Behavior Genetics
https://doi.org/10.1007/s10519-020-09996-6

ORIGINAL RESEARCH

The Association of Oxytocin Receptor Gene (*OXTR*) Polymorphisms Antisocial Behavior: A Meta-analysis

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Received: 22 July 2019 / Accepted: 4 February 2020

Abstract
Evidence suggests that the Oxytocin Receptor Gene (*OXTR*) influences human social cognition and behavior. *OXTR* has been investigated in relation to antisocial behavior, but studies examining this association have produced varying results in terms of the magnitude and significance of the association as well as which SNPs are implicated. This meta-analysis, based on 15 samples in 12 studies with a total sample of 12,236 individuals, examined the overall effects and consistency of associations between eight SNPs in *OXTR* and antisocial behavior. Random effects models identified a significant association between rs237887 and antisocial behavior ($r = 0.06$, $p = 0.002$) based on six studies that included a total of 6278 individuals. Sensitivity analyses suggest that these results were robust to exclusion of any individual study and publication bias. Nevertheless, the high levels of heterogeneity and quality control concerns with the original publications lead us to interpret this one significant finding with caution. We conclude that the available literature does not rule out, nor strongly support, an effect of *OXTR* on antisocial behavior.

Keywords Oxytocin receptor gene · Antisocial behavior · Aggression · Meta-analysis · Callous–unemotional traits

Introduction

Antisocial behaviors, which include recurrent actions leading to injury to others or arrest such as violent crime, verbal assault, and destruction of another's social standing (Dodge and Pettit 2003), are key symptoms in a variety of prevalent and debilitating psychiatric disorders. Outside of psychiatric diagnoses, the antisocial phenotype can manifest in a number of personality traits and allied behaviors, including aggression, impulsivity, delinquency, psychopathy, violence, and criminality (Baker et al. 2007). The current meta-analysis includes a variety of these traits and behaviors, which we will refer to collectively as antisocial behavior throughout for the sake of clarity. Given that antisocial behaviors manifest in numerous clinically relevant constructs that overlap phenotypically (Tackett et al. 2013), some authors have hinted at the possibility of shared neurobiological mechanisms that underpin such overlap. One such possibility is the neuropeptide system and, specifically, the Oxytocin Receptor Gene (*OXTR*; Feldman et al. 2016), as variation in this gene has previously been associated with antisocial behavior (Dadds et al. 2014; Hovey et al. 2016). Nonetheless, studies examining this association have produced varying results in terms of the magnitude and significance of associations as well as which SNPs are implicated. In the present study, we reviewed the current literature and meta-analyzed the association of *OXTR* with antisocial behavior.

Antisocial behavior and its etiology

Antisocial behavior is associated with a wide range of clinical phenotypes; thus, we adopted a broad approach to the constructs examined in the meta-analysis, including antisocial behavior, delinquency, aggression, conduct problems, and callous–unemotional traits. Although related, antisocial

Paper presented at the 48th Behavior Genetics Annual Meeting in Boston, Massachusetts Jun 20–23rd, 2018.

Handling Editor: Stephen A. Petrill, Ph.D.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10519-020-09996-6) contains supplementary material, which is available to authorized users.

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Published online: 14 February 2020

behaviors refer exclusively to violent and criminal actions whereas psychopathic traits, which include callousness, impulsivity, and narcissism, are characterized by affective and interpersonal traits (Hare 1996; Hare et al. 1991). We chose to exclude most facets of psychopathy with the exception of callous–unemotional traits, which involves interpersonal manipulation and lack of guilt and empathy. These traits are highly related to antisocial behavior and, in youth, predict the severity of future antisocial behaviors over and above antisocial behavior alone (Frick and White 2008). Behaviors that make up the antisocial phenotype are largely stable over time and predict a number of negative outcomes, including peer rejection, school dropout, and delinquency (Bowker and Etkin 2014; Huesmann et al. 2009; Kokko and Pulkkinen 2005; Moffitt 1993). Exploration of the etiology of these behaviors allows for further examination of how they differ and where they converge.

A relatively recent meta-analysis of twin and adoption studies (Rhee and Waldman 2002) found that estimates of additive genetic influences on aggression and a broad antisocial behavior phenotype were similar ($a^2 = 0.44$ and 0.47, respectively). Across the studies included in this meta-analysis, heritability estimates ranged from 20–64% (Rhee and Waldman 2007). Estimates of the heritability of antisocial behaviors varied as a function of the operationalization of the phenotype, assessment method, age, gender, and the method used to determine zygosity (Rhee and Waldman 2002; Viding et al. 2008a, b). For instance, estimates of additive genetic influence tend to be higher for broad conceptualizations of antisocial behavior compared with a single facet (e.g. aggression, conduct disorder, criminality) and heritability tends to be higher for children and decrease slightly in adults. Similar differences in etiology have been found for antisocial behavior with and without co-occurring callous–unemotional traits, such that the broader phenotype is more highly heritable (Eley et al. 1999; Viding et al. 2008a, b). Further, extant evidence suggests that the different types of antisocial behavior share a common etiology. Multivariate behavior genetic analyses have shown that the etiological components of aggressive and non-aggressive behaviors (Button et al. 2004; Eley et al. 2003) and dimensions of conduct disorder and callous–unemotional traits (Mann et al. 2018) are moderately correlated.

Genome-Wide Association Studies (GWAS) have tested the association of genetic variants with antisocial behavior across the genome. In the largest GWAS of aggression to date, Pappa et al. (2016) found that one SNP (rs11126630) was nearly genome-wide significant and gene-based analyses indicated that variation in *AVPR1a*, a gene that produces a neuropeptide closely linked to oxytocin (Gimpl and Fahrenholz 2001), was associated with aggression. A GWAS of broad-spectrum antisocial behavior (Tielbeek et al. 2017) did not identify any genome-wide significant SNPs, but did find that polygenic risk scores for antisocial behavior calculated from this GWAS predicted Antisocial Personality Disorder in a separate sample, indicating that the continuous antisocial behavior trait shares genetic influences with the categorial diagnosis.

