between sober and intoxicated states, with the magnitude of the effects being moderate for both men and women. Although this cannot be taken as evidence of an interaction between genes and alcohol on anger control, such an interaction would explain the results. Participants reported lower levels of anger control when alcohol intoxicated compared to when sober, and results suggests that genes explain a significant part of the variability between individuals in this change (i.e. some individuals difference in anger control between sober and intoxicated states is larger than others, and yet other individuals' levels of anger control might be stable across situations). The effect of alcohol consumption habits was regressed out from the variable prior to the analysis, in order to minimize blending of genetic effects on alcohol consumption habits with the gene-alcohol interaction. As noted, a likely explanation of the result would be that the effect of alcohol intoxication on anger control is different for individuals, depending on their

genotypes. Alternative explanations cannot, however, be ruled out using the questionnaire data. An alternative explanation would be, for example, that genes affect the way individuals choose their environments (gene-environment correlation). For example, in this case this could mean that certain individuals would, based on their genetic variants, actively seek out environments where they are more likely to consume alcohol and encounter situations in which controlling one's angry feelings would be more difficult (e.g. a rowdy pub). Another possibility could be that other environmental factors closely associated with alcohol intoxication, instead of alcohol consumption *per se*, interact with genes on anger control. Individuals could, for example, react differently to provocations based on their genotypes which could explain these results, provided that such provocations would be more frequent and severe in situations where people are intoxicated. Experimental studies could be used to separate between different explanations, and the results indicate that such studies would be worthwhile to conduct.

5.6 Moderating effects of oxytocin receptor gene single nucleotide polymorphisms on the effect of alcohol consumption on aggressive behavior

As shown by the correlations between alcohol consumption and aggressive behavior, alcohol was positively associated with aggressive behavior in the population-based sample. This was expected since the aggression-increasing effect of alcohol is widely acknowledged in the research field. Somewhat surprisingly, though, the causal effect of alcohol on increasing aggressive behavior as measured experimentally in Study III only bordered one-tailed significance. The mean of the participants' post-test BACs were somewhat lower than their average pre-test BACs, suggesting that some of the participants have been on the descending limb of intoxication for at least a part of the measurement of aggressive behavior. Although an effect of alcohol on aggressive behavior on the descending limb of intoxication has been shown (Dougherty et al., 1999), the effect seems to be more pronounced on the ascending limb (Giancola & Zeichner, 1997). Furthermore, the effect might have been more pronounced if a higher dose of alcohol would have been used (Bushman & Cooper, 1990; Ito et al., 1996).

For aggressive behavior, the rs4564970 polymorphism moderated the effect of alcohol consumption both using an experimental design (Study III) as well as using questionnaire data from a population-based sample (Study IV). Further, the rs1488467 polymorphism showed a trend towards an interaction with alcohol consumption on aggressive behavior in both

samples. In Study III, one group of participants received alcoholic beverages and the other group placebo beverages. In Study IV, alcohol consumption was measured using self-reports. Causality cannot be inferred based on the results of Study IV, but the results of the experimental study show that the effect of alcohol on aggressive behavior was causal, and that the rs4564970 polymorphism moderated the acute effects of alcohol consumption on aggressive behavior. In the experimental study, alcohol increased aggressive behavior in participants with the C:G genotype whereas it did not have such an effect for individuals homozygous for the G allele. In Study IV, the difference in aggressive behavior between participants with low versus high alcohol consumption habits was larger for those with at least one C allele on the rs4564970 polymorphism compared to participants with two G alleles. The effect was more pronounced in the experimental study, which could be due to more specific measurements of aggressive behavior and alcohol. No women were tested in Study III, but based on the findings in Study IV, there were no gender differences in the interaction. The effect size for the interaction between the rs4564970 SNP and alcohol on aggressive behavior in Study III was estimated to be around $\eta^2_{partial} = .051$ ($\eta^2 = .049$), and the effect size for the interaction between the rs4564970 SNP and alcohol consumption on self-reports of aggressive behavior in Study IV to around $\eta^2_{partial} < .001$ ($\eta^2 < .001$).

Two different mechanisms were proposed for interactive effects of *OXTR* SNPs and alcohol on aggressive behavior. The first was based on the cognitive deficits that occur when an individual is alcohol intoxicated, with particular focus of such effects on cognitive functions important in social encounters. The other explanation for the interaction discussed effects of alcohol on levels of OXT. Both explanations will be described in more detail below.

According to the executive functioning framework (Giancola, 2000), the likelihood that a person will behave aggressively after alcohol intake depends on the degree to which alcohol disrupts executive functioning such as the abilities to take the perspective of others, to be observant to facial expressions and body language of others, and to correctly interpret such cues particularly in socially ambiguous situations. OXT has been associated with socially important traits related to, for example, recognition of emotional facial expressions (Di Simplicio et al., 2009; Domes et al., 2007b; Marsh et al., 2010; Schulze et al., 2011; Van IJzendoorn & Bakermans-Kranenburg, 2012). It could therefore be that alcohol has a larger effect on aggressive behavior for those who, due to altered OXT signaling based on their genotypes on *OXTR* SNPs, have more difficulties with the above mentioned social abilities. It should be noted though, that there were no main effects of the rs4564970 and the rs1488467

SNPs on aggressive behavior. This indicates that if some individuals would have more difficulties with social abilities due to their OXT signaling, these difficulties would not be severe enough to prompt aggressive behavior when sober. Instead, the difficulties would emerge specifically when alcohol intoxicated. Participants tested for aggressive behavior using the RCAP in Study III did not see the (fictive) opponent, and therefore the results cannot in this case be explained by misinterpretations of body language or facial expressions. It could be argued, though, that not only can body language and facial expressions be misinterpreted as hostile, but also the underlying motivations of the other person although he or she cannot be seen or communicated with verbally. In other words, participants could have differed in how prone they were when alcohol intoxicated to infer the motivations of the opponent to be hostile and personal (e.g. "the opponent is out to annoy me and pick a fight") versus not personal and, for example, related to the game ("the opponent is just mad that he lost, it is nothing personal against me").

