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Association of the Oxytocin Receptor Gene (*OXTR*) with Childhood Aggression and Social Cognition

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An abstract of a thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Master of Arts in Psychology

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Abstract

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By Holly Poore

Aggression is a complex trait, influenced by a multitude of factors and has important implications for long-term life outcomes. Behavior genetic studies have found that aggression is moderately to highly heritable across the lifespan. Despite its high heritability, molecular genetic studies of aggression have had mixed results, with few genetic variants showing reliable associations. Recent research suggests that Oxytocin and the Oxytocin Receptor Gene (*OXTR*) influences social cognition and behavior in humans and animal models. The primary aim of this study is to examine associations between *OXTR* and measures of aggression in children and adolescents. Based on current animal models, it is hypothesized that *OXTR* will be associated with various forms of aggression. In the current investigation, we collected DNA and parent ratings of aggression for a total of 636 children ages 6-18 years old sampled from both unreferred twins as well as clinically-referred children. The investigation included 31 SNPs in *OXTR*. To operationalize *OXTR* in a gene-based test, a series of Exploratory Structural Equation Models (ESEMs) of the *OXTR* SNPs were conducted. The model with five factors fit best while still favoring parsimony and was used to characterize the underlying structure of the gene. Aggression was also modeled as both a unitary aggression factor and as two separate reactive and proactive aggression factors. A series of gene-based tests were then conducted such that the aggression factors were regressed on the latent *OXTR* factors and all covariates. The *OXTR* factors accounted for a significant portion of the variance in the unitary aggression factor (R^2 = 1.8%, $p<.001$), reactive aggression (R^2 = 1.2%, $p<.001$), and proactive aggression (R^2 = 5.8%, $p<.001$) over and above the contribution of the covariates. Social cognitive variables were available for a subsample of participants and the association between *OXTR* and social cognition was also examined. One through four factor models of *OXTR* were used in the association analyses between *OXTR* and social cognitions. *OXTR* consistently accounted for a significant proportion of variance in the percentage of correct responses in the sad and fearful emotion categories and the number of commission errors in the happy and angry emotion categories across the two, three, and four factor models of *OXTR.* Future research will focus on replicating these results in larger samples from a diverse group of cohorts.

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Table of Contents

Introduction 1

Method 12

Data Analysis 14

Results 20

General Discussion 29

Implications for Gene Based Tests using Structural Equation Modeling 33

Limitations/Future Directions 34

References 37

Tables 45

Figures 57

List of Tables and Figures

Table 1. Description of *OXTR* SNPs and Factor Loadings for Best-Fitting Model of *OXTR* using ESEM

Table 2. MAF in *OXTR* SNPs by Ancestry

Table 3. Call Rate for Each SNP

Table 4. *OXTR* ESEM Model Fit Statistics

Table 5. Intercorrelations of the Five *OXTR* Factors

Table 6. Aggression CFA Fit Statistics

Table 7. Factor Loadings for the Two Best-Fitting Models of Aggression

Table 8. Standardized Regression Coefficients for the Aggression Factors on the *OXTR* Factors

Table 9. Variance Explained by *OXTR* and Covariates

Table 10. *OXTR* ESEM Model Fit Statistics in the Subsample

Table 11. Associations of *OXTR* and Social Cognition in 1-4 Factor Models of *OXTR*

Figure 1. Haplotype Frequencies for Each Haplotype in the Reference and Current Study Sample

Figure 2. LD Map for the 33 *OXTR* SNPs in the Current Study Sample

Figure 3. LD Map for the 33 *OXTR* SNPs in the Reference Sample

Association between the Oxytocin Receptor Gene (*OXTR*), Childhood Aggression, and Social Cognition

Human aggression is a complex trait, influenced by a multitude of factors and has important implications for long-term life outcomes. Aggression is a key symptom in a variety of prevalent and debilitating psychiatric disorders including Oppositional Defiant Disorder and Conduct Disorder in children, and Antisocial Personality Disorder in adults (APA, 2013). In children, aggression can lead to negative peer outcomes like rejection, which can in turn lead to higher school dropout rates and delinquency (Bowker & Etkin, 2014). Aggressive behavior in school also impedes academic achievement as it disrupts the learning environment and causes the child to spend more time outside of the classroom. Aggression is stable over time such that, without intervention, aggressive children are likely to become aggressive adults (Kokko & Pulkkinen, 2005). In one study, levels of aggression at age eight were predictive of aggression levels in middle adulthood (Huesmann, Dubow, & Boxer, 2009). The adults with higher levels of aggression were also more likely to have negative outcomes across multiple domains of functioning, including criminal behavior and psychosocial functioning. Such negative life outcomes affect both the individuals and their communities and warrant further investigation into the etiology of aggression.

Aggression has been shown to have multiple subtypes that are primarily differentiated by the identified motive for the aggressive behavior. In mouse models, aggressive behavior, defined as behavior with the intention of biting another animal, is delineated into predation, infanticide, defense, and offense types (Maxson, 1992). Defense behavior refers to any aggressive behavior directed towards an intruder or potential threat and designed to defend territory while offensive aggressive behaviors are non-protective and are not in response to a threat. Investigations of the

etiology of these behaviors in mice indicate that the tendency towards offensive aggressive behavior is heritable, as demonstrated by increased aggression in generations of mice bred with more aggressive parents (Miczek, Maxson, Fish, & Faccidomo, 2001).

In humans, aggressive behavior can be differentiated by the underlying motives for the behavior, which is reflected in the distinction between reactive and proactive aggression (Dodge & Coie, 1987). Reactive aggression includes retaliatory behavior that is a defensive reaction in response to a perceived threat. Proactive aggression includes behaviors that occur without apparent provocation such as coercion, dominance, bullying, and instrumental aggression. Although some have argued that this distinction fails to consider aggressive behavior that may have multiple motives and that reactive and proactive aggression are highly related and frequently co-occur (Bushman & Anderson, 2001), research indicates that the construct can be meaningfully separated. A study of the factor structure of the Dodge and Coie (1987) teacher report of reactive and proactive aggression scale found that a 2-factor model, in which a large correlation between the two factors was observed, fit better than a model with a single aggression factor (Poulin & Boivin, 2000). In the same study, reactive and proactive aggression were differentially associated with peer status, leadership, social withdrawal, and victimization by a peer. When the shared variance between the two aggression factors was accounted for, peer status was negatively associated with reactive aggression and positively associated with proactive aggression while peer victimization was positively related to reactive aggression and negatively related to proactive aggression. Similarly, leadership was negatively associated with reactive aggression and positively associated with proactive aggression. Social withdrawal was positively associated with both forms of aggressive behavior, but the relationship was significantly higher for reactive aggression.

Reactive and proactive aggression are also differentially associated with other measures of psychosocial adjustment. In a meta- analysis of studies examining the relationship between reactive and proactive aggression and psychopathology, Card and Little (2006) found that reactive, but not proactive aggression, was related to internalizing problems, although the direction of this relation was moderated by symptom reporter. Both reactive and proactive aggression were associated with Executive Dysfunction and ADHD symptoms, but the association between these symptoms and reactive aggression was stronger. Finally, Jung Krahé, Busching (2007) found that reactive and proactive aggression were predicted by distinct risk profiles. Specifically, membership in the group with a high rate of social rejection predicted reactive aggression at a later time point, whereas only membership in the group with high affiliation with aggressive peers and academic failure predicted proactive aggression at a later time point.

Investigations into the etiology of aggression have found that aggression is influenced by both genetic and environmental factors. Estimates of the genetic influences on aggression vary widely. Estimates based on multi-informant reports of aggression range from 63% in a study of relational aggression (Tackett, Waldman, & Lahey, 2009) to 82% in a study of antisocial behavior (Arseneault et al., 2003). A recent review of the literature found that, in general, estimates range from 20-64% (Rhee & Waldman, 2011). Multivariate analyses have revealed a common, and highly heritable, factor of antisocial behavior which includes measures of conduct disorder, aggression, delinquency, and psychopathic traits (Baker et al., 2007). The heritability of this factor was estimated at .96 and provides evidence for a common etiological factor of these related behaviors. Continuity in aggressive and antisocial behavior symptoms from childhood to adolescence can be primarily attributed to genetic influences (Eley, Lichtenstein, & Moffitt,

2003). Although consistent estimates of the amount of variance genetic influences account for in aggressive behavior have not been found, there is considerable evidence that aggression is highly heritable and stable across the lifespan.

Studies of specific genes that account for this moderate heritability have found significant associations with a number of genes that influence neurotransmitter and neurohormonal levels and activity. Specifically, variation in Oxytocin (OXT) levels and the Oxytocin Receptor Gene (*OXTR)* may account for some of the genetic influences on aggression. Oxytocin, a neuropeptide that interacts with dopaminergic and opioid neurotransmitter systems in the brain, has been shown to be related to social behavior, partner preference, pair bonding, and reactive aggression in animal models (Donaldson & Young, 2008). Preliminary evidence also suggests that the neuropeptide is related to various aspects of social cognition and behavior in humans as well. Much of this research relies on observations of the effects of intranasal OXT administration on behavior.

Examination of the effects of intranasal oxytocin administration in animals has shown that increased oxytocin affects social behavior and aggression (reviewed in McCall & Singer, 2012). A study of common vampire bats found that bats who were given oxytocin were more generous when sharing food and participating in other-grooming (Carter & Wilkinson, 2015). Similarly, a study examining the effects of OXT in mice found that increased oxytocin in female, but not male, mice supported the formation of a conditioned social preference for a previously unfamiliar, same-sex mouse (Kosaki & Watanabe, 2016).