The oxytocin receptor gene and antisocial behavior

Specific *OXTR* polymorphisms have also been associated with antisocial behavior, although results are not consistent across studies. Callous–unemotional traits were associated with rs1042778 in a relatively small (N = 121) sample of children (Dadds et al. 2014). Similarly, a small (N = 236) case–control study of aggressive children and healthy adult controls found that rs1042778 and rs6770632 were associated with aggression in males and females respectively (Malik et al. 2012). Importantly, this study utilized an admixed sample (i.e. included participants of different ethnicities) but did not control for the effects ancestry has on results which arise due to differences in minor allele frequencies in populations of different ancestry (see Table 1 for ancestry information about each study). Although this study includes power analyses that seem to justify the sample size, the power calculations were predicated on an unrealistic expected effect size ($R^2 = 0.033$ for one SNP). GWAS have demonstrated that even pooling the effects of all common SNPs typically explains no more than 10% of the variance in psychiatric or behavioral phenotypes (Schizophrenia Working Group of the Psychiatric Genomics 2014; Visscher et al. 2017). A study using large population-based samples found that rs4564970, rs53576, rs2254298, and rs7632287 were significantly associated with delinquency and aggression in the first sample (N = 2372) but only the association between rs7632287 was replicated in a second sample (N = 1232; Hovey et al. 2016).

Several studies have reported that polymorphisms in *OXTR* interact with environmental variables to predict antisocial behavior (Loth et al. 2014; Waller et al. 2016). A lab study of the association between alcohol consumption and aggression (N = 116) found that rs4564970 interacted with alcohol consumption to predict aggression, although the main effect associations between aggression and the SNPs were not significant (Johansson et al. 2012a, b). In a moderately sized (N = 404) study of children identified as antisocial, the polymorphism rs53576 showed a significant main effect and interacted with social stress in predicting antisocial behavior (Smearman et al. 2015). In a small (N = 197) study of African American youth, the polymorphism rs53576 was found to moderate response to intervention for externalizing disorders (Glenn et al. 2018). In contrast, Sakai et al. (2012) found that none of ten *OXTR* SNPs tested were significantly associated with conduct disorder diagnosis in a moderately sized, admixed sample. Similarly, two other

Table 1 Characteristics of studies investigating associations with *OXTR* and antisocial behavior

Study	Year	Study design	Number of SNPs	Phenotype	Phenotype assessment	Sample size	Proportion male	Ancestry
Johansson A study 1	2012	Continuous	12	Aggression	Lab measure	460[a]	100	European
Johansson A study 2	2012	Continuous	12	Aggression	Lab measure	472	100	European
Johansson B	2012	Continuous	3	Aggression	AQ	3577	42	European
Malik	2012	Case–control	5	Aggression	CBCL and TRF	160 cases, 160 controls	69	Admixed
Sakai	2012	Case–control	10	Conduct disorder	DISC and DIS	419 cases, 193 controls	46	Admixed
Dadds	2013	Case–control	9	CU Traits	APSD and SDQ	121	73	European
Malik	2014	Case–control	9	Aggression	CBCL and TRF	182 cases, 182 controls	65	European
Loth	2014	Continuous	22	Conduct problems	SDQ	1445	48	European
Smearman	2015	Continuous	1	Conduct disorder symptoms	YSR	404	41	European
Hovey study 1	2015	Continuous	8	Delinquency	SRD	2294	43	European
Hovey study 2	2015	Continuous	3	Delinquency	SRD	1206	100	European
Waller	2016	Continuous	3	Antisocial behavior	Self-reported antisocial behavior scale	406	48	European
Glenn	2017	Continuous	2	Aggression	BASC	248	64	African
Kushner	2017	Continuous	1	Aggression	SRQ	307	48	Admixed

AQ buss and perry aggression questionnaire, *CBCL* child behavior checklist, *TRF* teacher report form, *DISC* diagnostic interview schedule for children, *DIS* diagnostic interview schedule, *APSD* antisocial process screening device, *SDQ* strengths and difficulties questionnaire, *YSR* youth self report, *SRD* self-reported delinquency questionnaire, *SRQ* social relations questionnaire

[a]The published sample size for this study was 116, which reflects the sample size available for the interactions published in the original study. The authors were contacted and were able to provide full data, which included larger samples sizes for the main effects (associations between SNP and aggression)

studies found no significant associations of *OXTR* SNPs with aggression (Johansson et al. 2012a, b; Malik et al. 2014).

There are several methodological concerns about candidate gene studies in general that may explain the inconsistencies found in the literature. 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 low statistical power. In a simulation study Sullivan (2007) modeled 10 genetically realistic SNPs in a sample of 500 cases and 500 controls. Under the null model, 31.4% of the simulations produced at least one false positive result. This false positive rate is well above the field's accepted rate of 0.05 and the sample size of 500 cases and 500 controls is large relative to the sample size of most candidate gene studies. Candidate gene by environment interaction studies have been plagued by even more severe methodological concerns, given the much lower statistical power of most interactions (Duncan and Keller 2011; McClelland and Judd 1993; Wahlsten 1991). A review of candidate gene by environment interaction studies found that although 96% of published novel interaction findings were significant, only 27% of the replication attempts met the same significance threshold (Duncan and Keller 2011).

In addition to concerns of statistical power and high rates of false positives, other methodological concerns highlighted previously, such as failing to control for the effects of ancestry and poor operationalization of the phenotype (i.e. dichotomizing a continuous phenotype), are common in this literature. Despite the methodological concerns with these candidate gene studies and the inconsistent reported findings, *OXTR* continues to be linked with aggression and related phenotypes in reviews and chapters examining the etiology of antisocial behavior in humans and animals (e.g. de Jong and Neumann 2017; Kumsta et al. 2013; Li et al. 2015; Winslow and Insel 2002). Thus, an in-depth and critical examination of the relation between *OXTR* and antisocial behavior, as well as the studies that have examined this relation, is warranted.

