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REVIEW

Candidate Genes for Aggression and Antisocial Behavior: A Meta-analysis of Association Studies of the *5HTTLPR* and *MAOA-uVNTR*

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Abstract Variation in central serotonin levels due to genetic mutations or experimental modifications has been associated with the manifestation of aggression in humans and animals. Many studies have examined whether common variants in serotonergic genes are implicated in aggressive or antisocial behaviors (ASB) in human samples. The two most commonly studied polymorphisms have been the serotonin transporter linked polymorphic region of the serotonin transporter gene (*5HTTLPR*) and the 30 base pair variable number of tandem repeats of the monoamine oxidase A gene (*MAOA-uVNTR*). Despite the aforementioned theoretical justification for these polymorphisms, findings across studies have been mixed and are thus difficult to interpret. A meta-analysis of associations of the *5HTTLPR* and *MAOA-uVNTR* with ASB was conducted to determine: (1) the overall magnitude of effects for each polymorphism, (2) the extent of heterogeneity in effect sizes across studies and the likelihood of publication bias, and (3) whether sample-level or study-level characteristics could explain observed heterogeneity across studies. Both the *5HTTLPR* and the *MAOA-uVNTR* were significantly associated with ASB across studies. There was also significant and substantial heterogeneity in the effect sizes for both markers, but this heterogeneity was not explained by any sample-level or study-level characteristics examined. We did not find any evidence for publication bias across studies for the *MAOA-uVNTR,* but there was evidence for an oversampling of statistically significant effect sizes for the *5HTTLPR*. These findings provide support for the modest role of common serotonergic variants in ASB. Implications regarding the role of serotonin in antisocial behavior and the conceptualization of antisocial and aggressive phenotypes are discussed.

Keywords Antisocial behavior · Aggression · Serotonin · MAOA · 5HTTLPR · Meta-analysis

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Introduction

Antisocial Behavior (ASB)

Antisocial behavior (ASB) is a topic of interest to researchers and clinicians alike. ASB is exhibited in markedly elevated levels in various clinical populations and is strongly associated with negative outcomes, including violent criminal behavior and substance abuse (APA 2000; Liao et al. 2004; Retz and Rosler 2009). ASB characterizes several childhood and adult disorders in the DSM-IV (APA 2000), including oppositional-defiant disorder (ODD) and conduct disorder (CD) in youth and antisocial personality disorder in adults. Beyond DSM-IV diagnoses, the antisocial phenotype includes traits such as aggression, delinquency, psychopathy, violence, and criminality (Baker et al. 2007; Liao et al. 2004; Verona et al. 2006).

The Etiology of ASB

Genetic influences account for 40–60 % of the variance in broad ASB (Ferguson 2010; Gunter et al. 2010; Rhee and Waldman 2002), although heterogeneity exists in the

magnitudes of heritability estimates for antisocial phenotypes across studies. Aggression has yielded heritability estimates similar in magnitude to ASB (Burt and Neiderhiser 2009; Craig and Halton 2009; Eley et al. 1999; Miles and Carey 1997; Rhee and Waldman 2010), whereas delinquency has yielded much lower estimates (Deater-Deckard and Plomin 1999; Eley et al. 1999) and psychopathy (particularly callous-unemotional traits) has yielded higher estimates ($\sim$50–80 %) (Gunter et al. 2010; Retz et al. 2004; Waldman and Rhee 2006). Sex differences have been reported in the magnitude of genetic and environmental influences on ASB during childhood, with female ASB yielding greater heritability (Eley et al. 1999; Jacobson et al. 2002), but by adulthood the genetic and environmental influences on ASB appear to be similar for males and females (Jacobson et al. 2002). There also appears to be variation in the etiology of ASB throughout development, and this variation may be due to transient, age-specific genetic effects (Silberg et al. 2007). Genetic influences on delinquency appear to increase with age (Burt and Neiderhiser 2009), whereas the heritability of aggression may or may not increase (Bergen et al. 2007; Burt and Neiderhiser 2009; Lyons et al. 1995). Some researchers have cautioned that there may be important differences across these antisocial constructs and that a narrower definition of ASB is necessary for reducing the heterogeneity of quantitative genetic findings (Gunter et al. 2010; Retz et al. 2004; Rhee and Waldman 2002; Yeh et al. 2010).

Despite this heterogeneity, there is evidence that measures of these distinct but overlapping phenotypes may tap a single etiological construct. Baker et al. (2007) found a large degree of phenotypic overlap among parent-, teacher-, and child-reported aggression, psychopathy, and conduct problems. Although quantitative genetic analyses of separate within-rater ASB composites resulted in heritability estimates similar to those reported in the literature, the heritability of a common ASB factor underlying parent, teacher, and child reports was 0.96, suggesting the factor was almost entirely explained by common genetic influences (Baker et al. 2007). Similarly, Lahey et al. (2011) found that a moderate-to-high proportion of the additive genetic variance in parent- and youth-reported externalizing dimensions (including inattention, hyperactivity-impulsivity, ODD, and CD) could be explained by a combination of global (broad psychopathology) and externalizing-specific higher-order genetic factors (Lahey et al. 2011). These findings suggest that distinct ASB phenotypes share common biological underpinnings.