Intranasal OXT administration in humans has also been shown to affect social behavior. In one study, participants who were administered oxytocin reported feeling more sociable towards others and were better able to recognize sad facial expressions compared to controls

(Kirkpatrick et al., 2014). Increased OXT also affects processing of negative social stimuli during memory encoding and retrieval (Weigand et al., 2013) and increases rates of cooperative behavior following unreciprocated cooperation (Rilling et al., 2012). Like the results from animal models, intranasal OXT administration in humans appears to have sexually dimorphic effects. OXT administration led female, but not male, participants to treat a computer partner more like a human partner as measured by their willingness to cooperate with it (Rilling et al., 2014). In males, but not females, OXT administration increased activity in the striatum, basal forebrain, insula, amygdala, and hippocampus, all of which play a key role in reward processing, social bonding, arousal, and memory. Hoge et al. (2014) studied the effects of oxytocin on social affective perception and learning in tasks in which participants evaluated neutral faces on the basis of competence, trustworthiness, and warmth. In this study, male participants in the treatment condition (those who were administered OXT) rated faces more negatively than controls while female participants in the treatment condition rated faces more positively.

Intranasal OXT administration has also shown some promising results in remediating the social cognitive and skills deficits experienced by people with Autism Spectrum Disorder (ASD; reviewed in Preti et al., 2014). In a double-blind, randomized control trial of OXT admiration in youth diagnosed with ASD, participants in the treatment condition showed improved performance on a social cognitive task compared to controls. Similarly, in a study of the effects of OXT on facial processing in adults with ASD, Domes et al. (2013) found that participants treated with OXT had increased right amygdala activity when presented with facial stimuli. This indicates the OXT may lead to enhanced processing of facial features and expression in adults with ASD.

It is important to note that, although this existing intranasal OXT literature suggests there is a causal relationship between OXT and behavior, there are also several methodological concerns about these studies. In a recent review, Walum, Waldman, and Young (2016) evaluated the results of three meta-analyses of intranasal OXT studies. They found that studies with healthy participants had an average statistical power of 16% while studies with clinical populations had an average of 12% power. This is problematic for two reasons. First, this means there is likely a high false negative rate in related studies, which interferes with replication and validation of findings. Second, it means that underpowered studies that did find a statistically significant effect likely have spuriously inflated effect sizes. These studies indicate that oxytocin may have an important role in social behavior, but they also have significant methodological limitations that temper the conclusions that can be made. In addition to methodological improvements in OXT manipulation in humans, investigation of naturally occurring OXT levels and the oxytocin receptor gene may provide more insight into the effects of oxytocin variation on human social behavior.

Extant research indicates that the oxytocin receptor gene (*OXTR*) influences OXT activity and, potentially, behavior. *OXTR* is located on chromosome 3 and encodes a G-protein coupled receptor that acts as a receptor for oxytocin. In animal model studies, *OXTR* can be deactivated and resulting behaviors can be observed. In studies of *OXTR* knockout mice, affected female mice displayed disruptive maternal behavior such as refusing to huddle with their pups and spending less time nursing (Higashida et al., 2010). Similarly, male *OXTR* knockout mice were more likely to display proactive aggression than their unaffected counterparts (Nishimori et al., 2008). Male mice lacking the oxytocin receptor gene due to mutation were unable to develop social memory, whereas mice with the gene intact showed normative social memory (Ferguson,

2000). This research also indicates that exploration of *OXTR* variation is warranted to provide more information about the development of social behavior and aggression.

Research on *OXTR* variation in humans implicates the gene in a variety of social cognitive and behavioral processes including parental attachment, romantic relationships, friendship, empathy, and psychopathology including ASD, depression, and schizophrenia (reviewed in Feldman, Monakhov, Pratt, & Ebstein, 2015). Several specific Single Nucleotide Polymorphisms (SNPs) within *OXTR* have been investigated in relation to social behavior and aggression. As with the intranasal OXT research, there are several methodological concerns about these candidate gene studies that limit conclusions that can be drawn from them. Specifically, candidate gene studies that examine the effects of a few SNPs in the same gene on a phenotype typically fail to replicate and are plagued by issues of power. In a simulation study, Sullivan (2007) modeled 10 genetically realistic *COMT* SNPs in a sample of 500 cases and 500 controls. Under the null model, 968 of 1000 (96.8) simulations produced at least one false positive result $p < .05$. Decreasing the threshold for significance with a Bonferroni correction ($p<.005$, adjusting for the 10 SNPs) decreased the false positive rate to .314. This false positive rate is well above the field's accepted rate of .05 and the sample size of 500 cases and 500 controls is large relative to the sample size of most candidate gene studies. Nevertheless, these studies may provide some information about which genes and gene regions should be further investigated when seeking to explain the etiology of social behavior and aggression.

The *OXTR* SNP rs237887 was associated with face recognition memory in a sample of 198 families from the UK and Finland (Skuse et al., 2014). These families were recruited if they had a child with a diagnosis of "high functioning" autism. For this SNP, AA homozygotes showed deficits in face recognition memory irrespective of diagnostic status. Similarly, in a

meta-analysis of the associations of 16 *OXTR* SNPs with ASD diagnosis, LoParo et al (2014) found that the SNP rs237887, as well as the SNPs rs7632287, rs2268491, and rs2254298, was significantly associated with ASD. In a follow-up gene based test of association in the same study, ASD was found to be significantly associated with *OXTR.*

A large-scale study of *OXTR* SNP variation in three Swedish samples also found significant associations of *OXTR* SNPs with social behavior (Walum et al., ,2012). 12 *OXTR* SNPs were genotyped in two samples: the Twin and Offspring Study in Sweden (TOSS, n=2,309) and the longitudinal Swedish Twin Study of Child and Adolescent Development (TCHAD, n=1,240). Rs7632287 was significantly associated with pair bonding traits in women in the TOSS and TCHAD sample. In girls, an association between this SNP and childhood social problems, which predicted pair bonding behavior later in life, was also found. Finally, the association between rs7632287 and social behavior was replicated in a third sample, the Child and Adolescent Twin Study of Sweden (CATSS, n=1,771), in which social interaction deficit symptoms were associated with the same SNP.

Specific *OXTR* polymorphisms have also been associated with aggressive behavior. High rates of callous unemotional traits were associated with rs1042778 and the CGCT haplotype of rs2268490, rs2254298, rs237889, and rs1331161193 in a sample of 220 children referred for assessment and management of disruptive behavior problems (Dadds et al., 2014). These children were between ages 4 and 16 and all met criteria for DSM-IV diagnosis of ODD or CD. In a second sample of 59 children recruited for emotional and behavioral problems, the association between rs1042778 and callous-unemotional traits was replicated and remained significant across gender and age groups. Similarly, a case control study of 160 children referred for “extreme, persistent, and pervasive aggression” and 160 healthy adult controls found that

rs1042778 and rs6770632 were associated with the aggressive phenotype in males and females respectively (Malik, Zai, Abu, Nowrouzi, & Beitchman, 2012).

A study of the association between alcohol consumption and aggression in 116 Finnish men found that two *OXTR* SNPs, rs4564970 and rs1488467, interacted with alcohol consumption to predict aggression (Johansson et al. 2012). The interaction between rs4564970 and alcohol consumption remained significant after correcting for multiple tests. A study of children identified as aggressive and antisocial tested the interaction between social stress and *OXTR* variation in predicting antisocial behavior (Smearman et al., 2015). The polymorphism rs53576 showed a significant main effect on behavior such that participants with the G allele exhibited higher levels of conduct problems. Those with the G allele of rs53576 who also experienced high social stress exhibited the highest levels of antisocial behavior. It is important to note that candidate gene by environment interaction studies have been plagued by the same, if not more severe, methodological concerns. A review of candidate gene by environment interaction studies found that although 96% of published novel findings were significant, only 27% of the replication attempts met the same significance threshold (Duncan & Keller, 2011). This review also suggests that these studies are routinely underpowered and that, like the intranasal OXT literature, positive findings of this type are more likely to represent false positive associations.

LoParo et al. (2015) modeled variation in *OXTR* as latent factors using structural equation modeling in a sample of Finnish men. This represented a novel statistical approach to gene based tests of association, which allowed the authors to capture variation in *OXTR* across the gene and increased power to detect a statistical association. The authors first conducted Exploratory Factor Analyses (EFAs) on 33 *OXTR* SNPs to determine the number of factors that best captured the variation in *OXTR.* The resulting best fitting model, which roughly corresponded to the

haplotype blocks in that region, was carried forward in an association test in which aggression was regressed on all *OXTR* factors. Using this approach, they found significant associations between *OXTR* and aggression.

Taken together, these findings suggest that *OXTR* may play an important role in aggression, social behavior, and social cognition. Social cognition has also been shown to affect aggressive behavior and subsequent negative life outcomes. Research suggests that, compared to nonaggressive peers, highly aggressive adolescents were less able to perceive another's point of view, which has important implications for social cognitive abilities (Batanova & Loukas, 2014). Highly aggressive people are also more likely to misidentify an emotion as anger compared to nonaggressive peers (Schönenberg & Jusyte, 2014), and were more likely to misidentify nonhostile intentions as hostile and to propose aggressive responses to neutral situations compared to their nonaggressive peers (Waldman, 1996). The association between aggression and social cognition also appears to differ between different types of aggression. Dodge and Coie (1987) found that boys who were reactively aggressive, compared to those that were proactively aggressive, were more likely to perceive neutral situations as hostile (hostile attribution bias) and had higher rates of intention-cue detection errors. This finding was replicated in a study in which reactively aggressive boys were more likely to demonstrate hostile attribution biases in a playgroup setting (Schwartz, 1998). The present study aims to investigate the relations between the social cognition and aggression constructs and examine the potential of shared etiology due to *OXTR.*

The present study

The overall goal of this study is to examine how genetic variation in *OXTR* is associated with aggressive behavior and deficits and biases in social cognition. Results from this study will

contribute to a better understanding of the causes and genetic risk factors for the development of aggressive behavior and related disorders (e.g. Oppositional Defiant Disorder, Conduct Disorder, and Antisocial Personality Disorders). In turn, a better understanding of the etiology of aggressive and social cognitive deficits may inform identification and treatment of aggression during early childhood.

The primary aim of this study is to examine associations between *OXTR* and measures of aggression. Based on current animal models and studies of genetic variation in *OXTR*, it was hypothesized that *OXTR* would be associated with aggression. The second aim is to test for evidence of a differential association of *OXTR* with reactive and proactive aggression. The third aim is to test the association of *OXTR* with social cognition. Of the studies examining the relationship between *OXTR* and social cognition, none that we know of use direct measures of social cognition. This is in comparison to studies that, for instance, ask participants to engage in social situations and infer social cognitive ability from behavioral observation. The present study includes measures of participants' ability to discriminate among facial displays of emotion and thus represents a more direct measure of social cognition. It was hypothesized that *OXTR* would account for a significant proportion of the variance in social cognition as measured by performance on various indices from a perception of facial emotion task.