The present meta-analysis

The primary aims of the current meta-analysis were to estimate the main effects of *OXTR* SNPs on antisocial behavior and to test for heterogeneity in these effects across studies. *OXTR* has been inconsistently associated with antisocial behavior and there is considerable variability across studies

in terms of which SNPs are significant and the magnitude of their effects. Due to the small number of studies currently available, however, we were unable to examine potential moderators that may explain heterogeneity in effects. Finally, we tested the sensitivity of results both to the inclusion of any single study and the influence of publication bias.

Methods and materials

Search and selection strategy

A systematic literature search was conducted by the investigators to find studies relevant to the current meta-analysis published before February 2018. The search focused on articles published in English that examined associations between SNPs in *OXTR* and aggression, conduct disorder, antisocial behavior, or callous–unemotional traits. The search was conducted using three online databases (PsycInfo, Google Scholar, and PubMed). Search terms used to identify studies were an exhaustive combination of terms identifying the gene ("*OXTR*," "*OXTR* gene," and "oxytocin receptor gene") and the phenotype of interest ("aggression," "conduct disorder," "psychopathic traits," "callous–unemotional traits," "CU," "antisocial behavior," and "antisocial traits). All articles returned from these searches were inspected for relevance and duplicates were deleted. Literature reviews and reference sections of these articles were examined for any relevant articles that may have been missing from the original search. In addition, the Google Scholar "cited by" function was used to search for relevant articles that cited the studies already included in the search. Inclusion criteria, described in more detail below, were applied to the final set of articles to determine which studies could be used in the current meta-analysis.

Inclusion and exclusion criteria

The following criteria were applied to the obtained studies to determine their inclusion in the present meta-analysis: (1) the study examined the association between at least one SNP in *OXTR* and antisocial behavior, trait aggression, conduct disorder, psychopathic traits, or callous–unemotional traits in humans; (2) The study reported data from at least one independent sample; (3) the study used a sample of at least 100 participants; (4) the authors reported the main effects of the *OXTR* SNPs on the phenotype or were able to provide this information when requested; and (5) the authors analyzed the association between genotype and phenotype using an additive model or were able to provide this type of analysis when requested.

15 studies with 20 independent samples were initially identified. Two samples in two separate studies (Buffone and Poulin 2014; Dadds et al. 2014) were excluded because the sample size was less than 100 participants (Ns = 59 and 69). The second sample in one of the above studies was excluded because it used a lab measure of aggression in response to a specific stimulus (i.e. an empathy manipulation) and did not include any other measure of antisocial behavior (Buffone and Poulin 2014). Two studies used the same sample, and the study that tested the largest number of SNPs was selected and the other was excluded (Beitchman et al. 2012; Malik et al. 2014). Finally, the authors of one study, which reported only interaction and not main effects, did not respond to email requests for information to calculate the main effects and was thus excluded (Yang et al. 2017). After applying exclusion criteria, 12 studies and 15 independent samples remained for analysis.

Data extraction

The following data were extracted from each article when possible: authors, year of publication, journal in which the study was published, title of article, number of independent samples, sample size(s), name of the sample (if relevant), proportion of males, study design, ethnicities of participants, age range, type of sample (community or clinic-referred), number of and rs#s for the specific *OXTR* SNPs included, phenotype measures and instrument of measurement, and effect sizes of each tested association. There were several instances in which the relevant effect sizes were not available and the authors were contacted via email and asked to provide the requisite information to calculate the effect size. This was the case when only interactions and not main effects were reported and when the authors selectively reported information about only SNPs that were significantly associated with the outcome measure. Some studies also did not report the effect size of the association but reported only the test statistic, group means, or frequencies. Whenever possible, information included in the original publication was used to calculate the effect size. When this was not possible the authors were contacted via email and asked to provide the requisite information or data.

Computation of effect sizes

A correlation coefficient (r) was chosen as the effect size to analyze as it allowed us to preserve the continuous nature of the additive models (i.e., models testing the association of levels of the phenotype across the three possible genotypes). In most cases, a correlation coefficient was not reported in the papers and was thus computed based on available data. When the necessary data were not reported, the authors were contacted and asked to provide the necessary information or data. The effect size computation methods for each study included in this meta-analysis are described below.

Importantly, when the correlation coefficient was obtained from an R^2 value, directionality was determined by arbitrarily choosing a "risk allele" (i.e., the minor allele) for each SNP that remained consistent across studies. In cases where the directionality of the association was already determined (when a beta coefficient was reported, for instance) the sign of the statistic was changed to be consistent with the minor allele representing the "risk allele" (see Supplemental Material available online for more detail).

Meta-analytic methods

Following previous meta-analyses (LoParo and Waldman 2015), SNPs were selected for inclusion in the meta-analysis if they were tested for association with antisocial behavior phenotypes in at least four independent samples. Meta-analyses of all *OXTR* SNPs were conducted separately using the *meta* package in R (Schwarzer 2007). In addition to analyses examining the association of a single SNP at a time, we conducted analyses with multiple SNPs that were in high LD ($r^2 > 0.87$) with each other. In some cases, these "LD groups" included only SNPs that were not studied individually (due to small study number) and in others included a SNP that was studied individually in addition to SNPs in high LD with that SNP. The *Q*-statistic, which is calculated using a χ^2, was used to test the significance of heterogeneity in effect sizes across studies and determine whether a fixed or random effects model was most appropriate. The I^2 indicates the proportion of variance in effect size estimates that is due to heterogeneity (Higgins and Thompson 2002). As significant and substantial heterogeneity was present for all SNPs, fixed effect results are not discussed (see Supplementary Table I for fixed effect results).