As previously noted, the second explanation relates to changes in OXT levels as a response to alcohol. Animal studies have shown alcohol to decrease levels of OXT in rat dams exposed simultaneously to ethanol and nicotine (McMurray et al., 2008), and to suppress the release of OXT from the isolated hypothalamo-neurohypophysial system (Hashimoto et al., 1985; Knott et al., 2000). In humans, alcohol decreases the levels of OXT at least in nulliparous and lactating women (Menella et al., 2005; Menella & Pepino, 2006) as well as during labor (Gibbens & Chard, 1976). In addition, it is known that OXT can, through its receptor, stimulate its own release (Neumann et al., 1996). Thus, alcohol could affect the change in OXT levels differently depending on the genotype of the individual on *OXTR* polymorphisms. More research is needed before the direction of the association between levels of OXT and aggressive behavior is clear. However, studies on humans indicate that low levels of OXT in the cerebrospinal fluid would be associated with higher levels of aggressive behavior (Jokinen et al., 2012; Lee, Ferris et al., 2009) and intranasally administered OXT reduces disruptive behaviors in individuals with Prader-Willi syndrome (Tauber et al., 2011). If the effects of alcohol were chronic, an interaction would indicate that effects of chronic alcohol use on OXT levels were different for the genotype groups, and that this in turn would affect aggressive behavior. Although acute alcohol intake, as noted earlier, decreases the levels of OXT, a study on rodents indicate that tolerance towards this effect is developed after chronic exposure to alcohol (Knott et al., 2000). In addition, a study by Silva, Madeira, Ruela, and Paula-Barbosa (2002) showed that degeneration of OXT-immunoreactive magnocellular

neurons of the paraventricular nucleus is seen in rats after prolonged exposure to ethanol; however, changes in mRNA levels of OXT were not seen due to compensatory mechanisms of the neurons. Although research on the effects of chronic alcohol use on OXT levels in humans is needed, it seems at this point that different reactions to the acute effects of alcohol based on *OXTR* genotypes of the individuals would be more likely than to chronic ones. The results of Study III also support the hypothesis that a possible interplay between the rs4564970 and rs1488467 and alcohol is acute in nature rather than chronic.

5.7 Moderating effects of oxytocin receptor gene single nucleotide polymorphisms on the effect of alcohol consumption on trait anger and anger control

Since trait anger and anger control are closely related to aggressive behavior (Spielberger, 1999), we hypothesized similar effects of the *OXTR* SNPs on these variables as for aggressive behavior. Both the rs4564970 and the rs1488467 SNPs showed interactive effects with alcohol on trait anger. The direction of the effects was the same as for aggressive behavior, that is, the association between trait anger and alcohol consumption was more pronounced for those participants who were carriers of at least one C allele than for those who were homozygous for the G allele. The effect was similar for both the rs4564970 and the rs1488467 SNPs. The effect sizes were small, with the interaction between the rs4564970 SNP and alcohol consumption on trait anger being estimated to around $\eta^2_{partial} = .001$ ($\eta^2 = .001$), and the effect size for the interaction including the rs1488467 SNP to around $\eta^2_{partial} = .002$ ($\eta^2 = .002$). There were no differences between men and women with regards to the interactions between *OXTR* SNPs and alcohol on trait anger. No effects were found for the anger control variables.

The two proposed mechanisms for interactions between *OXTR* polymorphisms and alcohol consumption on aggressive behavior can also be discussed with regards to anger. According to one of the proposed explanations, differences between intoxicated individuals in aggressive behavior could emerge if some individuals have more difficulties with social abilities such as noticing and correctly interpreting others' emotions and intentions based on their OXT signaling. Such difficulties could be especially pronounced when intoxicated because of the impairments in cognitive functioning that intoxication entails. Social situations can often be more or less ambiguous, and intoxicated individuals are hypothesized to have more

difficulties interpreting such situations (Giancola, 2000; Lange, 2002). This has been indicated, for example, by the fact that intoxicated individuals more often misinterpret others' negative facial expressions as angry compared to sober individuals (Attwood et al., 2009). Trait anger measures the propensity for an individual to react to situations with angry feelings and an individual behaving aggressively is often also angry, especially in cases of reactive or hostile aggressive behaviors (Geen, 2001). Aggressive behavior in intoxicated individuals who tend to, for example, incorrectly interpret others intentions as hostile and provocative, is likely to be accompanied, if not driven, by emotional responses such as feelings of anger or irritation. The interactive effects between the rs4564970 and the rs1488467 and alcohol consumption were more pronounced for trait anger than for aggressive behavior in Study IV, which could indicate that individuals with at least one C allele at these loci react to alcohol consumption by being more prone to react with feelings of anger, and further that a part of these individuals behave aggressively as a consequence, as compared to individuals with two G alleles. It should also be noted that these *OXTR* SNPs did not affect the *change* in anger control between self-reported sober and intoxicated states. Anger control explicitly measures control of behavior when a feeling of anger already is present, whereas trait anger and aggressive behavior do not, giving further support to the notion that the interactions could result from differences between the genotypes in the effects of alcohol on underlying feelings of irritation and anger proceeding aggressive behavior rather than by the effects of alcohol on behavioral control of these feelings.

The other explanation refers to the decreasing effects of acute alcohol consumption on levels of OXT (Gibbens & Chard, 1976; Hashimoto et al., 1985; Knott et al., 2000; McMurray et al., 2008; Menella et al., 2005; Menella & Pepino, 2006). High levels of OXT have not only been associated with lower levels of aggressive and disruptive behavior (Jokinen et al., 2012; Lee, Ferris et al., 2009; Tauber et al., 2011) but also with reduced neural activation in the amygdala in men (e.g. as a response to angry and fearful faces; Kirsch et al., 2005). Thus, the decreasing effects that alcohol seems to have on OXT levels (Gibbens & Chard, 1976; Hashimoto et al., 1985; Knott et al., 2000; McMurray et al., 2008; Menella et al., 2005; Menella & Pepino, 2006) may in turn also affect underlying emotions such as anger through altered amygdala activity. The hypothesis is that this effect could be different depending on the individual's genotype at *OXTR* SNPs.