Candidate Genes for ASB

Evidence for the moderate to high heritability of ASB has kindled the search for specific genes that may be responsible for the variation in this phenotype. Molecular genetic studies of ASB have focused strongly on serotonergic system neurotransmitter genes (Gunter et al. 2010; Retz and Rosler 2009), as elevated impulsivity and aggression have been observed in humans and animals with rare genetic mutations that affect serotonin levels (Brunner et al. 1993; Nordquist and Oreland 2010). Serotonergic neuronal projections synapse in regions previously implicated in aggression, including the hypothalamus and the amygdala, and there is evidence that projections from the orbitofrontal cortex may inhibit serotonergic activity within the raphe nuclei, which in turn project to these regions (Carver et al. 2008). Serotonergic genotypes have been associated with amygdalar reactivity to fearful stimuli (Hariri et al. 2002), which in turn, has been associated with male aggression in some contexts (Carre et al. 2013). In addition, selective serotonin reuptake inhibitors have been shown to affect the perception of emotionally-valenced social information, including the recognition of facial emotions (Merens et al. 2007), for which individuals displaying increased ASB show deficits (Marsh and Blair 2008), and startle response (Harmer et al. 2004), which has been found to differ in individuals with CD (Fairchild et al. 2008). Emotional dispositions (including trait aggression) in humans and animals, which reflect cross-situational behavioral biases, have also been associated with serotonin receptor density (Cyders and Smith 2008) and MAOA activity (Alia-Klein et al. 2008). Consequently, there seems to be fairly strong evidence connecting serotonergic system variation to ASB.

Investigators have sought to apply these findings to common genetic variants in humans that appear to impact serotonin neurotransmitter levels. Variants in *5HTT* and *MAOA* have been the most frequently examined candidates for association (Gunter et al. 2010). We meta-analyzed the association of ASB with variants in *5HTT* and *MAOA* (specifically the *5HTTLPR* and the *MAOA-uVNTR*) for the following reasons: (1) these genes are theoretically plausible candidates as risk factors for aggression and ASB due to their influence on relevant neurological pathways, and (2) as functional markers in these two genes have been the most commonly tested for association with antisocial phenotypes, a large number of studies were available for inclusion in a meta-analysis.

The Monoamine Oxidase A Promoter Variable Number of Tandem Repeats (*MAOA-uVNTR*)

The MAOA enzyme metabolizes monoamine neurotransmitters, including serotonin (Sabol et al. 1998). The promoter region of *MAOA* located on the short arm of the X chromosome contains a 30 base pair variable number of tandem repeats sequence (VNTR) consisting of 2, 3, 3.5, 4, or 5 repeated copies (Kim-Cohen et al. 2006; Sabol et al. 1998).

Transcription of the 3-repeat (short) allele results in reduced MAOA activity and thus increased serotonin in the synapse, putatively increasing risk for aggression and ASB. The frequency of the "risk" allele in nonclinical samples of European ancestry ranges from 0.3 to 0.4, although the frequency of this allele in individuals of Asian and African ancestry appears to be substantially higher (~0.6 in both groups; Sabol et al. 1998). In contrast, the 4-repeat (long) allele results in increased MAOA activity and is considered the low-risk allele (Kim-Cohen et al. 2006). Of the less common alleles, the 3.5-repeat has shown evidence of activity similar to that of the 4-repeat and is thus considered high activity, whereas the 2-repeat is usually grouped with the 3-repeat allele and considered low activity (Kim-Cohen et al. 2006). Classification of the 5-repeat allele has been inconsistent across studies.

A complication arises given *MAOA*'s location on the X chromosome. Because females have two X chromosomes whereas males have only one, heterozygosity may be present in females but not males. As *MAOA* expression for heterozygous allele carriers remains unclear, many investigators have selected all-male samples or eliminated heterozygous females from their samples (e.g., Beitchman et al. 2004; Derringer et al. 2010).

The Serotonin Transporter-Linked Polymorphic Region (*5HTTLPR*)

The human serotonin transporter gene (*5HTT*) contains a 20–23 base pair (bp) repeat element (*5HTTLPR*) with a 44 bp insertion/deletion resulting in "long" and "short" (528 bp and 484 bp, respectively) variants (Heils et al. 1996). The homozygous long (l/l) genotype has been associated with increased 5HTT transcriptional efficiency as compared with the heterozygous (s/l) or homozygous short (s/s) genotypes (Cadoret et al. 2003; Heils et al. 1996). The increase in transcriptional efficiency of the l/l genotype appears to result in higher rates of serotonin reuptake in serotonergic cells (platelets and lymphoblasts) (Greenberg et al. 1999; Lesch et al. 1996), putatively reducing the availability of synaptic serotonin and subsequently the risk for ASB. Prevalence of the short allele in community samples of European ethnic background typically is 0.4 (e.g., Gerra et al. 2005; Gonda et al. 2009), although there is evidence that the short allele is more prevalent in individuals of Asian ancestry (~0.7; Liao et al. 2004) and less prevalent in individuals of African ancestry (~0.2; Lotrich et al. 2003).