Sensitivity analyses

Given the small number of studies available for analysis and the heterogeneity observed in results, sensitivity analyses to test the robustness of the results were warranted. Remove-one analyses, in which one study is systematically removed and the change or stability in results is observed, were conducted to test the sensitivity of analyses to the inclusion of any given study and identify studies that may exert undue influence on the results (Harrison 2011).

Publication bias

Various contemporary publication bias metrics were investigated for use in the current study. Of these, the Copas and Shi method, which models the probability of publication as a function of statistical significance and effect size (Copas 2013; Copas and Shi 2000, 2001), was chosen as it has been shown to outperform other methods in the presence of significant heterogeneity (Schwarzer et al. 2010) and the method uses all available studies, not just those that have significant effects (Simonsohn et al. 2014). These analyses were conducted using the *meta* and *metasens* packages in R (Schwarzer 2007; Schwarzer et al. 2017; Team 2017).

Gene-based test of association

An omnibus gene-based test of association between antisocial behavior and *OXTR* was conducted using random effects model p values. The gene-based test was conducted in KGG, a software package that combines SNP-based p values with estimates of linkage disequilibrium (LD) among the SNPs to estimate the significance of the association between the phenotype and the gene (Li et al. 2011). We used the GATES test, which uses an extended Simes procedure to integrate SNP based p values.

Power analyses

Given concerns about statistical power in candidate gene studies and the influence power in the original studies has on the results of the meta-analysis, power calculations for each study and each SNP were conducted. Study-level power analyses, which take into account sample size, alpha level, degrees of freedom, and percent of variance accounted for in the phenotype (Abecasis 2010), were calculated. Further, given the small number of studies available for analysis, we also conducted meta-analytic power analyses that calculate power as a function of the pooled sample size, effect size, and level of heterogeneity (Valentine et al. 2010).

Results

Meta-analytic associations of *OXTR* with antisocial behavior

Data from 12 studies with 15 independent samples, including one unpublished dataset, were included in this meta-analysis. Information about each study, including study design, population included, and number of SNPs tested can be found in Table 1. Of note, the Emory unpublished dataset refers to a sample of children for whom genotype information on some *OXTR* SNPs were available. There are no published studies examining the association between *OXTR* SNPs and aggression using this Emory sample. In addition, full data from the Johannson et al. (2012a, b) lab study were available and thus the sample size included in this analysis is larger than that reported in the published study. In total, 43 *OXTR* SNPs were analyzed for association with antisocial behavior across studies. Only eight of these SNPs were examined in 4 or more samples and were

therefore included in the individual meta-analyses. Grouping SNPs in high LD with each other in the same analysis allowed us to examine the effects of 6 additional SNPs, for a total of 14 SNPs. Table 2 displays information about each of these eight individual SNPs and four LD groups, the meta-analysis estimated correlation coefficient from random effects models, their p values, and the heterogeneity tests using the *Q*-statistic, its associated p value, and corresponding I^2 value. Forest plots for all eight SNPs are displayed in Figs. 1, 2 and 3.

There was evidence of appreciable heterogeneity for each SNP, with I^2 estimates ranging from 49% (rs237887) to 86% (rs1042778). Although the test of heterogeneity for rs237887 was not significant, there was still evidence of appreciable heterogeneity (*Q* statistic = 9.92, p value = 0.08, $I^2 = 49$). In addition, *Q*-statistics typically are underpowered when the numbers of studies are small, as they are here. This fact, coupled with the heterogeneity in phenotype, assessment, and sample types, lead us to conclude that there may still be appreciable systematic heterogeneity for this SNP. The associated *Q*-statistics for the remaining seven SNPs were all statistically significant ($p < 0.05$).

As shown in Table 2, only the association between rs237887 and antisocial behavior, based on six studies and total sample size of 6278 individuals, was significant ($r = 0.06$, 95% CI 0.02, 0.1, $p = 0.002$) using the random effects model (Fig. 1). As a further test of this association, we included the regression coefficients for rs237887 from the two largest GWAS of antisocial behavior (Pappa et al. 2016; Tielbeek et al. 2017) in the current analysis. The correlation in these GWAS between aggression and rs237887 was near-zero and nonsignificant ($r = 0.003$ $p = 0.94$) whereas the correlation with antisocial behavior was small and nominally significant ($r = 0.09$, $p = 0.045$). These results indicate that the associations for rs237887 were nominally replicated in one study but not the other. The meta-analytic point estimate and p value were relatively unchanged with the inclusion of data from these GWAS ($r = 0.06$, $p = 0.008$), but the level of heterogeneity increased substantially (*Q*-stat = 84.13, p value < 0.001, $I^2 = 92$). We next conducted the gene-based test of association between *OXTR* and antisocial behavior using the SNP p values from the random effects models. As most studies included in these analyses had predominantly European Ancestry samples, all studies were analyzed together. The gene-based p value was significant ($p = 0.02$).