Finally, as mentioned previously, extant studies of the association between *OXTR* and behavior have several methodological drawbacks, including focusing on only one or very few markers across the genes, conducting statistical tests for each marker in a piecemeal fashion, and inadequate corrections for multiple testing. The present study aims to address these problems by including multiple genetic markers across the gene and using omnibus gene-based tests of association, rather than testing each individual marker one by one.

Method

Participants

The current study included 636 children ages 6-18 years (mean age =11.7, SD = 3.5) recruited from several sources. At-risk probands and their siblings were recruited from the Center for Learning and Attention Deficit Disorders and the Psychological Center at Emory University, specialty clinics that provide assessment and treatment for children with learning, behavioral, and/or emotional problems. Diagnostic status of these children was not used to determine eligibility for the present study. In addition, a subset of twins from the Georgia Twin Registry, a representative sample of twins born in Georgia between 1980 and 1991, were recruited to participate in the study. 86.5% of this sample was of European ancestry, 7.3% were African American, 2.3% were Latino, and 3.9% were of other or mixed ethnicity.

In the clinic sample, data were collected in participants' homes. Twin data were collected during a visit to the laboratory. Children completed an extensive battery of executive function assessments and provided buccal cell samples for DNA extraction. Primary care givers completed questionnaires that assessed their children's behavior, temperament, and symptoms of DSM-IV childhood disorders including Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), Attention Deficit Hyperactivity Disorder (ADHD), and related traits such as aggression and antisocial behavior. For the subset of twins, a total of 125 participants, social cognitive measures including facial perception of emotion were available.

Genotyping

Participant DNA was collected from Buccal cells using a 30-mL solution of 4% sucrose, which participants were asked to rinse in their mouths for 1 minute (Ficks, 2014). Following

collection, samples were labeled, refrigerated, and transported to the laboratory for storage. Samples were later transferred to a laboratory at Emory University for genotyping. DNA was quantified by gel electrophoresis using Quantity One (BioRad, Hercules, CA). DNA concentrations were normalized to 10 ng/ µl and were not used if they fell below 5 ng/µl. DNA was plated at 10 or 20 ng for Sequenom genotyping. The iPLEX chemistries and the MassARRAY system (Sequenom, Inc., San Diego, CA) were used to generate Sequenome genotypes. Samples were duplicated within-plate for quality control to assess assay integrity.

Measures

Aggression. Aggression was measured through parent report on Dodge and Coie's (1987) 12-item aggression scale. Parents were asked to rate the frequency with which their child committed various aggressive acts from 0 ("never") to 5 ("almost always"). Previous investigations (Dodge & Coie, 1987) have demonstrated that more specific aggression dimensions (reactive and proactive) may be derived from this scale. Teacher report of aggressive behavior across the 12 items yielded 3 items that loaded highly on the reactive aggression factor (e.g. "when tested, strikes back," "blames others in fights," and "overreacts angrily to accidents") and only moderately on the proactive aggression factor. Conversely, there were 3 items that loaded highly on the proactive aggression factor (e.g. "gets others to gang up on peer," "uses physical force to dominate," and "threatens and bullies others") and only moderately on the reactive aggression factor. Some have criticized this categorization as an arbitrary oversimplification of a more complex phenotype (Bushman & Anderson, 2001) and there is considerable overlap between the two scales ($r = .76$; Dodge & Coie, 1987). The correlation between the scales in this sample was also high ($r = .65$, $p<.001$). In the current investigation, we will analyze aggression as both a unitary construct and as two separate factors to test the

potential differential association of *OXTR* with reactive and proactive aggression while still examining the association with aggression overall.

Social Cognition. Social cognitive measures were collected from a facial emotion perception task. This computerized task required participants to identify and differentiate between grayscale images of faces displaying various emotions. Each image was a face that displayed one of four emotions (happy, sad, fearful, or angry) with one of two levels of intensity such that each emotion had a high and low intensity version. Participants completed 8 blocks of 20 trials where each block was defined by a different target emotion with two blocks for each emotion. The order of the blocks was randomized. Additionally, before each block, participants were shown a target emotion and asked to press a button as quickly as possible when they saw the emotion twice in a row. The facial emotion stimuli were then presented on the screen. Each face was presented for 1 second with a 1.5 second interstimulus interval. The trials within each block were randomized so that approximately half of the trials contained the target emotion and half contain another emotion stimuli. Data from this task included for each target emotion the number of correct responses, errors of omission, errors of commission, and which emotion stimulus was present when the commission error occurred. For this study, proportion of correct responses in each emotion condition (the number of correct responses divided by the sum of correct responses and number of omissions) and the total number of commission errors for each target emotion were used. The first describes participants' responses to target emotions and the second describes participants' responses to non-target stimuli.

Data Analysis

Assessing Genotyping Quality

Genotyping quality for each SNP was examined in the following ways. Of note, although quality control analyses were conducted on the full sample of genotyped individuals, which included both children and their parents, only the children's data was used to model the associations between *OXTR* and aggression.

Call Rate. SNP call rate was calculated as the percentage of individuals who were successfully genotyped for a given SNP divided by the total number of individuals for whom genotyping was attempted.

$$SNP\ call\ rate = \frac{Number\ of\ individuals\ successfully\ genotyped}{Number\ of\ indivudals\ successfully\ genotyped + unsuccessfully\ genotyped}$$

The call rate in this sample was lower than is typically found (range = 13-56.1%). Multiplexing, which allows multiple SNPs to be genotyped on a single chip, was attempted in this study. It was believed that up to thirty-eight SNPs could be included on each chip, however this process was not successful at the laboratory that was used. As such, SNP call rates are lower than average (see Table 3 for SNP call rates for each SNP in the analyses).

Hardy-Weinberg Equilibrium. Hardy-Weinberg Equilibrium (HWE; Hardy, 1908; Hosking et al., 2004) describes the expected number of heterozygotes in a population given the proportion of homozygotes of the major and minor alleles for a given SNP. HWE is a commonly examined index of potential genotyping error. Deviation from HWE was tested for each SNP in the current investigation using the program PEDSTATS (Wigginton & Abecasis, 2005), which provides basic summary statistics for datasets containing genetic pedigree information. PEDSTATS tests HWE by computing a probability of expected genotypes for each SNP conditional on the minor allele frequency and uses that distribution to determine the significance of deviation from HWE. HWE tests were conducted in the full sample and in the founders only

(the parents of the children). Notably, in clinical samples that are selected for a trait of interest (ADHD, in this sample), deviation from HWE in a full sample including parents and children may be indicative of an association between SNPs and the trait rather than genotyping error. To account for this, HWE was assessed in the founders (parents) separately. If HWE is violated in the full sample, but not in the parent subsample, this indicates that the deviation may be driven by the overrepresentation of affected individuals in the sample or the presence of non-independent observations. SNPs that deviated significantly from HWE ($p<.001$, to correct for multiple testing) in the parent subsample were excluded from further analyses.

Minor Allele Frequency. The frequency of the less common (minor) allele of a SNP in the sample was defined as the number of minor alleles in the sample out of the total number of alleles. The minor allele frequency (MAF) for each SNP in the current sample was compared with the MAF previously found in the 1000 Genome Project's European and African ancestry samples (1000 Genomes Project Consortium, 2015; see Table 2 for MAF for each SNP in the sample). MAF was calculated using the following equation:

$$MAF = \frac{(2\ x\ minor\ allele\ homozygotes) + heterozygotes}{2\ x\ (minor\ allele\ homozygotes + heterozygotes + major\ allele\ homozygotes)}$$

Missing Data. As mentioned previously, there was a considerable level of missing data in this sample. The effect of the missing data was examined by comparing the current sample data to a larger reference sample, the International HapMap Project (Gibbs et al., 2003). The haplotype structure and frequency in the current sample was compared to that found in HapMap data. Haplotypes blocks are a series of SNPs that are very highly correlated with each other through linkage disequilibrium (LD). If the haplotype block frequency in the current sample was similar to that in the reference sample, it would indicate that the sample data is still a close

approximation of the reference genome. Haploview (Barrett, Fry, Maller, & Daly, 2005) was used to characterize the LD and haplotype structure of the reference and current study samples. Figure 3 shows the LD plot of the SNPs used in the current analyses in the HapMap reference sample. This map shows the degree of relatedness between the SNPs and the solid black lines connecting SNPs together represent the haplotype blocks in the data. The same structure was imposed on the sample data (Figure 2) and the haplotype frequency between the two data sets was compared. Figure 1 represents the frequencies for each haplotype in the two datasets; the HapMap frequencies are on the top and the sample data are below. The haplotype frequencies between the two datasets were roughly similar such that frequencies were not more than 10% different and the rank ordered frequencies were the same as well.

To further test the pattern of missingness in the genotyping data, the association between the pattern of missingness and correlations between the SNPs were examined. A correlation matrix of the pattern of missing genotype data was created by coding each genotype at each SNP as either missing or not missing (coded as "0" or "1," respectively). This matrix was correlated with a correlation matrix of the SNPs in R (R Core Team, 2013). The pattern of missingness and correlations between the SNPs were moderately and positively correlated ($r = .25$). This indicates that SNPs that are missing are more likely to be in high LD with each other than are SNPs that were successfully called.

A total of 46 SNPs in *OXTR* and flanking regions were originally genotyped. 13 SNPs were excluded because they significantly deviated from Hardy-Weinberg Equilibrium ($p<.001$) in founders. No SNPs were excluded from the full analysis due to Minor Allele Frequency, although alternative models of *OXTR* that excluded SNPs with a low minor allele homozygote genotype frequency were run to assess the robustness of the *OXTR* models. SNPs with low call

rates were also not excluded as the current analyses used Full Information Maximum Likelihood. More details about these procedures are provided in the following sections. After assessing genotyping quality, 33 SNPs remained for further analyses.