5.8 Suggestions for future research

Research is needed to clarify the neural areas and neurocognitive mechanisms underlying the interactive effect of polymorphisms and alcohol on aggressive behavior and anger indicated in this thesis. Many findings from molecular genetic association studies have not been replicated, and although an interaction between the rs4564970 and rs1488467 SNPs and alcohol was indicated in two separate samples using two different study designs, replications in additional samples are warranted. In addition, the relationship between genetic variants at these polymorphisms and their relationships with the quantity and functioning of OXT receptors in the brain and OXT levels need to be clarified. Although the exact route through which an interactive effect between *OXTR* polymorphisms and alcohol would affect aggressive behavior could not be identified in this thesis, different mechanisms were suggested. Heinz et al. (2011) proposed a cognitive neurobiological model for the relationship between alcohol and aggressive behavior. The model presented below (Figure 7) originates from the Heinz et al. (2011) model, but has been adapted to specifically illustrate a hypothesized mechanism for the association between alcohol and aggressive behavior with regards to OXT. It will be a task for future research to test the assumptions of the proposed model.

As noted in the introduction, two brain areas implicated in aggressive behavior during alcohol intoxication are the prefrontal cortex (PFC) and the amygdala (e.g. Coccaro et al., 2011; Nelson & Trainor, 2007). Acute alcohol intoxication impairs PFC functioning and executive cognitive functions subserved by it, such as information processing and attention. This in turn is hypothesized to affect, for example, the ability to notice and correctly interpret ambiguous stimuli in social situations (e.g. Giancola, 2000; Heinz et al., 2011). The amygdala is important in the regulation of emotions, which has been shown in that it is activated, for example, in response to threat and negative affect, and when processing socially important stimuli such as facial expressions (Adolphs & Spezio, 2006; Davidson, Putnam, & Larson, 2000; Haxby, Hoffman, & Gobbini, 2002). Furthermore, the relation between the PFC and the amygdala has been suggested to be of particular relevance (e.g. Bufkin & Luttrell, 2005; Coccaro et al., 2011), since the PFC provides inhibitory connections to the amygdala hypothesized to affect suppression of negative emotions (Davidson et al., 2000). The impairment of PFC functioning as a consequence of alcohol intake can affect aggressive behavior directly, for example, by impairing the ability to take the perspective of others, or to interpret situational information (Giancola, 2000). The impairment in PFC functioning as a consequence of alcohol intoxication is also hypothesized to affect aggressive behavior

indirectly through amygdala activation in two ways: by disruption of the inhibitory connections of the PFC to the amygdala due to alcohol intoxication (Heinz et al., 2011) and indirectly by making the individual more prone to misinterpret situational factors as threatening or provoking (as shown with regards to facial expressions; Attwood et al., 2009), which in turn would activate the amygdala.

Heinz et al. (2011) suggests that chronic alcohol intake could affect the amygdala by impairing serotonergic neurotransmission in the amygdala, which in turn could disinhibit limbic processing. The model proposed in this thesis, however, hypothesizes that the amygdala could be relevant also with regards to acute effects of alcohol through the effects of alcohol on levels of OXT (Figure 7). Acute alcohol intoxication seems to decrease levels of OXT (Gibbens & Chard, 1976; Hashimoto et al., 1985; Knott et al., 2000; McMurray et al., 2008; Menella et al., 2005; Menella & Pepino, 2006). OXT is related to amygdala activity. For example, animal models show that the amygdala contains a high concentration of OXTRs (Gimpl & Fahrenholz, 2001; Huber, Veinante, & Stoop, 2005), and gene expression for OXTRs in the amygdala has been shown to be required for normal social recognition in mice (Choleris et al., 2007). The amygdala is central for the effects of OXT also in humans (MacDonald & MacDonald, 2010). Intranasally administered OXT reduces the neural activation in amygdala related to negative aversive stimuli such as angry or fearful faces (Domes et al., 2007a; Gamer et al., 2010; Kirsch et al., 2005) as well as to betrayal in a trust game (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008). Gamer et al. (2010) suggest that increased OXT might affect a change in focus towards positive social stimuli. Therefore, it is hypothesized that alcohol decreases levels of OXT which in turn increase amygdala reactions in response to negative emotional and social stimuli. Furthermore, this effect is hypothesized to differ between individuals based on their genotypes at *OXTR* polymorphisms. Increased amygdala activation in response to angry faces has been shown to correlate with traits related to aggressive behavior both in individuals with clinically high levels of aggressive behavior (Coccaro et al., 2007) and general samples (Beaver, Lawrence, Passamonti, & Calder., 2008; Carré, Murphy, & Hariri, in press). Tost et al. (2010) showed that a polymorphism (rs553576) in the *OXTR* was associated with amygdala activation during processing of facial expressions of emotion. Also the volume of amygdala has been associated with *OXTR* polymorphisms (Furman, Chen, & Gotlib, 2011; Inoue et al., 2010). In addition, a gene-environment interaction affecting the amygdala was shown by Cousijn et al. (2010). They showed larger increases in phasic amygdala activity in response to happy and fearful

faces for carriers of a common functional deletion in a gene coding for the 2b-adrenoreceptor compared to that of non-carriers under stressful conditions. No effect of the genotype was observed under the control condition when stress was not induced, showing that effects of genotypes on amygdala activity can become apparent only under specific environmental conditions (Cousijn et al., 2010).