Sensitivity analyses and publication bias

A sensitivity analysis was performed for rs237887, given its significant association, and is presented in Table 3. Effect sizes ranged from 0.05 to 0.07 when each study was removed and the 95% confidence intervals and p values were quite stable. This indicates that the results of this study are robust

Table 2 Meta-analytic results of *OXTR* SNPs with antisocial behavior

SNP	Position	Minor Allele	Number of samples	Total sample size	*Q*-statistic	*Q*-stat p value	I^2	Random-effects correlation	CI (95%)	p value
rs7632287	8,749,760	A	5	5893	27.5	< 0.001	85	− 0.003	− 0.07, 0.07	0.94
rs1042778	8,752,859	T	11	11,364	76.5	< 0.001	86	0.03	− 0.02, 0.09	0.26
rs237885	8,753,857	G	5	2156	11.5	0.02	65	0.03	− 0.04, 0.10	0.42
rs237887	8,755,356	G	6	6278	9.9	0.08	49	0.06	0.02, 0.10	< 0.01
rs2268493	8,759,154	C	4	1549	9.0	0.03	67	− 0.06	− 0.15, 0.02	0.16
rs2254298	8,760,542	A	7	5473	22.7	< 0.001	73	− 0.01	− 0.07, 0.05	0.64
rs53576	8,762,685	A	12	7712	22.8	0.01	56	0.01	− 0.03, 0.05	0.69
rs4564970	8,768,722	C	4	8357	17.4	< 0.001	82	− 0.01	− 0.07, 0.04	0.65
LD groups										
rs7632287 + rs237884 + rs6770632			8	6850	34.5	< 0.001	80	0.01	− 0.05, 0.07	0.71
rs4564970 + rs35413809			5	9789	17.5	0.002	77	− 0.01	− 0.05, 0.03	0.68
rs2268492 + rs2268493			6	3236	22.2	< 0.001	76	− 0.02	− 0.10, 0.06	0.56
rs2254298 + rs2268491			7	5277	2.6	0.85	00	0.01	− 0.01, 0.04	0.28

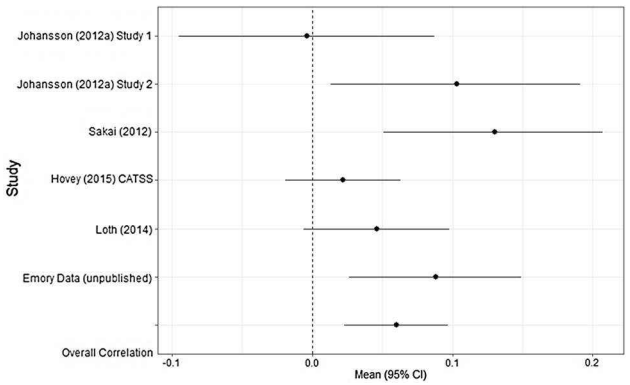

Fig. 1 Forest plot of random effects correlation for rs237887

to the inclusion or exclusion of any given study and are unlikely to be unduly influenced by any individual study.

Publication bias was examined using the Copas and Shi correction method for all eight SNPs included in the meta-analyses. We report the influence of publication bias for all eight SNPs (see Table 4), regardless of significance, but will discuss only the results for rs237887 here. There was no evidence of publication bias for rs237887 as the corrected effect size ($r = 0.06$, $p < 0.001$) was identical to the uncorrected effect size ($r = 0.06$, $p < 0.01$).

Power analyses

We conducted power analyses for each individual study and each SNP. Full results of study-level power analyses are available in Supplementary Table II. In general, power estimates were quite variable across studies and SNPs. For rs237887, the highest study power achieved was 0.83 while the lowest was 0.05 and the median power achieved was 0.40. For rs7632287, power ranged from 0.20 to 0.87, with a median of 0.39. For rs1042778, power ranged from 0.05 to 0.97, with a median of 0.42. For 237,885, power ranged from 0.09 to 0.59, with a median of 0.28. For rs2268493, power ranged from 0.11 to 0.78, with a median of 0.30. For rs2254298, power ranged from 0.05 to 0.99, with a median of 0.09. For rs53576, power ranged from 0.06 to 0.59, with a median of 0.09. Finally, power for rs4564970 ranged from 0.29 to 0.76 with a median of 0.35.

To examine the power of our meta-analyses, we estimated power to detect an association given a small but meaningful effect size of 0.06, observed in the association