Analyzing the Association between *OXTR* and Aggression

All analyses were conducted using Mplus (Version 7.2; Muthén & Muthén, 2014). The Mean and Variance adjusted Weighted Least Squares (WLSMV) estimator was used to account for the categorical nature of the *OXTR* SNPs and aggression items (Brown, 2006). Analyses were fit to the data using full-information maximum likelihood (FIML), which allows for missing data and produces less biased parameter estimates compared to listwise and pairwise deletion (Enders & Bandalos, 2001). FIML involves a small modification of the multivariate normal loglikelihood function which allows the Y matrix (an N x K matrix of data) to have different dimensions between observations. A series of Exploratory Structural Equation Models (ESEMs; Asparouhov & Muthén, 2009) of the SNP data in Mplus was conducted to compare models with one through eight factors. The highly correlated nature of the SNPs caused technical problems in model convergence and two SNPs, which were perfectly correlated with many other SNPs in the data, were excluded (rs2270465 and rs888566). We also tested a Confirmatory Factor Analysis (CFA) model in which SNPs loaded onto factors that roughly corresponded to the haplotype blocks derived using Haploview (Barrett et al. 2005). The haplotype structure derived from Haploview included blocks that only comprised one SNP, which indicates that SNP was not in high LD with any other SNPs in the current sample. This CFA model included seven factors that modeled haplotype blocks that included more than one SNP. As such, some SNPs that were included in the ESEMs were excluded from the CFA analyses all together. These SNPs were rs237864, rs2268484, rs1042778, rs237886, rs11131149, rs237856, and rs9827955.

The best fitting model of the ESEMs and CFAs was brought forward to examine the associations between the factors and the latent aggression trait. In the association analyses, SNPs loadings onto latent factors were fixed to the values estimated from the best fitting ESEM model. To adjudicate which ESEM model fit best, we used the RMSEA.LB index (Preacher et al., 2013) which selects the model with the fewest number of factors required to bring the lower bound of the 90% RMSEA confidence interval below .05. This places increased value on model parsimony and controls for the phenomenon in which increasing factors improves model fit, but diminishes the model's interpretability. We have reported the following additional fit statistics: the χ^2 test statistic and its associated degrees-of-freedom (*df*), the Comparative Fit Index, the root mean square error of approximate (RMSEA) and its associated 90% confidence interval, and the weighted root mean-square residual (WRMR).

Four models of the aggression data were tested to estimate how to best characterize the latent aggression construct: a model in which all twelve items of the Dodge and Coie (1987) scale loaded onto a single factor, one in which only the six items of that scale purported to tap reactive and proactive aggression loaded onto a single factor, a two factor model with reactive and proactive aggression factors correlated, and a two factor model in which reactive and proactive factors were orthogonal.

The latent aggression factor(s) were regressed on the latent *OXTR* factor(s) and all covariates in a series of regression analyses. Participants were clustered within families, thus the "CLUSTER" option in Mplus was used to account for non-independence and autocorrelation in the data. The effect sizes for the associations between aggression and *OXTR* and social cognition and *OXTR* were estimated by comparing the percent of variance in the latent aggression factor(s) or social cognitive variables explained by models which included only covariates and models

which included covariates and *OXTR* latent factors. This procedure yielded an R^2 and P-value for the significance of the combined effects of all latent *OXTR* factors on the latent aggression factor over and above the effects of the covariates. Genotype dosage values ranged from 0 (a genotype with no minor alleles) to 2 (a genotype with two minor alleles) with a value of 1 indicating a heterozygous genotype.

Analyzing *OXTR* and Social Cognition

Social cognitive data were only available on a subsample (N=127) of the original sample. This posed several problems that were not seen in the analyses with the full sample. First, decreased sample size reduces the ability to accurately estimate the many model parameters in the five factor *OXTR* model. Second, the decreased sample size increased the likelihood of empty cells in the variance covariance matrix which includes each predictor variable's covariance with every other variable. For instance, the homozygote minor allele is the least common genotype of the three for each SNP. In a smaller sample, the frequency of this genotype decreases dramatically relative to a larger sample. In this situation, the cross classification of two SNPs can include zero participants who are minor allele homozygotes for both SNPs. As such, ESEMs of 1 through 4 factors were estimated in the *OXTR* data for the reduced subsample and the association between *OXTR* and social cognition. These models also included a reduced number of SNPs. 11 SNPs with minor allele homozygote genotype frequency of greater than 9 in the subsample were chosen to reduce the chances of empty cells in the cross classification of two or more SNPs.

Results

Operationalizing *OXTR* and Aggression

A series of ESEMs of the SNP data were conducted to compare the fit of one through eight factor models in which all SNPs loaded onto each factor (See Table 4 for fit statistics and Table 5 for intercorrelations between the five factors). The standard errors of the parameter estimates in models with six factors and above were not able to be computed which indicated that the model was not identified. This could be due to several factors including the high correlations between SNPs due to high LD. Nevertheless, the five correlated factor model emerged as the best fitting model as it was the model with the lowest number of factors that also satisfied the RMSEA.LB index criteria (see Table 1 for factor loadings). The fit from this model was compared to the seven factor CFA model that corresponds to the haplotype blocks in the data. The CFA model fit was poor (χ^2 (279) = 3493.94, CFI = .67, RMSEA = .1 (.1-.12), WRMR = 3.67). As such, the five factor ESEM model was brought forward for association analyses with aggression and social cognition.

Several sensitivity analyses were conducted to test the robustness of the ESEM factor loadings and fit. Eight SNPs were identified as having a very low frequency (less than eight cases) of participants with two minor alleles. First, to test how this might affect model fit, eight alternative five factor ESEM models were run. In each model, one of the SNPs with a low proportion of minor allele homozygotes was removed and all remaining SNPs were included (see Table 4 for fit statistics). The χ^2 value for each model was lower when compared to the value of the five factor model with all SNPs (critical χ^2 (25) = 37.65), although the models cannot be directly compared as they are not nested. The additional fit statistics in the alternative models were nearly identical to the fit of the original model. Second, the heterozygous and homozygous minor allele categories were combined for these eight SNPs such that individuals with a heterozygous and homozygous minor allele genotype both had a value of 1. The factor loadings

for this alternative model were correlated with the factor loadings of the original model to get an overall measure of how much this affected the model. The correlations between the first two factors were small (r = .02 and r = .17, respectively) while the correlations between the third, fourth, and fifth factors were large (all rs = .99). The average correlation across the five factors was moderate (r = .63). Two alternative models were brought forward into the association analyses of *OXTR* and aggression to address the potential impacts of these discrepancies. These included one model in which all eight SNPs with a low proportion of minor allele homozygotes were removed and a model in which the heterozygous and homozygous minor allele genotypes were combined. Results for these analyses are presented along with the main analyses from the original five factor model.

Aggression was operationalized by comparing the fit of four alternative models of the twelve-item Dodge and Coie (1987) aggression scale (see Table 6 for fit statistics and Table 7 for standardized factor loadings). A model with two correlated factors representing reactive and proactive aggression and a model with the same six items loading on a single factor fit best. Both models were carried forward in the association analyses to further test if the relation between *OXTR* and aggression differed by type of aggression or if it was characterized equally well by a single aggression factor.

Associations between *OXTR* and Aggression

Relation of Covariates with Aggression. The relation of seven covariates with the aggression factors were tested. The covariates were proportion of European ancestry, proportion of Hispanic ancestry, age, sex, age squared, the interaction of age and sex, and the interaction of age squared and sex. The proportion of African ancestry was excluded from the model because it was nearly perfectly correlated with proportion of European ancestry. The proportion of Asian

ancestry was excluded because the frequency of Asian individuals was very rare in this sample. A series of models in which the general aggression factor, reactive, and proactive aggression were separately regressed on all covariates were run to test which covariates were significantly related to aggression. The first model included all terms and subsequent models dropped one covariate at a time beginning with the highest order term (the interaction of age squared and sex) and continuing through the interaction of age and sex, age squared, the two ethnicity variables, sex and then age.

Age squared (β = -.01 (.003), $p<.001$), sex (β = -.35 (.1), $p<.001$), and age (β = -.07 (.01), $p<.001$) were significantly related to reactive aggression. Age squared (β = -.01 (.004), $p<.01$), the interaction of age and sex (β = -.08 (.04), $p<.05$), sex (β = -.34 (.12), $p<.01$), and age (β = -.04 (.02), $p<.05$) were significantly related to proactive aggression. The standard errors of the parameters in a model in which the association between *OXTR* and the reactive and proactive aggression factors was simultaneously estimated and the interaction of age and sex was included only in the proactive aggression model could not be estimated. The contribution of this interaction term to the variance of proactive aggression was small, so the term was excluded from further analyses. The same procedure was used to determine which covariates should be included in the association analyses with the one factor model of aggression. Age squared (β = -.01 (.003), $p<.001$), sex (β = -.35 (.1), $p<.001$), and age (β = -.06 (.01), $p<.001$) were significantly related to the general aggression factor. Covariates that were significantly related to the aggression factors in these models were included in subsequent analyses. None of the ethnicity variables were significantly related to reactive or proactive aggression, but minor allele frequency can vary greatly between different ethnic populations. To ensure that the association between *OXTR* and the aggression factors were not affected by ethnicity, alternative association

analyses that included the ethnicity covariates were run in sensitivity analyses and are reported below.

Effects of *OXTR* on Aggression. The simultaneous effects of the five latent *OXTR* variables on reactive and proactive aggression were tested while controlling for the previously described covariates by examining the change in variance explained in the latent aggression variables when the five *OXTR* variables were included in the model versus a model in which they were excluded. The associations between *OXTR* and the latent reactive and proactive aggression variables were both significant (R^2 = 1.2% and 5.8%, ps<.001, respectively) as was the association between *OXTR* and the general aggression factor (R^2 = 1.8%, p<001). Table 9 includes the incremental contribution of *OXTR* in the variance of aggression in the primary and alternative models. *OXTR* was differentially associated with reactive and proactive aggression such that *OXTR* accounted for more variance in proactive compared with reactive aggression. To further test this association, the regression coefficients across reactive and proactive aggression on *OXTR* were equated. The mode in which the regression coefficients were equated fit worse (χ^2 = 1089.43, RMSEA = .03 (.02, .03), CFI = .97, WRMR = 1.25) compared to the model in which the regression coefficients were freely estimated (χ^2 = 1048.28, RMSEA = .03 (.02, .03), CFI = .97, WRMR = 1.25) although the chi square difference test was not significant ($\Delta\chi^2$ = 41.2 (44), p >.05).