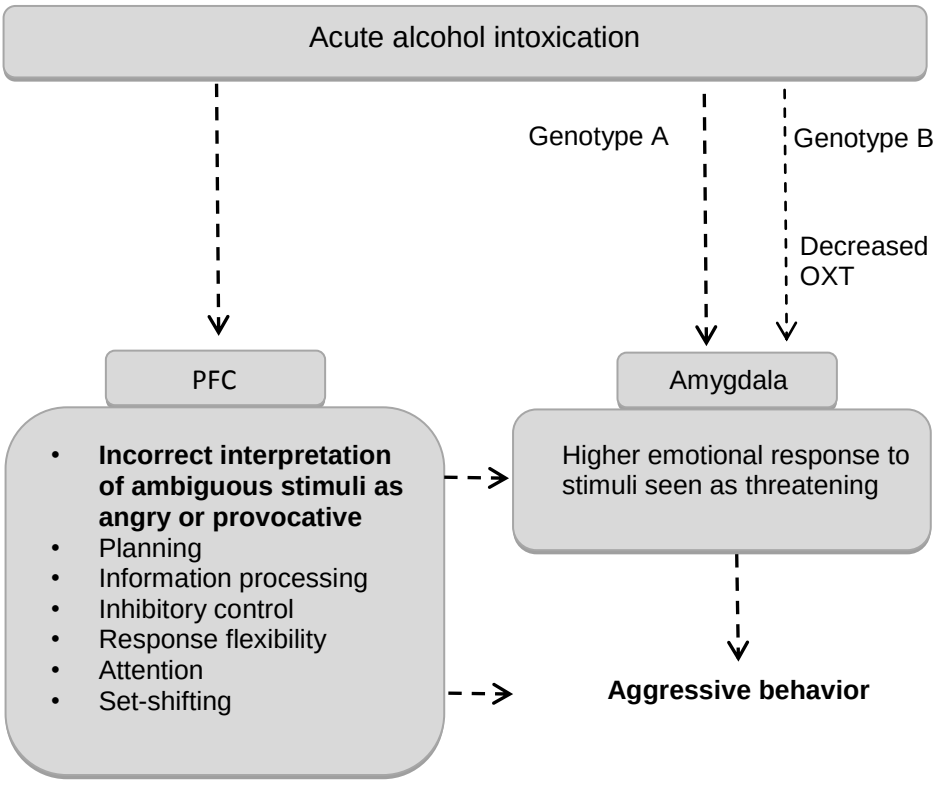

Figure 7. A hypothetical model of the effects of alcohol on aggressive behavior through alcohol's effects on the prefrontal cortex as well as on amygdala in relation to changes in levels of oxytocin. The model and figure are adapted from Heinz et al. (2011). PFC = prefrontal cortex, OXT = oxytocin.

A large part of G x E studies have been influenced by the thought that some individuals are more vulnerable to adverse effects of the environment than others due to their genetic variants at specific loci (Belsky & Pluess, 2009). This model is commonly referred to as the stress-diathesis model. In this case, alcohol is seen as having an adverse effect on aggressive behavior for some individuals due to their genetic makeup. Belsky and Pluess (2009), however, point out that in some cases, such individuals might not necessarily only be more prone to adverse environmental effects, but might instead be more susceptible towards both

negative and positive effects of environmental factors. If individuals with heightened reactions to negative environmental factors at the same time show heightened reactions to positive or supportive environmental factors (or to the lack of negative ones), this could be seen as support for a susceptibility model according to Belsky, Bakermans-Kranenburg, and Van IJzendoorn (2007). Both in studies III and IV, individuals with at least one C allele at the rs4564970 SNP (in the case of aggressive behavior) and at both the rs4564970 and rs1488467 SNPs (in the case of trait anger) showed besides the highest levels, also the lowest levels of aggressive behavior and trait anger under low alcohol consumption or in the placebo condition. A lack of alcohol intoxication would probably not be enough alone to elicit a larger decrease in aggressive behavior in participants with at least one C allele compared to those with two G alleles, not least because it seems clear in this case that sobriety is to be considered a default state rather than an environmental factor. However, other factors that normally decrease aggressive behavior could, in the sober state, affect individuals who are also more prone to the adverse effects of alcohol due to their genotypes to a higher degree than other individuals. It would be interesting to investigate whether the interaction between the rs4564970 and the rs1488467 *OXTR* SNPs reflect a specific vulnerability to the effects of alcohol, or whether it reflects a general susceptibility to factors that affect aggressive behavior (in either facilitative or inhibitory fashions).

Since anger and aggressive behaviors are complex in nature, it is likely that they are affected by numerous genes (Plomin et al., 2001). Similarly, it is likely that SNPs in or near of genes other than the *OXTR* could interact with alcohol in affecting aggressive behavior and anger. Other genes suggested to be of importance in explaining aggressive behavior when alcohol intoxicated include, for example, serotonergic (Bevilacqua et al., 2010; Heinz et al., 2011) and GABAergic genes (Heinz et al., 2011). Tikkanen et al. (2010) showed that alcohol use and the MAOA gene interacted in predicting violent recidivism in a sample of violent alcoholic offenders. It would be interesting to test if this effect would be found also in non-criminal samples with lower alcohol consumption levels. It seems that MAOA might have had a tendency to affect alcohol consumption in the sample used in the Tikkanen et al (2010) study (see Tikkanen et al., 2009), and laboratory studies could effectively be used to shed light on the possible effects of the interaction on aggressive behavior when influences of rGE is effectively eliminated. It is also important to remember that instead of acting in isolation, neurotransmitters often show complex interactions (Miczek et al., 2007; Pihl & Benkelfat, 2005; Seo, Patrick, & Kennealy, 2008). This will most certainly be the case also with regards

to the relationship between oxytocin and aggressive behavior displayed when alcohol intoxicated. Indeed, research suggests that oxytocin shows relationships, for example, with vasopressin (Åkerlund et al., 1999), serotonin (Siever, 2008), sex steroids (Gimpl & Fahrenholz, 2001; Lee et al., 2009), and possibly the dopamine system (Smeltzer, Curtis, Aragona, & Wang, 2006). As noted by Siever (2008), the intricate relationships between different neurotransmitters need to be clarified further in order to fully understand complex behaviors such as aggression.

In addition, the samples used in the present thesis consisted of a population-based sample and a sample of university students. It would be interesting to analyze interactions between the suggested *OXTR* SNPs and alcohol in a sample consisting of highly aggressive individuals. For example, genotype frequencies could be compared between two groups of individuals incarcerated for violent offences (matched for type and severity of offence): individuals who committed their offence while under the influence of alcohol, and individuals who committed their offence in a sober state. Laboratory paradigms, such as the RCAP, could also be used to experimentally investigate the interaction, in a similar manner as in Study III.