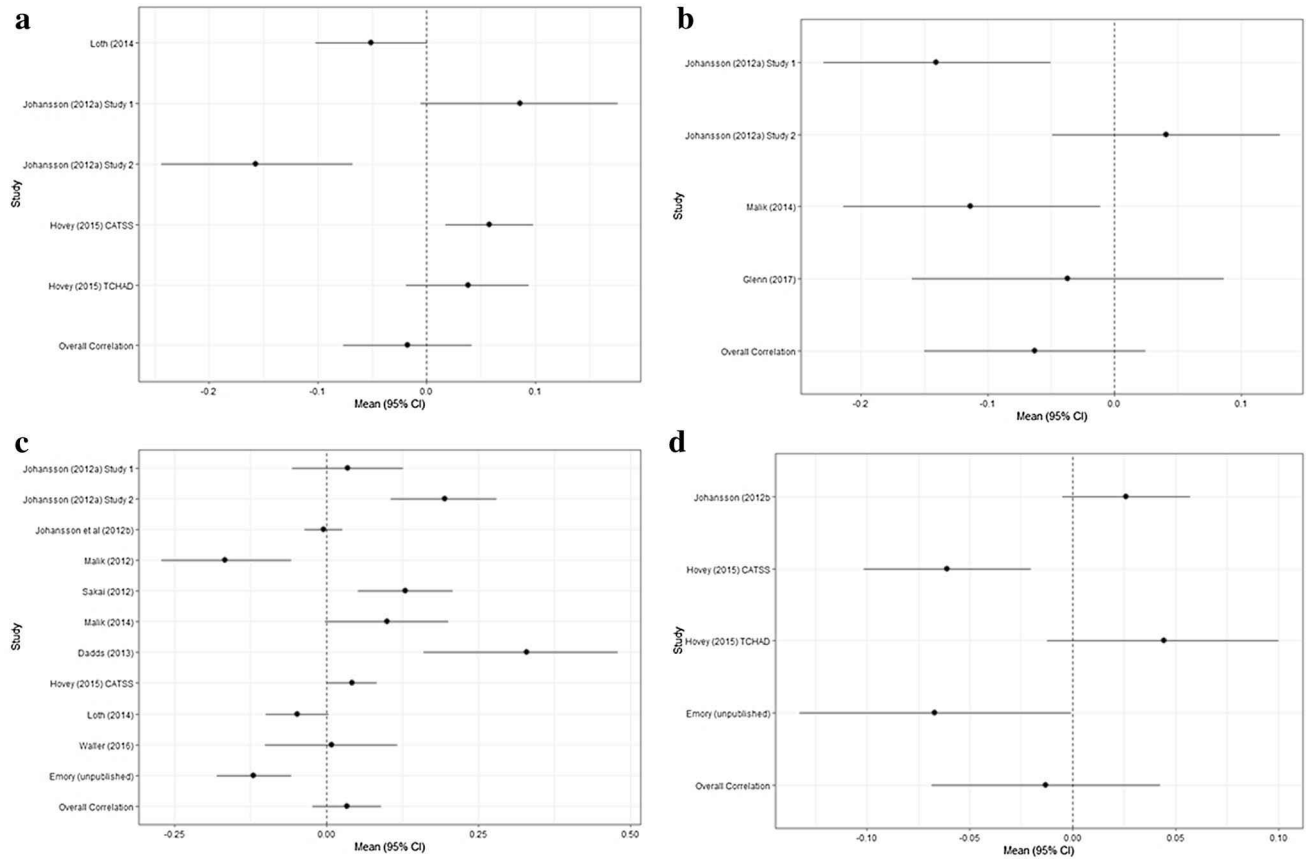

Fig. 2 Forest plots of random effects correlations **a** rs7632287, **b** rs2268493, **c** rs1042778, **d** rs4564976

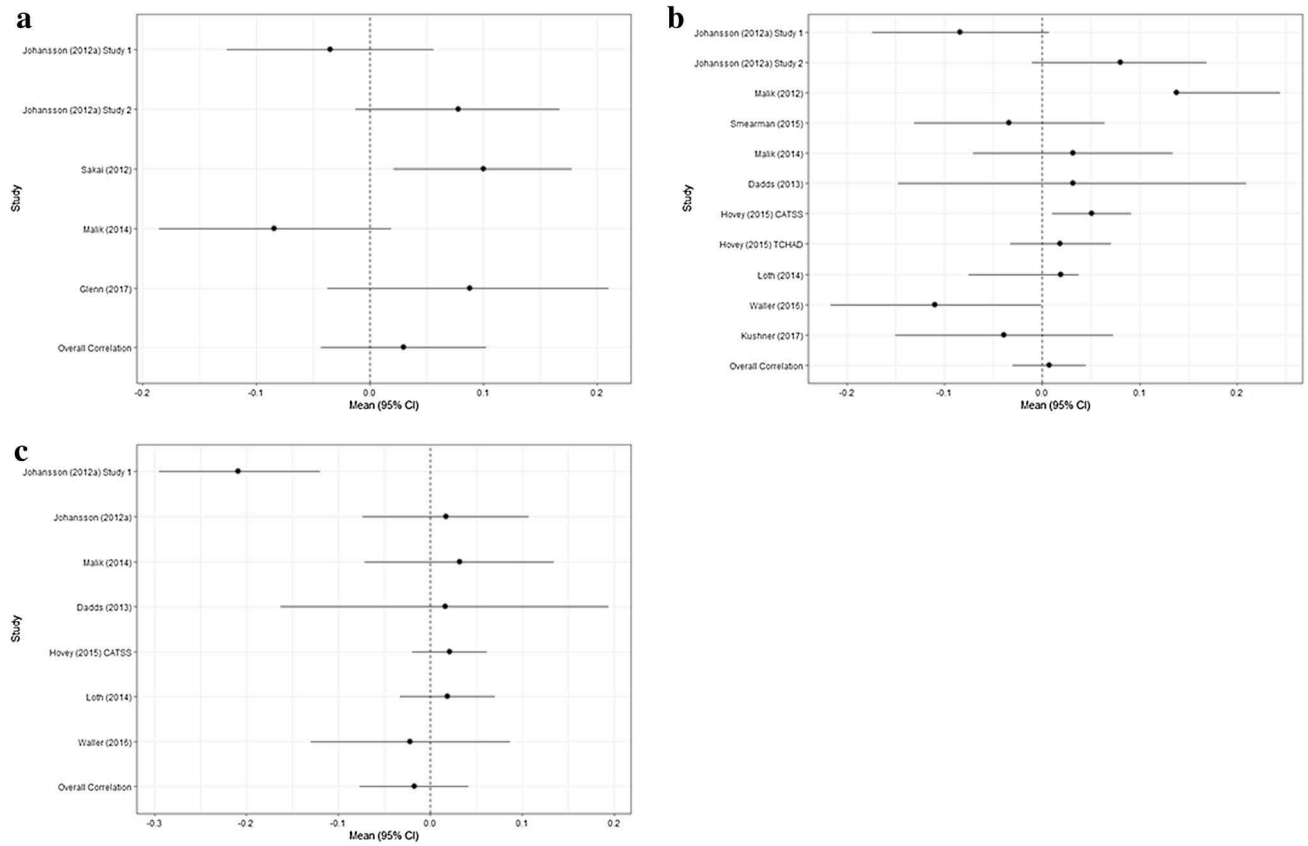

Fig. 3 Forest plots of random effects correlations **a** rs237885, **b** rs53576, **c** rs2254298

Table 3 Remove-one sensitivity analyses for rs237887

Study removed	Random-effects correlation	95% CI	Random effects p value
None	0.06	0.02, 0.10	0.002
Johansson et al. (2012a) study 1	0.07	0.03, 0.11	0.001
Johansson et al. (2012a) study 2	0.05	0.01, 0.09	0.010
Sakai et al. (2012)	0.05	0.01, 0.08	0.010
Hovey et al. (2016) CATSS	0.07	0.03, 0.11	0.001
Loth et al. (2014)	0.07	0.02, 0.11	0.010
Emory data (unpublished)	0.05	0.01, 0.10	0.010

with rs237887, and a small ($I^2 < 50\%$) level of heterogeneity. With two exceptions, the SNPs included in this meta-analysis were adequately powered (0.80 or higher) to detect an effect of that size. Power for rs237885 was 0.40 and 0.30 for rs2268493.