Alternative Models of the Effects of *OXTR* on Aggression. The effects of the five latent *OXTR* variables on reactive and proactive aggression as well as on a general aggression factor were tested in sensitivity analyses of three alternative models to test the robustness of the five factor model of *OXTR* and the associations mentioned above. The first model included the ethnicity covariates proportion of European ancestry and proportion of Hispanic ancestry. The

same method was used in which the difference between R^2 in the full model including *OXTR* and covariates and the model including only the covariates was determined to be the amount of incremental variance accounted for by the *OXTR* factors. *OXTR* accounted for 1.6% of the variance in the general aggression factor, which was very similar to the R^2 accounted for in the primary *OXTR* model. The association between *OXTR* and reactive aggression was also significant (R^2 = 1.3%, p<.001) and of similar magnitude to the effect size found in the primary *OXTR* model. The association between *OXTR* and proactive aggression was larger in magnitude compared to the primary model (R^2 = 8.7%, p<.001).

The second alternative model was one in which all SNPs with a homozygote minor allele genotype frequency less than eight in the sample were removed from analyses. In this model, *OXTR* accounted for 2.7% of the variance in the general aggression factor (R^2 = .027, p<.001) and 3.7% and 5.8% of the variance in reactive and proactive aggression respectively (ps<.001).

The final alternative model was one in which the heterozygote and homozygote minor allele genotype categories were combined for SNPs with a homozygote minor allele genotype frequency less than 8 in the sample. In this model, *OXTR* accounted for 2.5% of the variance in the general aggression factor (R^2 = .025, p<.001) and 3.2% and 6.1% of the variance in reactive and proactive aggression respectively (ps<.001).

Operationalizing *OXTR* and Social Cognition

A series of ESEMs of the SNP data were conducted to compare the fit of one through five factor models in which all SNPs loaded onto each factor. The fit statistics for these models are presented in Table 10. The three factor model fit well and met the RMSEA.LB criteria. The five factor model also fit well, but was not used in further analyses as it included factors onto

which no SNPs loaded significantly. Because these hypotheses were primarily exploratory, the models of *OXTR* with one through four factors in the subsample were carried forward in the association analyses between *OXTR* and social cognition.

Associations between *OXTR* and Social Cognition

The Relation of Covariates with Social Cognition. The relation of the seven covariates with the eight social cognitive variables were tested. The covariates were proportion of European ancestry, proportion of African ancestry, age, sex, age squared, the interaction of age and sex, and the interaction of age squared and sex. The proportion of Hispanic ancestry was excluded from the model because it was perfectly correlated with proportion of European ancestry. The proportion of Asian ancestry was excluded because the frequency was so rare in this subsample. In a procedure similar to the one used to test the associations of the covariates and aggression factors, a series of models in which the eight social cognitive variables were separately regressed on all covariates was run to test which covariates were significantly related to social cognition.

The percent of correct responses of all four emotions (happy, sad, fearful, and angry) were only significantly associated with age ($\beta = .22$, $p<.01$, $\beta = .3$, $p<.001$, $\beta = .27$, $p<.01$, $\beta = .28$, $p<.01$ respectively). The number of commission errors in the happy emotion category was significantly associated with proportion of European ancestry ($\beta = .09$, $p<.05$), the squared age term ($\beta = 1.58$, $p<.01$) and age ($\beta = -.23$, $p<.05$). The number of commission errors in the sad emotion category was significantly associated with proportion of European ancestry ($\beta = .06$, $p<.05$), the squared age term ($\beta = 1.48$, $p<.01$), and age ($\beta = -.25$, $p<.001$). Commission errors for fearful emotions were significantly associated with proportion of European ancestry ($\beta = .06$, $p<.05$), age squared ($\beta = 1.4$, $p<.05$), and age ($\beta = -.28$, $p<.01$). The number of commission errors for the angry emotion category was significantly associated with the proportion of

European ancestry (β =.1, p<.01) and the interaction of age and sex (β = 1.28, p<.001). Although not significantly associated with the number of commission errors for anger, age and sex were also included in this model, because the higher order interaction term was included.

Effects of *OXTR* on Social Cognition. The simultaneous effects of the latent *OXTR* factor(s) on each of the eight social cognitive variables were tested while controlling for the previously described covariates by examining the change in variance explained in the social cognitive variables when the *OXTR* factor(s) were included in the model versus a model in which they were excluded. A series of models that tested the association of *OXTR* with the social cognitive variables in which *OXTR* was modeled as one, two, three, and then four latent factor(s) were run and the results are presented below (see also Table 11).

One Factor Model of OXTR. The associations between *OXTR* and the percent of correct responses for happy, sad, angry, and fearful emotions were not significant (R^2 = 0%, 0%, .1%, and .1%, ps>.05, respectively). The associations between *OXTR* and the number of commission errors for happy, angry, and fearful emotions were not significant (all R^2s = 0%, p>.05). In contrast, the association between *OXTR* and the number of commission errors for the sad emotion category was significant (R^2 = 6.7%, p<.001).

Two Factor Model of OXTR. The associations between *OXTR* and the percent of correct responses for happy and angry emotions were not significant (R^2 = 1.7% and .1% ps>.05, respectively). In contrast, the associations between *OXTR* and the percent of correct responses for the sad and fearful emotions were significant (R^2 = 5.4% and 3.7% ps<.01, respectively). There were also significant associations between *OXTR* and the number of commission errors for the happy (R^2 = 2.6%, p<.05), sad (R^2 = 24.4%, p<.001), and angry (R^2 = 4.6%, p<.001),

emotion categories. The association between *OXTR* and the number of commission errors in the fearful emotions category was not significant (R^2 = 1.6%, p=.16).

Three Factor Model of OXTR. The associations between *OXTR* and the percent of correct responses for happy and angry emotions were also not significant in this model (R^2 = 1.7% and .6%, ps>.05, respectively). There were significant associations between the percent of correct responses in the sad (R^2 = 5.4%, p<.01) and fearful (R^2 = 4%, p<.01) emotion categories. *OXTR* was also significantly associated with the number of commission errors in the happy and angry emotion categories (R^2 = 2.5% p<.05 and 5.8% p<.01 respectively). The associations between *OXTR* and the number of commission errors made in the sad and fearful emotion categories were not significant (R^2 = .3% and 1.5% ps>.05, respectively).

Four Factor Model of OXTR. The associations between the percent of correct responses for the happy and angry emotions were also not significant in this model (R^2 = 1.6% and .8%, ps>.05, respectively). *OXTR* was again significantly associated with the percent of correct responses in the sad and fearful emotion categories in this model (R^2 = 6.3% and 4.3%, ps<.01, respectively). The association between the number of commission errors made in the fearful emotion category was not significant (R^2 = 1.4%, p>.05), but there were significant associations between *OXTR* and the number of commission errors in the happy (R^2 = 2.1%, p<.05), sad (28.1%, p<.001), and angry (R^2 = 8.7%, p<.01) emotion categories.

Sensitivity Analyses with Missing Data

To assess the robustness of the associations of *OXTR* with aggression and social cognition, the proportion of SNPs with missing genotypes, defined as the number of missing genotypes out of the 31 possible genotypes for each participant, was correlated with the

aggression and social cognition outcome variables. The proportion of missingness was not significantly correlated with any of the social cognition variables (see Table 12 for correlation coefficients), but it was significantly, or marginally significantly, correlated with the aggression factors. The correlations between missingness and the general aggression, reactive, and proactive aggression factors were small and positive ($r = .13$, $p = .03$, $r = .13$, $p = .03$, $r = .11$, $p = .09$, respectively). The proportion of missingness was then carried forward as a covariate in the association analyses to test if this relationship spuriously inflated the associations found between *OXTR* and aggression. When the proportion of missing data was included as a covariate in the analyses, *OXTR* accounted for 1.5% of the variance in general aggression ($R^2 = .015$, $p < .01$), and for 2.3% and 6.3% of the variance in reactive and proactive aggression, respectively (ps <.001).

Discussion

The primary goals of this study were to explore the associations of *OXTR* with aggression and social cognition. Previous research implicates *OXTR* in the development of aggression (Smearman et al., Johannson et al., 2012) and social cognition (Skuse et al., 2014; Walum et al., 2012) in humans. It was hypothesized that variation across *OXTR* would be associated with variation in aggression and social cognition. As discussed previously, there are several methodological concerns regarding studies that examine the association between individual SNPs and a phenotype (Sullivan, 2007). We aimed to address these concerns by modeling *OXTR* as a set of latent factors with the genotyped SNPs as factor indicators. This allowed us to simultaneously test the contribution of multiple SNPs across the gene and thus increase power to detect statistical associations.

Multiple models of *OXTR* were tested. Of the ESEMs, the five factor model fit best and met the RMSEA.LB criteria which favors the best fitting and most parsimonious model (Preacher, 2013). The robustness of this five factor model was tested by removing SNPs with a low homozygote genotype minor allele frequency one by one, removing all of these SNPs in the same model, and combining the homozygote minor allele category with the heterozygote category. Each of these modifications improved model fit and so they were carried forward as alternative models of the association between *OXTR* and aggression.

We found a significant association between aggression modeled as a unitary construct and *OXTR* such that *OXTR* accounted for a significant proportion of the variance in aggression over and above the contribution of the covariates. This association held across multiple alternative models including one in which SNPs with a homozygote minor allele genotype frequency of less than eight in the current sample, one in which the homozygote minor allele category was combined with the heterozygote category in these rare SNPs, and one which included ethnicity covariates. These models were included to test the robustness and sensitivity of the best fitting model and associations found between *OXTR* and aggression.