5.9 Implications of the results

If individuals with at least one C allele on the rs1488467 and / or the rs4564970 SNPs indeed are more prone to react to alcohol with elevated levels of anger and aggressive behavior (i.e. this finding is successfully and repeatedly replicated), one question that arises is whether there are any implications of these findings for violence prevention? Informing individuals about proneness for adverse reactions to alcohol based on their genetic variants would be a possible way to proceed. Such an approach has been used, for example, regarding Alzheimer's disease, breast cancer, and diabetes (Bloss, Shork, & Topol, 2011; Heshka, Palleschi, Howley,Wilson, & Wells, 2008). Informing individuals about risk related to their genotypes have not, however, been particularly effective in changing their behavior (Bloss et al., 2011; Heshka et al., 2008). In order to analyze effects of (fictive) information of genotype on aggressive behavior, we tested 40 male university students aged 18-47 years (M = 25.02, SD = 5.60). The participants were randomly divided into three groups: one group were informed that they had a genotype associated with high levels of aggressive behavior, one group were informed that they had a genotype associated with low levels of aggressive behavior, and the third that they had a genotype so rare that its association with aggressive behavior was not known (the control

group). Neither group actually had their genotypes tested, although they did provide saliva samples using real, but dated, self-collection kits. Based on preliminary analyses, the groups differed significantly in self-reported aggressive behavior as measured using the Aggression Provocation Questionnaire (O'Connor, Archer, & Wu, 2001), $F(2, 36) = 4.237$, $p = 0.022$, $\eta^2_{partial} = 0.19$, $\eta^2 = .06$ (pre-test levels were modeled as a covariate). The control group and the group receiving information that their genotype was associated with low levels of aggressive behavior did not differ ($p = .60$). The group that had been told that they have a genotype associated with aggressive behavior did, however, show significantly higher levels of self-reported aggressive behavior than the other two groups ($ps < .05$). The groups did not differ in their levels of aggressive behavior before receiving information regarding their genotypes. Informing individuals that they are at risk for behaving aggressively can also cause some anxiety, as suggested by our preliminary results, $F(2, 37) = 3.958$, $p = .028$, $\eta^2_{partial} = 0.18$, $\eta^2 = .18$, which should also be taken into consideration. It might be that the participants' recollections of themselves as aggressive or not were affected after they had been given information about their genotypes, so that they perceived themselves more in accordance with the received information. It cannot, however, be excluded that participants who receive information that they are predisposed to behave aggressively would actually increase their aggressive behavior, especially since individuals can have an (often false) impression that genetic effects are deterministic. Before considering informing individuals about their genotypes with relation to aggressive behavior in sober or alcohol intoxicated states, careful studies of possible effects of such information should be conducted. In either case, it is crucial to remember that the effect sizes of main (or interactive) effects of single polymorphisms on complex behavior are, in most cases, very small (e.g. Manolio et al., 2009) as also indicated by the effect size approximations in the present thesis. It is interesting to note, however, that based on our preliminary findings, it is possible that the effect sizes of informing individuals about their genotypes might actually be *larger* than the effect sizes of an actual individual polymorphism on behavior. According to Dempfle et al. (2008), G x E findings need to be convincing and have a high predictive or discriminative power in order for them to be useful in clinical practice (e.g. pharmacogenetics or lifestyle recommendations). Further, their opinion is that if the effect of exposure (in this case to alcohol) is detrimental to both genotype groups, but stronger in one group than the other, it may be beneficial for all individuals to avoid the exposure.

Another possible implication of our results relates to the use of genotype information in criminal trials or in assessments of risk for recidivism. The growing number of studies on genetic risk factors for violent and aggressive behavior as well as on interactions between genetic and environmental factors influencing such behavior has sparked interest in genetic research from criminal justice professionals (Bernet, Vnencak-Jones, Farahany, & Montgomery, 2007). Recently, a court case in Italy resulted in a reduced sentence for a convicted murderer, because the court considered it to be a mitigating factor that he carried a MAOA genotype that has been linked to aggressive behavior (Baum, 2011; Feresin, 2009), and citing genetic research in court is likely to become more popular (Appelbaum, 2005). Besides decreasing sentences, results from molecular genetic association studies could potentially be used to increase sentences due to higher risk of recidivism (Baum, 2011). Furthermore, Tikkanen et al. (2011) recently suggested based on their study of alcoholic violent offenders, that incorporating genotype information regarding the MAOA gene could result in more accurate assessments of risk for recidivism when using the Hare Psychopathy Checklist-Revised (Hare, 1991) in such populations.

Several issues should be taken into account when considering the results of behavior genetic studies. First, both heritability estimates and polymorphisms indicated by molecular genetic association studies explain variation between individuals in a behavior or trait and should thus be interpreted on a population level and not on an individual level. If, for example, a polymorphism is found to influence aggressive behavior with an average effect size of 2% in the population, this does not mean that it explains 2% of a particular individual's aggressive behavior. Whereas the aggressive behavior displayed by person A can be largely due to genetic factors, person B can behave aggressively due to environmental circumstances. Based on such studies, it can, however, be said that individuals have different likelihoods of behaving aggressively, and thus, that certain risk factors (e.g. genetic) associated with, for example, aggressive behavior can be identified (Appelbaum, 2005). Complex human behavior, such as aggressive behavior, is likely to be influenced by a number of polymorphisms, each with a (very) small effect (Plomin, DeFries, McClearn, & McGuffin, 2001). As noted by Novelli in a paper by Feresin (2009), the effects of one polymorphism cannot be isolated from, for example, protective effects of other polymorphisms, and it is not likely that we will be able to identify all polymorphisms that influence aggressive behavior (i.e. explain all interindividual variance due to genetic factors). Furthermore, genes also interact with environmental factors, as shown in many recent studies (e.g. Dick, 2011; Rutter et al., 2006;

Rutter & Silberg, 2002). The results of the present thesis suggest that the *OXTR* polymorphisms only explain interindividual variation in aggressive behavior when individuals are alcohol intoxicated, and should not be misinterpreted as a risk factor for aggressive behavior or anger overall. The role of alcohol further complicates the picture by raising questions such as to which degree the consumption of alcohol was voluntary.