Discussion

We performed meta-analyses of the association of *OXTR* SNPs with antisocial behavior using data from 12,236 individuals drawn from 12 studies and 15 independent samples (although analyses of each individual SNP only included a subset of this total). We found significant associations of antisocial behavior with rs237887, based on six studies and a total sample of 6,278, and the *OXTR* gene as a whole.

Interpretation of findings

The polymorphism rs237887 is located in Intron 3 of *OXTR* and is thus not involved in protein coding. If this SNP is truly indicative of a causal association with aggression, it may be in high linkage disequilibrium (LD) with another protein coding SNP in that region or may be involved in regulatory functions, such as activity in enhancer regions, eQTLs, or transcription factor binding sites (Krivega and Dean 2012; Maurano et al. 2012; Pennacchio et al. 2013). Of note, none of the studies used in this meta-analysis reported significant associations between rs237887; however, after calculating the correlations for rs237887 in the Sakai et al. (2012) and Johansson (2012a Study 2) studies, we found

Table 4 Random effects effect sizes and copas and shi corrected effect sizes

SNP	Random-effects correlation	95% CI	Random effects p value	Corrected random-effects correlation	95% CI	Corrected random effects p value
rs4564970	− 0.01	− 0.07, 0.04	0.65	− 0.01	− 0.06, 0.04	0.60
rs237885	0.03	− 0.04, 0.10	0.42	0.03	− 0.03, 0.10	0.36
rs237887	0.06	0.02, 0.10	< .0.01	0.06	0.02, 0.09	< 0.001
rs53576	− 0.002	− 0.04, 0.03	0.99	0.01	− 0.03, 0.04	0.67
rs2254298	− 0.01	− 0.07, 0.05	0.64	− 0.02	− 0.08, 0.04	0.57
rs1042778	0.03	− 0.02, 0.09	0.26	0.03	− 0.03, 0.09	0.36
rs7632287	− 0.003	− 0.07, 0.07	0.94	− 0.003	0.07, 0.07	0.94
rs2268493	− 0.06	− 0.15, 0.03	0.16	− 0.06	− 0.14, 0.01	0.10

evidence of significant effects. The authors of the Johansson (2012a Study 2) study provided us with raw data, which included a larger sample size than was used in the published study. Thus, the significant finding in our analyses could be due to increased power from the additional participants. It is also possible that the use of a correlation versus a chi-square test (used in both aforementioned studies) may have increased power to detect an association due to the tests' differing sensitivities to the size and distributions of samples. More generally, meta-analyses typically increase power to detect effects relative to individual studies by reducing the standard error of the weighted effect size (Cohn and Becker 2003); thus, it is possible that our meta-analysis increased power to detect this effect. Previous candidate gene studies have shown associations between this SNP and social cognitive abilities (Skuse et al. 2014), empathy (Wu et al. 2012), and Autism Spectrum Disorder (LoParo and Waldman 2015), which may indicate that this SNP affects aggression indirectly through its effect on social cognitive abilities more generally. Indeed, the G allele at rs237887, which was associated with increased antisocial behavior in the current study, has previously been associated with superior social cognition (Skuse et al. 2014). Nevertheless, these studies are plagued by similar methodological and statistical concerns and this potential link should be interpreted with caution. An illustration of these statistical concerns is seen in our study-level power analyses, which demonstrate that power to detect associations with this SNP, as well as the other SNPs we tested, was quite variable across studies and was generally much lower that the ideal cutoff of 0.80. A gene-based test of the meta-analytic p-values for all eight SNPs in *OXTR* suggested that the gene as a whole may be associated with antisocial behavior. However, the null hypothesis of the GATES test is that no SNP in the gene is significant (Li et al. 2011); thus, the gene-based test was guaranteed to be significant given the results for rs237887. Furthermore, sensitivity analyses suggested the magnitude and significance of the observed association between rs237887 and antisocial behavior was robust to the exclusion of any given study and the influence of publication bias. Finally, meta-analytic power analyses showed that, with two exceptions, we were adequately powered to detect a reasonable effect size (r = 0.06), suggesting that these results adequately characterize the available literature on the associations between *OXTR* and antisocial behavior.

The overall effect size for rs237887 was small ($r = 0.06$) relative to effect sizes typically seen in psychology. Nonetheless, this effect size is consistent with those observed in contemporary genetic studies that examine the association of individual SNPs with complex behavioral traits, even in meta-analyses (Ficks and Waldman 2014; LoParo and Waldman, 2015) and GWAS (Schizophrenia Working Group of the Psychiatric Genomics 2014). The importance of studying the association of individual SNPs or genes with a given phenotype is not diminished, but the expectation should be that each variant will have only a very small effect and that, consequently, each phenotype will be influenced by many genetic variants.

That said, the methods and statistical procedures used to test these associations have a significant impact on the interpretation of results, such that careful examination of methodology is warranted before interpreting an effect. For example, as previously noted, candidate gene studies tend to produce inconsistent findings that have not been replicated in better-powered large scale GWAS. The literature linking polymorphisms in *OXTR* and antisocial behavior is no exception. Our review of the literature highlights a number of methodological and statistical concerns with individual studies, including low statistical power, incorrect treatment of admixed samples, and unnecessary dichotomization of inherently continuous phenotypes. These concerns about the quality of the original publications are borne out in our meta-analytic results. First, despite numerous studies linking specific SNPs in *OXTR* to antisocial behavior (e.g. rs1042778 and rs53576), meta-analytic effect sizes for these SNPs were small and not significant. Second, and

more importantly, we observed appreciable heterogeneity in the associations between antisocial behavior and each SNP. However, due to the small number of studies we were unable to conduct moderator analyses. Several moderators may have influenced the heterogeneity observed in effect sizes, including study design, operationalization of the antisocial phenotype, nature of the sample, and age of the sample, to name just a few. However, it is also possible that random sources of heterogeneity, such as the quality control issues previously mentioned as well as the variability in point estimates one would expect from underpowered studies, explain this high level of heterogeneity.