Significant associations were also found between reactive and proactive aggression and *OXTR*, which also held across the multiple alternative models. This is consistent with a previous lab study in a different sample that tested the association between *OXTR* and aggression by modeling *OXTR* as a series of latent factors (LoParo et al., 2015). This suggests that *OXTR* is associated with aggression in children and that this association was not spuriously significant due to non-normally distributed variables and SNPs with low minor allele frequency. *OXTR* was also differentially associated with reactive and proactive aggression such that *OXTR* accounted for 2% more variance in proactive aggression compared with reactive aggression. We further tested

this association by comparing the fit of a model in which the regression coefficients between reactive and proactive and *OXTR* were equated. We observed a decrement in model fit, although the chi square difference test was not significant. This gives some credence to the distinction between the two aggression domains, which has previously been questioned (Bushman & Anderson, 2001), although more research is needed to further investigate this finding.

The proportion of variance accounted for by *OXTR* in the aggression factors was distinguishable across the four models. Compared to the primary five factor model, the models in which the SNPs with a homozygote minor allele genotype frequency of less than eight in the current sample were removed or combined accounted for more variance in the general aggression factor and in reactive aggression. These differences were not large (between 1and 2.5%), but they may suggest that *OXTR* is slightly better modeled when SNPs with low minor allele frequency are removed. The results from the primary five factor models of *OXTR* and models in which ethnicity covariates were included were comparable for the general aggression and reactive aggression factors. For the model that included ethnicity covariates, *OXTR* accounted for approximately 3% more of the variance in proactive aggression.

One through four factor ESEM models of *OXTR* in the subsample for which social cognitive data were available were tested such that all SNPs loaded onto each factor. The five factor model was excluded from further analyses as it included factors onto which no SNPs loaded significantly. Analyses of the associations between *OXTR* and social cognition were primarily exploratory and, as such, all four remaining models of *OXTR* were carried forward to test the associations between *OXTR* and the social cognitive variables. By doing so, we were able to examine both the incremental contribution of *OXTR* to the variance in social cognition and the effect of the *OXTR* model in estimating this contribution.

The one factor model of *OXTR* did a poor job of characterizing the variance in almost all the social cognitive variable. The percentage of variance explained in the number of commission errors in the sad emotion category was significant, but this association is almost certainly over-estimated as *OXTR* accounted for upwards of 20% of the variance in this variable in the subsequent models, which likely also represents an inflated effect. The percentage of variance in the social cognitive variables across the two, three, and four factor models was, for the most part, comparable and consistent. Associations that were significant in the two factor model were also likely to be significant in the subsequent three and four factor models. Although the variance explained by the *OXTR* factors was similar across the models (differences of .01%-.3.9% for most variables), the percentage of variance increased slightly as the number of factors included increased. It is unclear if this is a spurious effect of including more factors in the model or if more factors better characterized the variance across *OXTR.* Examination of this question is outside the scope of this paper and further research should be done to explore this, perhaps with simulated data. The exception to this pattern is found in the number of commission errors in the sad emotion category variable. As mentioned, the one factor model of *OXTR* accounted for 6.7% of the variance in this variable. The two and four factor models accounted for 24.4% and 28.1% of the variance, respectively. However, in the three factor model, *OXTR* accounted for only .3% of the variance, a contribution that was not statistically significant. The finding that *OXTR* accounts for over 20% of the variance in this variable almost surely represents an inflated effect, a point that becomes even more likely when one examines the discrepancies between the variance accounted for by the two and four factor models of *OXTR* and the three factor model.

Taking these uncertainties into account, the results of the association analyses between *OXTR* and the social cognitive variables should be interpreted with caution and as preliminary.

Nonetheless, the hypotheses that *OXTR* would be significantly associated with social cognition were consistently supported for the percent of correct responses in the sad and fearful emotion categories and the number of commission errors in the happy and angry emotion categories. Interestingly, *OXTR* does not appear to account for variance in the ability to correctly identify any particular emotion. This provides some initial evidence that the Oxytocin Receptor Gene accounts for variation in human social cognitive abilities in general.

Implications for Gene Based Tests using Structural Equation Modeling

The results of these analyses have several methodological implications for gene based tests in a latent variable framework. First, the model was sensitive to the inclusion of SNPs with low minor allele frequencies, as demonstrated by the change in model fit when a single SNP with low homozygote minor allele frequency was removed. Models that excluded these SNPs fit better than the full model and explained more variance in the three aggression factors. This may indicate that models that exclude SNPs with low MAF better characterize variation in *OXTR* and are more stable. This could also be due to the structural equation modeling (SEM) platform, which favors normally distributed variables.

One potential drawback of using SEM to model variation in a gene is the highly correlated nature of SNP data. SNPs that are in very high LD with each other are often nearly perfectly correlated which causes technical issues in model-fitting and convergence. It could be that excluding SNPs in high LD with each does not diminish the model's ability to capture variation in an outcome variable, but it is still possible that important variation is being lost by using a latent variable approach as we are not able to examine the contribution of any individual SNP. There are several methodological factors left to consider, but results from this study may

provide evidence that structural equation modeling can be used to capture variation in a gene better than testing single SNPs individually.

Limitations and Future Directions

There are several limitations that should be considered when interpreting the results of the current study. First, as mentioned previously, there was a high rate of missing data in the SNP genotypes. There are several different mechanisms of missingness, including missing not at random, missing at random, and data that is missing completely at random. Data that is missing not at random is missing for a systematic reason that is not measurable given available data. In other words, it is missing in association with a specific variable, but that variable is not measured in the data (as described in Little, Lang, Wu, and Rhemtulla, 2016). Data is missing at random when the pattern of missingness is systematic and associated with a variable that is measured in the data. Finally, data that is missing completely at random has missingness patterns that are uncorrelated with any variables included in the dataset or with any unmeasured variables. In this case, the missingness does not follow a pattern and is not associated with any particular variables.

The proportion of missing data was found to be significantly, or marginally significantly, correlated with the general, reactive, and proactive aggression factors. This indicates that the data is likely missing not at random, because the pattern of missingness is systematic and associated with several variables measured in the data. To examine the effects this association may have had on the association analyses with *OXTR* and aggression, sensitivity analyses using proportion of missing data as a covariate were conducted. The amount of variance in the aggression variables explained by *OXTR* was very similar in magnitude compared to the full and alternative model association analyses. This suggests that although missing data was associated with

aggression, this association may not have biased the results of the analyses between *OXTR* and aggression.

The utilization of a gene-based approach for testing the association between *OXTR* and aggressive and social cognitive means that we were unable to infer the specific nature of the associations. Specifically, we were unable to examine the direction of effects or identify risk alleles in particular SNPs. This method is meant to serve as an initial test of the contribution of *OXTR* to variance in aggression and social cognition, which has been accomplished in this study. Because this gene-based approach was used, this effect is more likely to be replicated across samples that genotype different SNPs. In addition, candidate gene studies that test the association of only a few SNPs are also unable to identify specific causal variants as the SNP that emerges as significant is just as likely to be in high LD with the true causal variant.

Another limitation of this study is sample size. Studies of the associations between SNPs and behavioral variables require very large sample sizes as the effect sizes of these associations are typically quite small. This was an issue in the association studies with the social cognitive variables which included only 127 participants. The significant results in both sets of association analyses with relatively small sample sizes likely means that these effects are inflated estimates of the true effect in the population. The small sample size may also have limited our ability to detect significant associations between certain social cognitive variables and *OXTR.* Future research will focus on replicating these results in a larger and more diverse sample that includes cohorts from across the United States and Europe, a sample size of nearly 25,000 individuals. This increased sample size will increase power to detect and accurately estimate associations between *OXTR,* aggression, and social cognition. The increased sample size may also increase variation in the *OXTR* SNPs that will limit the number of SNPs that are perfectly correlated with

each other. This may increase the number of SNPs that can be included in the models of *OXTR.* This will have the additional benefit of further examining the effects of including more SNPs in gene-based tests using SEM.

The current investigation utilized a gene-based testing approach to examine the extent to which *OXTR* contributes to variation in aggression and social cognition in children and adolescents. Our findings suggest that variation in *OXTR* is associated with variation in aggression and social cognition in this sample. These findings should be interpreted with caution and represent preliminary results that require further investigation. Future research will focus on replicating the current study in a larger, diverse group of individuals.

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Table 1. *Description of OXTR SNPs and Standardized Factor Loadings for Best-Fitting Model of OXTR using ESEM.*

SNP	Location (bp)	*OXTR* Factor Structure				
		1	**2**	**3**	**4**	**5**
rs237860	8731445	-.304***	-.061	-.479***	-.009	-.026
rs237864	8731866	-.015	-.062	-.121	-.008	.086
rs2268484	8732264	-.068	.746***	-.439***	.219**	-.001
rs237866	8732443	-.055	-.534***	.713***	.015	.086
rs17049496	8732702	.023	.374***	-.289**	.155	-.089
rs2270463	8733391	-.905***	.018	.032	-.325**	.215
rs6793441	8733537	.128*	-.053	.649***	.093	.147
rs2072582	8733693	.227***	-.166	-.308***	-.139	-.027
rs10490800	8736020	.257*	.774***	.192*	-.024	.025
rs237868	8736476	.780***	.099	-.193**	-.011	-.032
rs4686300	8737062	.539***	-.382***	.015	.026	.008
rs237871	8737712	.869***	.486**	-.055	-.124	-.012
rs151462	8739921	.793***	.310	-.059	-.169*	.021
rs6777678	8745375	-.061	.582***	.756***	.008	-.154
rs7629329	8746650	-.390***	-.138	.614***	.075	.067
rs11720238	8749653	-.245***	.079	.924***	-.045	-.207
rs1042778	8752859	.027	.306**	.267***	-.547***	.002
rs237886	8753901	.040	-.064	-.211**	.895***	.127
rs11706648	8754861	.159**	-.251	-.057	-.685***	-.236
rs237887	8755356	-.055*	-.176	-.228**	.939***	.033
rs918316	8756495	-.005	.714***	-.005	-.279*	.710***
rs9840864	8756791	.063	.446***	.028	.085	.960***
rs2268491	8758712	.162*	-.032	-.12	.249**	.707***
rs11131149	8761165	.069	-.175	.419***	-.521***	-.334***
rs237894	8764845	-.103	.115	-.014	-.479***	.343***
rs4564970	8768722	.581***	.043	.089	-.016	.557***
rs1488467	8771545	.839***	-.134	.180	.078	.573***
rs17049547	8783940	.107	.120	.094	.527***	-.585***
rs17365093	8785094	.230	-.005	.018	.857***	-.780***
rs237856	8788370	.008	-.078	-.095	-.444***	.417***
rs9827966	8854430	.138	.356***	.067	.089	.040

Note. Base pair position obtained from the Genome Reference Consortium Human Build 38 patch release 7 (GRCh38.p7) published in 2016. *<.05, **<.01, ***<.001.