This discussion is closely related to philosophical questions. For example, should factors that reduce the capacity of an individual for self-control (based on probabilistic inferences), reduce moral responsibility for his or her actions (a question raised by e.g. Appelbaum, 2005), or be taken into account in risk assessment. Morse (2004) argues that it is the mere presence or absence of diminished rationality (required for responsibility) that is of interest for the criminal justice system, not the possible underlying causes. Although we, as researchers in the field of behavior genetics are not necessarily optimally suited to address philosophical questions like these, it is my opinion that it is our responsibility to assist criminal justice professionals in interpreting the results of our research so that precipitated or erroneous conclusions may be avoided. This is not, however, an unproblematic issue as addressed by researchers in the field of psychiatric ethics (e.g. see Austin, Goble, & Kelecevic, 2009; Miller, 2008; Morse, 2004; Stone, reprint 2008; Wettstein, 2001). Psychologists and psychiatrists have different roles when they are in a client-clinician relationship, than for example, when they are in the role of a scientific researcher, or when giving expert testimony in the court (Wettstein, 2001), and these multiple roles can be seen as problematic from an ethical point of view (as addressed e.g. by Stone, reprint 2008).

5.10 Methodological considerations

An obstacle often encountered in G x E research is the difficulty to disentangle the effects of interactions from those of correlations between genes and environmental factors, especially if measured genetic variants are not used (Rutter & Silberg, 2002). Gene-environment correlation (rGE) refers to the situation when the probability to be exposed to certain environmental factors is influenced by an individual's genotype (Moffitt et al., 2006). As already noted earlier in the discussion, the effect of rGE cannot be excluded in Study II. Genes could affect the environments that individuals are exposed to, which in this case would, for example, mean that certain individuals would, based on their genetic variants, actively seek out environments where he or she would be more likely to consume alcohol and

encounter situations in which controlling one's angry feelings would be more difficult. In Study IV, the rs4564970 and the rs1488467 SNPs did not influence alcohol consumption, making it unlikely for rGE to have confounded the results. By randomly assigning individuals to either the alcohol manipulation group or the placebo group in Study III, the effect of rGE could be excluded.

Studies have shown that genes influence alcohol consumption and alcohol dependence (Dick & Foroud, 2003; McGue, 1999; von der Pahlen et al., 2008). Genes influence the initiation of alcohol use (Pagan et al., 2006), and also vulnerability to alcohol addiction (McGue, 1999). An alternative explanation is that genetic effects on alcohol use could in fact imply rGE, that is, differences in the propensity to seek out alcohol (which logically could be viewed as an environmental factor). As noted by Prescott, Madden and Stallings (2006), exposure to alcohol is not universal, and is arguably self-initiated to an extent. Therefore, alcohol might not be considered a "pure" environmental factor. The potential effect of rGE on the original studies in this thesis was discussed above. Next, a few comments specifically addressing potential confounding of genetic effects of alcohol use will be discussed in light of the original studies. In Study II, the effect of alcohol consumption was regressed out from the variable measuring the difference in anger control between the sober and intoxicated states in order to try and separate genetic effects on alcohol consumption from the analysis. Moreover, regarding genetic effects on anger control regarding the sober and the intoxicated states, models where the effect of alcohol consumption had been regressed were fitted, yielding comparable results. In Study IV, the measured SNPs did not, as mentioned earlier, affect alcohol consumption, but interactions with other genes influencing alcohol could not be excluded. In Study III, alcohol was administered to randomly selected individuals who were then compared to a placebo group, and therefore, possible confounding resulting from genetic effects on alcohol consumption was eliminated.

With regards to studies III and IV, it is important to keep in mind that the rs4564970 and the rs1488467 polymorphisms are in high LD with each other, and that the results regarding these SNPs are therefore highly correlated. In addition, the results could also be due to LD between the rs1488467 / rs4564970 and other functional variants affecting OXTR function. In the sample of Study III, no participant was homozygous for the C allele on either the rs1488467 or the rs4564970 SNPs. In the GSA sample (Study IV), seven participants were homozygous for the C allele for the rs1488467 SNP and ten for the rs4564970 SNP. These were, however, too few to analyze separately, and were therefore grouped together with the heterozygotes.

This means that it is impossible based on these studies to determine whether the effect of the C allele on aggressive behavior when alcohol intoxicated is linear, or if dominance effects are at play.

Rutter (2008) has noted that in some instances an interaction between measured genetic variants and environments can be an artifact of scaling issues. In studies III and IV of the present thesis, we found indications that the rs4564970 and the rs1488467 moderate the effect of alcohol on traits related to aggressive behavior and anger. Since different measures were used both for alcohol (self-reports and acute alcohol intake in laboratory conditions) and aggressive behavior (self-reports and a laboratory measure of aggressive behavior), the possibility that the G x E would in this case be an artifact of scaling variations is reduced. A similar effect of the G x E was indicated on trait anger, a phenotype related to aggressive behavior, strengthening the notion that the interactions were not a result of scaling variations. The participants were randomized to the alcohol versus placebo groups in Study III, which excludes yet another possible source for artifactual results (Rutter, 2008).

Studies I, II and IV were based on self-reports and might be susceptible to recall problems and response bias, especially for anger control regarding the intoxicated state. Furthermore, alcohol expectancies were not measured, and therefore, the participants' expectancies of the effect of alcohol on their anger control might have influenced their recollections of anger control regarding the alcohol intoxicated states. Studies show, however, that the pharmacological effects of alcohol on behavior are larger than potential expectancy effects (Exum, 2006). In Study I, although the results indicated some interesting differences in anger control between the sober and intoxicated states with regards to trait anger and alcohol consumption, the effect sizes of the interactions were small. Intoxication was not specified when asking the participants to rate their usual levels of anger control in this state, and although the majority of participants most likely interpreted intoxication to refer to alcohol intoxication, it cannot be ruled out that a small minority might have answered the questions also with intoxication by drugs in mind. According to the National Institute of Health and Welfare in Finland (Rönkä & Virtanen, 2009) approximately 8% in the age range of 15-34 years had tried the most widely used drug, cannabis, the year preceding the data collection, with less than 2% of the total age range having tried some other drug. Only a fraction of these individuals were likely to have used drugs in a constant manner. Floor effects on the difference score in anger control were, although possible, not likely to have exerted a great impact on the results (the reader is kindly advised to consult Study II for more information).