Ultimately, the number and quality of available studies significantly limited our ability to come to a definitive conclusion about the association between *OXTR* and antisocial behavior. We did find one significant SNP which withstood correction for multiple tests, publication bias, and sensitivity analyses. Thus, we cannot rule out the possibility that the current literature points to a significant role of *OXTR* in antisocial behavior. However, our concerns about the methods and statistical methods of the studies included, coupled with high observed heterogeneity, lead us to interpret this one positive result with caution. More and better-powered future studies will help disentangle potentially real effects of *OXTR* from noise caused by methodology and heterogeneity.

These results also bear important general implications for candidate gene studies conducted within psychology and psychiatry. Although candidate gene studies might use a more fine-grained phenotypic measure than large-scale GWAS, candidate gene studies provide inconsistent evidence at best and misleading evidence at worst. Given that only one of the fourteen SNPs was significant across studies, there is little evidence that *OXTR* plays a meaningful role in the etiology of antisocial behavior. This finding is not surprising, as previous meta-analyses and narrative reviews have highlighted the inconsistency and non-replicability of candidate gene studies for nearly a decade (Culverhouse et al. 2018; Duncan and Keller 2011). The current meta-analysis adds to the growing literature that suggests that candidate gene studies do not provide reliable information about the etiology of the studied phenotype and that genome-wide approaches should be favored. More specifically, it suggests that claims of a causal association between *OXTR* and antisocial behavior should be interpreted with caution.

Strengths and limitations

Several strengths and limitations should be considered when interpreting results from this meta-analysis. Many studies have reported associations between *OXTR* SNPs and antisocial behavior, but the SNPs that show significant associations, as well as the direction and magnitude of effects, vary across studies. This makes it difficult to evaluate which SNPs are associated and to what degree, if at all. This meta-analysis is the first to examine the effects of *OXTR* SNPs on antisocial behavior and thus may help interpret the broad and diverse literature linking these two domains. We also provide a critical review of the studies examining this association and comment on concerns that limit the interpretation of findings from this body of literature.

Despite these strengths and the importance of this first attempt to aggregate the effects of *OXTR* across the literature, there are several limitations that should be considered. First, each SNP-based meta-analysis included only four to twelve studies. This number of studies is low relative to that typically included in meta-analyses and indicates that, although the current results accurately characterize the existing literature, they are susceptible to change with the publication of even a few more studies. This is especially true given the inconsistency in findings across existing studies. The use of confidence intervals when interpreting the overall effect sizes addresses this limitation to some degree. Similarly, although significant heterogeneity was observed for each SNP, the low number of studies included in the analyses precluded examination of the extent to which systematic moderators account for this heterogeneity.

Second, although broad antisocial behavior, delinquency, aggression, and callous–unemotional traits are moderately to highly related and influenced by common genetic effects (Baker et al. 2007), there are some important differences in the etiology of these phenotypes. Estimates of the heritability of antisocial behaviors vary as a function of the operationalization of the phenotype (Rhee and Waldman 2002; Viding et al. 2008a, b) and it is possible that by combining studies which examined different aspects of the antisocial phenotype, we were unable to capture genetic variation specific to each type of antisocial behavior. As the number of studies testing this association grows, a more in-depth examination of genetic effects specific to each antisocial phenotype will become possible.

Future directions

Future studies should focus on several areas when examining the genetic influences on antisocial behavior. First, obtaining the requisite information to determine effect sizes for each study proved difficult as most studies did not report an effect size, and many excluded any information about the effects of a SNP if its association was not significant. Although the inclusion of many SNPs in a single study makes it more difficult to report results for each, in the future researchers should make every effort to make this information easily available. This is especially important given the utility of meta-analysis as a tool to interpret a large body of literature.

Second, many of the studies used in the current meta-analysis reported case–control status of antisocial behavior, sometimes even in studies in which continuous measures were available. Using dimensional measures can increase power to detect association (Kotov et al. 2017), which may partly explain the heterogeneity of effect sizes. Researchers should attempt to use continuous measures whenever possible in the future.

Third, there have been few genome-wide association studies that have found loci consistently associated with antisocial phenotypes. One potential explanation for this is that most antisocial behaviors are examined continuously (with the exception of Conduct Disorder) and it is difficult to find cohorts large enough for GWAS that include dimensional measures. Nonetheless, as larger samples become more common, researchers should focus on genome-wide approaches for determining the etiology of antisocial behaviors. Given the difficulty of obtaining large samples for GWAS, researchers should consider conducting gene-based tests wherein they analyze multiple SNPs in the same gene. This allows researchers to characterize the gene's effects on a phenotype due to most of the genetic variation in a gene, as opposed to just the limited genetic variation associated with a single SNP, which increases power to detect associations and provides a more comprehensive picture of the influence of a specific gene.

Acknowledgements The authors would like to thank Drs. Scott Lilienfeld, Rohan Palmer, and Kim Wallen for their mentorship and support during the process of the first author's qualifying exam, which included completion of this meta-analysis.

Author contributions All authors developed the study concept. HEP completed literature search and extracted study information. All authors contributed to the computation of study effect sizes. HEP completed all analyses. HEP drafted the paper and IDW provided critical revision. All authors approved the final version of the paper for submission.

Compliance with ethical standards

Conflict of interest Holly E. Poore and Irwin D. Waldman do not have any competing interests or disclosures to report.

Human and Animal Rights and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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