Table 2. *MAF in OXTR SNPs by Ancestry*.

SNP	MAF European Ancestry	MAF African Ancestry	MAF in Study Sample	ΔMAF
rs237860	.35	.18	.34	.01
rs237864	.15	.07	.11	.04
rs2268484	.22	.35	.31	.09
rs237866	.43	.08	.4	.03
rs17049496	.02	.29	.05	.03
rs2270463	.22	.23	.02	.20
rs6793441	.35	.42	.3	.05
rs2072582	.19	.16	.12	.07
rs10490800	.07	.19	.07	0
rs237868	.26	.38	.24	.02
rs4686300	.04	.03	.04	0
rs237871	.28	.45	.28	0
rs151462	.33	.47	.35	.02
rs6777678	.22	.41	.22	0
rs7629329	.35	.19	.32	.03
rs11720238	.17	.04	.14	.03
rs1042778	.38	.32	.40	.02
rs237886	.46	.42	.43	.03
rs11706648	.32	.13	.31	.01
rs237887	.46	.24	.41	.05
rs918316	.05	.24	.08	.03
rs9840864	.22	.47	.24	.02
rs2268491	.11	.27	.11	0
rs11131149	.38	.34	.42	.04
rs237894	.29	.08	.25	.04
rs4564970	.09	.26	.11	.02
rs1488467	.06	.05	.04	.02
rs17049547	.06	.22	.09	.03
rs17365093	.20	.18	.15	.05
rs237856	.50	.03	.45	.05
rs9827966	.08	.36	.08	0

Note. Minor allele frequency in European ancestry is based on the *Europe: 1000 Genomes Super Population*. Minor allele frequency in African ancestry is based on the *Africa: 1000 Genomes Super Population.* The ΔMAF column represents the difference between the MAF in the 1000 Genomes European sample and the current study sample.

Table 3. *Call Rate for Each SNP.*

SNP	SNP Call Rate
rs237860	51.7%
rs237864	41.4%
rs2268484	51.5%
rs237866	51.8%
rs17049496	51.8%
rs2270463	54.5%
rs6793441	31.6%
rs2072582	47.5%
rs10490800	56.1%
rs237868	42.6%
rs4686300	50.6%
rs237871	42.5%
rs151462	48.7%
rs6777678	52.4%
rs7629329	45.3%
rs11720238	54.2%
rs1042778	53.3%
rs237886	48.9%
rs11706648	46.4%
rs237887	51.6%
rs918316	53.4%
rs9840864	53.6%
rs2268491	55.8%
rs11131149	51.7%
rs237894	51.3%
rs4564970	39.5%
rs1488467	51.6%
rs17049547	53.4%
rs17365093	13.0%
rs237856	50.0%
rs9827966	53.8%

Table 4. *OXTR ESEM Model Fit Statistics.*

Model	χ^2 (df)	CFI	RMSEA (90% CI)	WRMR
1 Factor	4218.7*** (434)	.8	.09 (.09-.09)	3.94
2 Factors	2591.23*** (404)	.89	.07 (.07-.07)	2.78
3 Factors	1975.23*** (375)	.92	.06 (.06-.07)	2.18
4 Factors	1492.54*** (347)	.94	.06 (.05-.06)	1.74
5 Factors	1158.06***1 (320)	.96	.05 (.05-.05)	1.44
Alternative Models				
rs2270463 removed	1017.87*** (295)	.96	.05 (.04-.05)	1.35
rs237871 removed	1008.98*** (295)	.96	.05 (.04-.05)	1.37
rs6777678 removed	994.94*** (295)	.96	.05 (.04-.05)	1.35
rs11720238 removed	1090.23*** (295)	.96	.05 (.05-.05)	1.44
rs237887 removed	1043.03*** (295)	.89	.05 (.05-.05)	1.41
rs9840864 removed	939.44*** (295)	.97	.05 (.04-.05)	1.31
rs1488467 removed	1038.78*** (295)	.96	.05 (.05-.05)	1.38
rs17365093 removed	1014.96*** (295)	.96	.05 (.04-.05)	1.37
Heterozygotes and Minor Allele Homozygotes combined	955.94*** (320)	.97	.04 (.04-.05)	1.29
Rare SNPs Removed	437.65*** (148)	.99	.04 (.04-.05)	.96

Note. ***p<.001

Table 5. *Correlations among the Five OXTR Factors*.

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Factor 1					
Factor 2	-.05				
Factor 3	-.13*	.03			
Factor 4	.02	-.17	.12		
Factor 5	-.15*	-.19*	.05	.34***	

Note. *p<.05, **p<.01, ***p<.001.

Table 6. *Aggression CFA Fit Statistics*.

Model	χ^2 (df)	CFI	RMSEA (90% CI)	WRMR	rRP
1 factor with 12 items	165.56*** (54)	.99	.06 (.05-.08)	.9	
1 factor with 6 items	26.82*** (9)	.99	.06 (.04-.09)	.62	
2 correlated factors	13.61 (8)	1.0	.04 (0-.07)	.42	.91
2 uncorrelated factors	1366.65*** (9)	.48	.54 (.52-.57)	6.81	

Note. ***<.001. rRP is the correlation between the reactive and proactive aggression factors.

Table 7. *Factor Loadings for the Two Best Models of Aggression.*

Item	General Aggression	Reactive Aggression	Proactive Aggression
Item 2	.81***	.82***	
Item 6	.81***		.76***
Item 7	.82***	.83***	
Item 8	.74***		.84***
Item 9	.82***	.83**	
Item 12	.89***		.91***

Note. ***p<.001

Table 8. *Standardized Regression Coefficients for the Aggression Factors on the OXTR Factors.*

***OXTR* Factor**	**General Aggression β (SE)**	**Reactive Aggression β (SE)**	**Proactive Aggression β (SE)**
OXTR1	-.12 (.07)	-.13 (.07)	-.1 (.07)
OXTR2	-.04 (.08)	-.01 (.08)	-.08 (.1)
OXTR3	.05 (.06)	.06 (.07)	.04 (.08)
OXTR4	-.08 (.07)	-.01 (.07)	-.21* (.09)
OXTR5	.08 (.07)	.04 (.07)	.15 (.09)

Note. *p<.05

Table 9. *Variance Explained by OXTR and Covariates.*

	R^2 Full Model	R^2 Covariates Only	Difference	Significance
5 Factor Model				
One Aggression Factor (6 items)	.165	.147	.018	F (5, 628) = 14.96, p<.001
Reactive Aggression (3 items)	.165	.153	.012	F (5, 628) = 9.0, p<.01
Proactive Aggression (3 items)	.170	.112	.058	F (5, 628) = 44.02, p<.001
5 Factors Rare SNPs Removed				
One Aggression Factor (6 items)	.174	.147	.027	F (5, 628) = 20.59, p<.001
Reactive Aggression (3 items)	.139	.102	.037	F (5, 628) = 27.07, p<.001
Proactive Aggression (3 items)	.195	.137	.058	F (5, 628) = 45.39, p<.001
5 Factor Rare SNP Categories Combined				
One Aggression Factor (6 items)	.172	.147	.025	F (5, 628) = 19.02, p<.001
Reactive Aggression (3 items)	.134	.102	.032	F (5, 628) = 23.28 p<.001
Proactive Aggression (3 items)	.198	.137	.061	F (5,628) = 47.92 p<.001
Ethnicity Covariates Included				
One Aggression Factor (6 items)	.166	.15	.016	F (5, 628) = 12.09, p<.001
Reactive Aggression (3 items)	.166	.153	.013	F (5, 628) = 9.82. p<.01
Proactive Aggression (3 items)	.207	.120	.087	F (5, 628) = 42.9, p<.001

Table 10. *OXTR ESEM Model Fit Statistics in the Subsample.*

Model	χ^2 (df)	CFI	RMSEA (95% CI)	WRMR
1 Factor	167.23*** (44)	.76	.15 (.13-.18)	1.71
2 Factors	82.14*** (34)	.91	.22 (.08-.14)	.94
3 Factors	34.58 (25)	.98	.06 (0-.1)	.53
4 Factors	15.40 (17)	1.0	0 (0-.08)	.29
5 Factors	5.00 (10)	1.0	0 (0-.05)	.16

Note. ***p<.001

Table 11. *Associations of OXTR and Social Cognition in 1-4 Factor Models of OXTR.*

Social Cognitive Variable	1 Factor R^2	2 Factors R^2	3 Factors R^2	4 Factors R^2
Percent Correct Happy	0	.017	.017	.016
Percent Correct Sad	0	.054**	.055**	.063**
Percent Correct Angry	.001	.001	.006	.008
Percent Correct Fear	.001	.037**	.040**	.043**
Commission Errors Happy	0	.026*	.025*	.021*
Commission Errors Sad	.067**	.244***	.003	.281***
Commission Errors Angry	0	.046**	.058**	.087**
Commission Errors Fear	0	.016	.015	.014

Note. The contribution of the *OXTR* factors to the variance in the social cognitive variable was calculated by subtracting the amount of variance accounted for by *OXTR* and covariates minus the variance accounted for by just the covariates. *p<.05, **p<.01, ***p<.001.