In addition, it was not possible to specify the amount of alcohol consumed in specific situations when self-reports of the usual level of anger control when intoxicated were used.

Experimental studies, on the other hand, allow the amount of alcohol intake to be controlled for but the generalizability of the results of such studies to aggressive behavior or anger outside the laboratory might not be quite as good as for results from studies using self-report questionnaire data. This taken into consideration, the construct and external validities of experimental laboratory paradigms of aggressive behavior have been supported and it has been concluded that the results of such studies can be generalized to aggressive behavior in real life (Anderson & Bushman, 1997; Giancola & Chermack, 1998). Aversive noise was used instead of electric shocks in Study III. It could be argued that giving electric shocks is a more explicit measure of aggressive behavior than administering aversive noise; however, the use of aversive noise is likely to capture more of the interindividual variation by a lower threshold to respond aggressively. Aggressive behavior as measured with the RCAP correlated significantly ($r = 35$, $p > .05$) with self-reported aggressive behavior (measured with the AQ) for sober individuals but not for alcohol intoxicated individuals using the sample in Study III. This may be because it is not specified in the AQ if the items reflect aggressive behavior when sober or intoxicated and aggressive behavior when sober does not entirely predict who will behave aggressively when alcohol intoxicated and who will not. A decision was made not to use a balanced placebo design, since we were primarily interested in the pharmacological effects of alcohol and thus wanted to control the effect of expectations by using a placebo group. Moreover, studies indicate that an antiplacebo group rarely serves its purpose, because it is difficult to administer comparable levels of alcohol as in the experimental group without the participants noticing (Exum, 2006).

Besides the ability to control for the amount of alcohol intake in experimental studies, other environmental factors can be controlled for to a higher degree than in comparison to questionnaire data. Also, conclusions about the causality of the relationship between alcohol and aggressive behavior can be drawn because of random assignment of participants to alcohol and placebo groups. On the other hand, because of ethical considerations, limited amounts of alcohol can be administered in experimental studies and Graham et al. (2006) note that intoxication levels in naturalistic settings, especially in pubs, often exceed those of laboratory studies. This is not a limitation regarding questionnaire studies, however. Since experimental studies are more expensive and especially time-consuming, substantially higher sample sizes, and thereby increased statistical power, can be obtained using self-report

questionnaire data. Furthermore, whereas experimental laboratory studies often rely on convenience samples because of practical issues (as was the case in Study III), it is easier to acquire a population-based sample using questionnaires. In conclusion, both experimental and questionnaire studies have their pros and cons, which can partly be taken into account by using both methods.

In Study IV, a population-based sample of Finnish men and women was used. Although the genetic background of Finns is quite homogenous, differences do exist (Nelis et al., 2009; Salmela et al., 2008). Such differences could in the population-based sample have caused spurious results only if these differences in genetic background would geographically coincide with differences in aggressive behavior or anger, in other words, if individuals in a part of Finland where an allele would be more common would have higher levels of aggressive behavior and anger than individuals in another part where the allele would be significantly less common. This is a highly unlikely scenario. All participants were Finnish-speaking. In Study III, Finnish university students were tested. Although all participants were tested in Finnish, participants were recruited both from Finnish- and Swedish- speaking universities and thus Swedish was the mother tongue of some of the participants. The participants were randomly allocated to the placebo and the experimental group and the groups were balanced for language of the participants ($\chi^2 = 2.62$, $p = .11$). Language of the participants was assessed using the following information: if the participant had a typically Finnish-or Swedish name, if they attended the Finnish- or Swedish speaking university in Turku, as well as language used in e-mail communication with the participants. Moreover, no differences in genotype frequency of the significantly associated SNPs were seen between the two language groups. Taken together, the interactions are most likely not the result of differences in genetic background between the Finnish- and Swedish- speaking participants. In addition, the Swedish-speaking population in Finland shows a rather high degree of Finnish genetic admixture (Virtaranta-Knowles, Sistonen, & Nevanlinna, 1991). It should, however, be examined if the interactive effects are replicated in samples of different genetic origin than the Finnish since the effects of polymorphisms can vary between different ethnic groups (e.g. regarding MAOA; Widom & Brzustowicz, 2006).

The participants in the experimental study were between 18 and 30 years old, and the majority of the participants in the population-based sample were in the same age range. In this age group, crime rates drop from having peaked in the late adolescence (Bloningen, 2010). On the other hand, aggressive behavior seems to be a moderately stable behavior (Huesmann et al.,

2009; Kokko & Pulkkinen, 2005; Loeber & Hay, 1997). There might also be some age related changes with regards to anger. Studies suggest that proneness to react with anger to situations might decrease somewhat with increasing age, and that older persons could be more inclined to control their angry feelings (Phillips, Henry, Hosie, & Milne, 2006; Spielberger, 1999). Future studies are needed to test if the findings of the present thesis replicate in different age groups. Although age would have a main effect on anger and aggressive behavior, it is not necessarily the case that the relationships between trait anger, anger control and alcohol consumption, or the interactive effects between alcohol and *OXTR* SNPs, would look different in older ages. However, other factors such as decreases in alcohol consumption with increased age (e.g. Kerr, Greenfield, Bond, Ye, & Rehm, 2009), or changes in the settings where alcohol usually is consumed (e.g. bars versus at home), could affect the frequency of aggressive behaviors shown when intoxicated.

The overall response rate (45%) of the second data collection of the GSA study was somewhat low, but it should be kept in mind that the questionnaire was extensive and covered sensitive sexuality- and aggressive behavior-related topics. Although the response rate is comparable to other sexuality- (e.g. Bailey, Dunne, & Martin, 2000; Långström & Zucker, 2005) and aggression-related survey studies (e.g. Hall Smith, Thornton, DeVellis, Earp & Coker, 2002), it may not be fully representative of the population. The response rate for highly aggressive individuals, with low levels of anger control, might be somewhat lower than the response rate for highly controlled individuals. Vink et al. (2004) estimated non-response rates in a family sample by using data from respondents as proxy for the data from their non-responding family members. They noted that those from less cooperative families tended to show, for example, higher levels of aggressive behavior and alcohol problems. These effects were not, however, significant after correction for multiple testing, and the authors concluded that data in studies with modest response rates is relatively unbiased (response rate in the study was 32.3% for twins and 40.2% for siblings) (Vink et al., 2004). Furthermore, the GSA sample is comparable to other Finnish population-based samples on different characteristics such as mean age of first intercourse (Mustanski, Viken, Karpio, Winter, & Rose, 2007 and rates of sexual abuse (Sariola & Uutela, 1994). The participants in the sample consisting of university students were significantly less aggressive than the participants in the population-based sample ($p < .01$), but the effect size of the difference was small ($\eta^2_{partial} = .04$, $\eta^2 = .04$). Some studies suggest that low academic performance is associated with more violent behavior

(Loeber, Lacourse & Homish, 2005), which could partly explain the difference in aggressive behavior between the samples.

Although the GSA sample consisted of twins as well as their siblings, there were no significant differences between siblings and twins on the variables of interest, and comparisons with other studies (Helweg-Larsen & Bøving Larsen, 2002; Mustanski et al., 2007; Sariola & Uutela, 1994) indicate that generalizability of the results is not limited to twins only. This is in line with other studies suggesting that there are no differences between twins and singletons on most psychological traits, with the exception of language development and obstetric complications (Rutter, 2006), as well as weight (Andrew, Hart, Snieder, de Lange, Spector, & MacGregor, 2001).

Quantitative genetic twin methods, used in Study II, rely on the assumption that the effect of the environment on making twins more similar to each other is the same for MZ and DZ twins (the equal environments assumption; EEA). Another assumption is that there is no assortative mating with regards to the trait in question. A violation of the EEA would result in overestimation of the additive genetic component if the environments of MZ twins are more similar to each other than that of DZ twins, whereas presence of assortative mating would result in an underestimation of the *A* component (Frisell, Pawitan, Långström, & Lichtenstein, 2012; Plomin et al., 2001). Studies indicate that the EEA is reasonable and justified in most cases (Hettema, Neale, & Kendler, 1995; Kendler, Neale, Kessler, Heath, & Eaves, 1993; Rutter, 2006). The degree of assortative mating is modest for most traits (Plomin et al., 2001), and Frisell et al. (2012) showed that although there was assortative mating for violent offending, it did not have a major effect on variance components.

SUMMARY AND CONCLUSIONS

The relationship between aggressive behavior and alcohol consumption is well-known, but still highly complex with traits such as anger and anger control influencing it. In the present thesis, the associations between alcohol consumption and anger-related traits as well as aggressive behavior were analyzed, with specific focus on interactions between alcohol and genetic effects. To our knowledge, the thesis was the first to investigate interactive effects between polymorphisms and alcohol consumption on anger as well as control of anger. In addition, it was the first to experimentally examine interactions between polymorphisms and alcohol on aggressive behavior in humans. Below, the key findings and conclusions of the thesis are outlined.

1. Levels of anger control were lower in self-reported intoxicated states than in sober states. High levels of trait anger and alcohol consumption were associated with larger differences in anger control between sober and intoxicated states, and can thus be considered risk factors for low anger control, which in turn might affect aggressive behavior.

2. The results showed that additional information can be gained by separating between anger control regarding sober and intoxicated states. Thus, researchers should consider distinguishing between behavior and feelings shown in sober and intoxicated states, for traits that are associated with, and known to be affected by alcohol intoxication. In cases where this is not done, thought should be put on possible confounding between sober and alcohol intoxicated states and on the possible implications of this.

3. Anger control was shown to be influenced by genetic effects both regarding self-reported sober (27% for men, 34% for women) and intoxicated states (29% for men, 37% for women). The large part of the genetic effects for anger control was common between these two states. It should also be noted that the majority of interindividual variance was explained by nonshared environmental effects, highlighting the importance of, for example, situational factors.

4. The difference in anger control between sober and intoxicated states was influenced to a moderate degree by genes. Although this result could be explained by a gene-

environment correlation (i.e. genes influencing the propensity to seek out environments where both alcohol consumption and decreases in anger control are probable), a more likely explanation is that individuals differ in their susceptibility to the effects of alcohol on impairing control of angry feelings.

5. In studies III and IV, two polymorphisms in the *OXTR* were identified as interesting with regards to interactive effects with alcohol consumption on aggressive behavior and anger. The rs4564970 *OXTR* SNP interacted with alcohol consumption in influencing aggressive behavior both in a sample where aggressive behavior was measured using a laboratory paradigm and in a population-based sample when self-reports of aggressive behavior was used. Furthermore, the rs4564970 and the rs1488467 SNPs moderated the effects of self-reported alcohol consumption on trait anger. It seems that carriers of at least one C allele are more susceptible to the anger and aggression increasing effects of alcohol than individuals homozygous for the G allele. These SNPs did not influence the difference in anger control between sober and intoxicated states and thus, these *OXTR* SNPs were hypothesized to moderate the effects of alcohol consumption on underlying feelings rather than control of these feelings.

In conclusion, based on the results of the present thesis, it is reasonable to expect that individual differences in the way people react to the effects alcohol have on anger and aggressive behavior are in part explained by individual differences in genotypes. For trait anger and aggressive behavior, the rs1488467 and the rs4564970 SNPs of the *OXTR* gene are worth investigating further with respect to such interactions. Furthermore, our results suggest that it is likely that interactive effects between genetic variants and alcohol on anger control also exist, but it will be a task for future research to try and identify the polymorphisms underlying such an interaction.

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