Table 12. *Correlations between Outcome Variables and Proportion of Missing Data.*

	Proportion of Missing Data r (p value)
Percent Correct Happy	-.05, p = .58
Percent Correct Sad	-.09, p = .34
Percent Correct Angry	-.06, p = .55
Percent Correct Fearful	-.08, p = .37
Commission Errors Happy	.03, p = .74
Commission Errors Sad	-.02, p = .85
Commission Errors Angry	.09, p = .32
Commission Errors Fearful	.04, p = .64
General Aggression	.13, p = .03
Reactive Aggression	.13, p = .03
Proactive Aggression	.11, p = .09

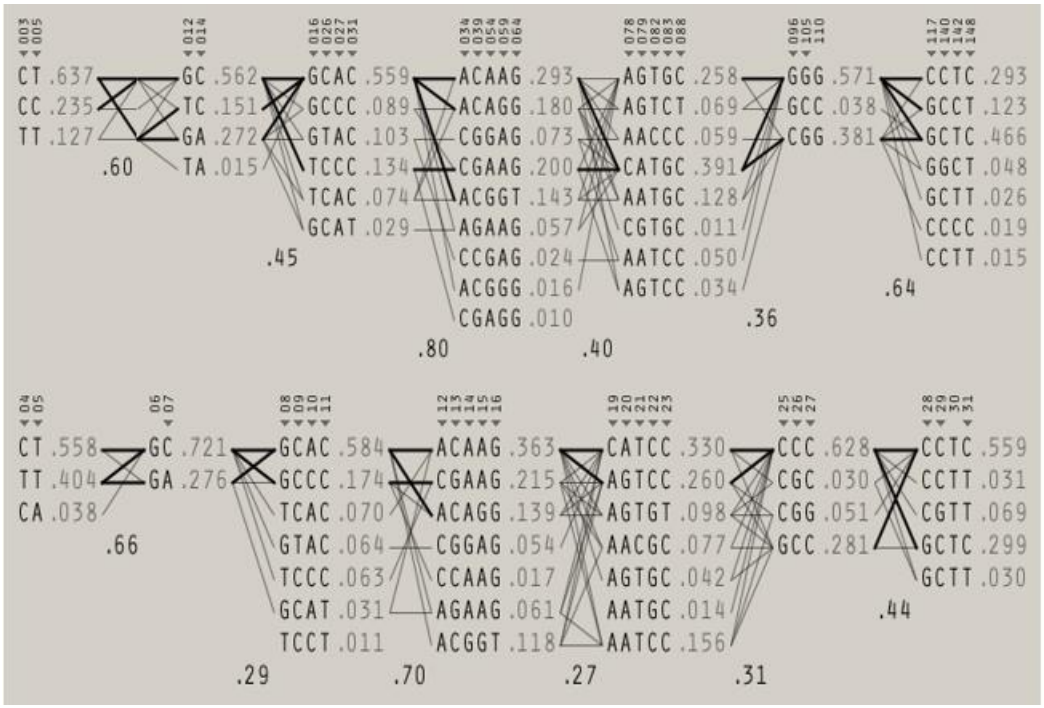

Figure 1. Haplotype frequencies for each haplotype in the two datasets; the HapMap frequencies are on the top and the sample data are below.

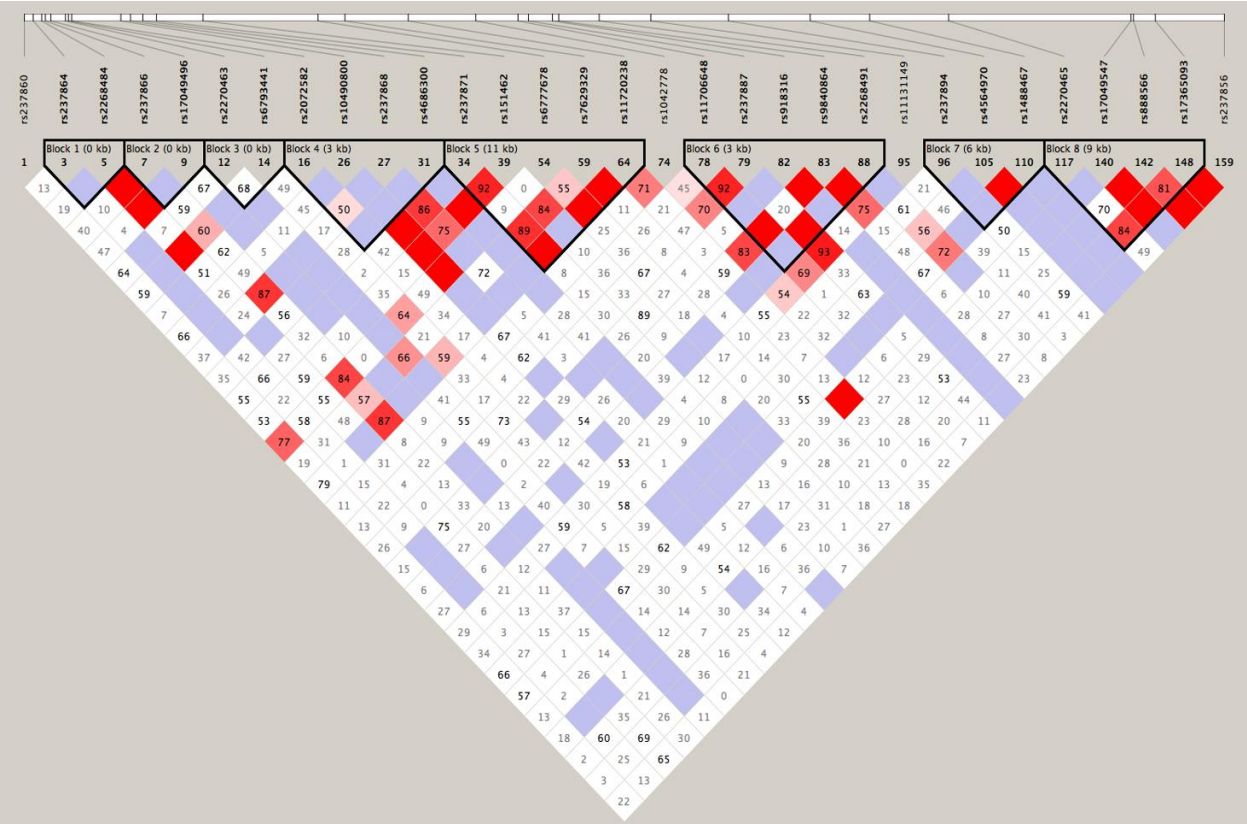

Figure 2. Linkage disequilibrium (LD) map for the 33 oxytocin receptor gene single nucleotide polymorphisms (SNPs) in the current study sample. Boxes are shaded according to the D' values of the corresponding SNPs (red, D'=1; white, D'=0). The numbers in the boxes refer to D' values.

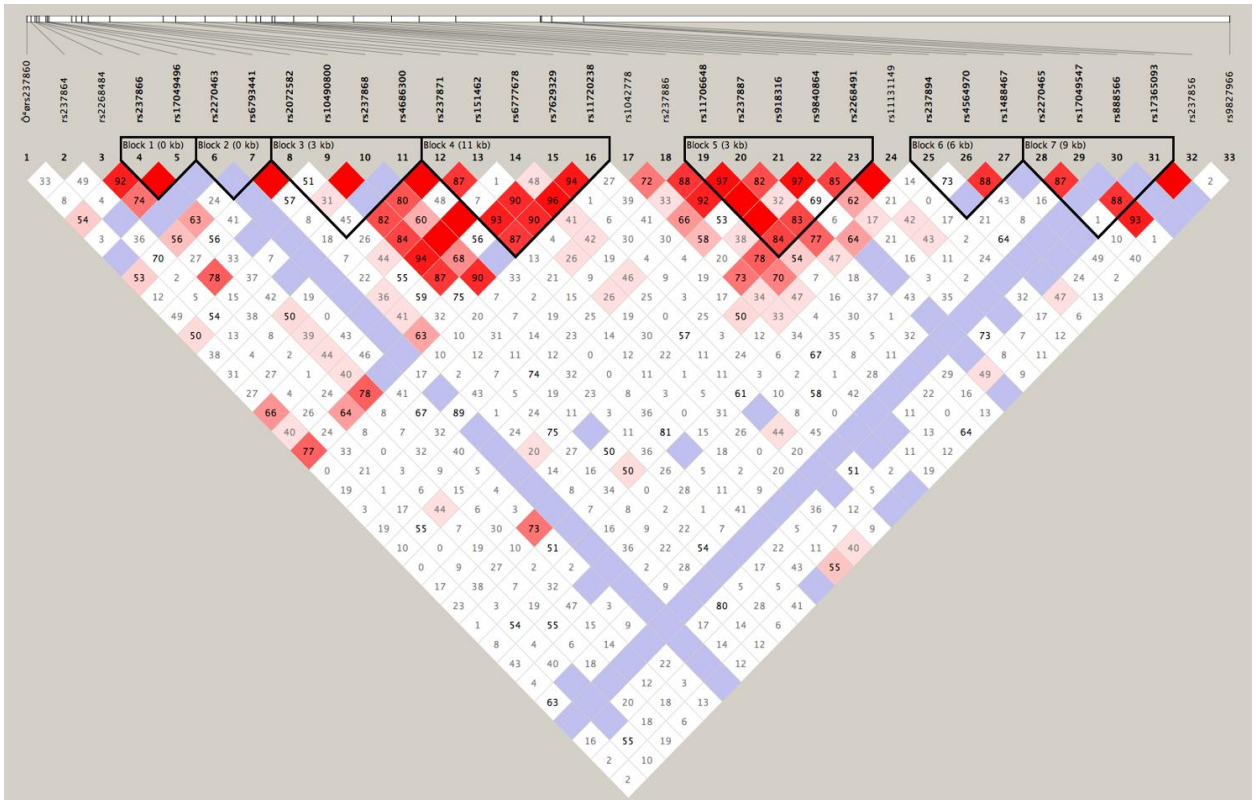

Figure 3. Linkage disequilibrium (LD) map for the 33 oxytocin receptor gene single nucleotide polymorphisms (SNPs) in the HapMap reference sample. Boxes are shaded according to the D' values of the corresponding SNPs (red, D'=1; white, D'=0). The numbers in the boxes refer to D' values.