Examining Genetic Main Effects Versus Gene–Environment Interactions

Of relevance to the current investigation's focus on the main effects of these genetic variants on human behavior is the recent plethora of gene × environment (G × E) interaction studies in this literature. Since Caspi et al. (2002) reported that associations between the *MAOA-uVNTR* and ASB were moderated by child maltreatment, many studies have abandoned the examination of main effects in favor of GXE interactions for the *MAOA-uVNTR* and various putative environmental indices of adversity (e.g., Beitchman et al. 2004; Caspi et al. 2002; Derringer et al. 2010; Foley et al. 2004; Hart and Marmorstein 2009; Kim-Cohen et al. 2006). Kim-Cohen et al. (2006) conducted a meta-analysis of GXE studies across five non-clinical samples and reported a significant interaction such that individuals with the low activity *MAOA-uVNTR* allele showed greater increases in ASB given exposure to maltreatment than those with the high activity allele.

Notwithstanding the excitement that many researches have felt at the prospect of GXE interactions in the development of complex traits, there is growing evidence that we must be wary of these findings. A meta-analysis of GXE studies for the *5HTTLPR* and stressful life events in the development of depression [initially reported by Caspi et al. (2003)] demonstrated that many have been fraught with methodological and interpretive flaws, including inconsistencies in the designated "risk" genotype(s) and indices of environmental risk across studies as well as loose standards for replication (Munafo et al. 2009; Risch et al. 2009). Indeed, although a more recent meta-analysis of the interactive effects of *5HTTLPR* and stressful life events in depression that included a larger number of studies reported a significant GXE effect, the authors acknowledged that their results may have been affected by errors or bias present among the individual studies included in the analysis (Karg et al. 2011). Another recent review of GXE studies of psychiatric disorders and relevant traits by Duncan and Keller (2011) reported strong evidence for publication bias and low power among GXE studies, suggesting that many if not most published significant GXE findings are false positives. Indeed, non-experimental studies typically have far less power to detect interactions than main effects in the absence of sampling strategies that are specifically designed for detecting interactions (McClelland and Judd 1993; Wahlsten 1991), an observation that supports Duncan and Keller's (2011) implication that many published GXE studies likely have capitalized on chance findings. Thus, although GXE studies initially provided an attractive solution as to why theoretically-plausible candidate genes show only small, inconsistent associations with complex traits, many are now skeptical regarding the credibility of GXE findings. Indeed, before proceeding to examine how theoretically- or empirically-derived genetic loci influence ASB in the context of varying environments, it is important that we first examine and determine with some level of confidence whether these widely examined

genetic variants show robust, replicable evidence for association.

The Current Study

The aims of the current investigation were threefold. First, we conducted meta-analyses of the main effects of *5HTTLPR* and *MAOA-uVNTR* on ASB phenotypes in order to characterize the magnitude and significance of associations across studies. Second, we determined the extent of heterogeneity and tested for publication bias among the effect sizes of included studies. Finally, we tested to what extent various sample and study moderator variables explained the observed heterogeneity in effect sizes across studies.

Methods

Study Selection

Studies were identified for the current meta-analysis using the PubMed library database, the Proquest Dissertations and Theses: Full Text database, and the Google Scholar search engine. Search terms coupled a genetic component to identify the markers of interest (i.e., "MAOA," "5HTTLPR," "5 HTTLPR," "5HTTLPR") with a phenotypic component to identify various forms of ASB (i.e., "aggression," "antisocial," "psychopathy," "CD," and "oppositional defiant disorder"). Reference sections of the identified publications as well as recent review articles were examined in an effort to yield additional studies. Studies of ASB in children, adolescents, or adults published in English by September, 2012 that reported testing statistical associations between at least one of the genetic markers of interest (*MAOA-uVNTR* or *5HTTLPR*) and any antisocial phenotype were included in the current investigation. Studies were excluded if participants were clinically-referred for psychiatric disorders other than ASB (e.g. mood disorders, psychotic symptoms, suicidality, intellectual disability, or substance abuse) with the exception of ADHD, which has been shown to share considerable phenotypic and genetic overlap with ASB (Angold et al. 1999; Silberg et al. 1996; Thapar et al. 2001). Studies were also excluded if the data required for calculating an effect size were not provided within the text of the article and could not be obtained from the author(s).

Data from 31 studies were included in the meta-analysis for *MAOA*. Of the initial pool of 66 studies, 19 were excluded because their samples overlapped with those in larger studies, and thirteen were excluded because participants were referred for other psychiatric disorders. In three studies there was not enough information available to calculate an effect size for use in the meta-analysis. Citations and effect sizes for studies included in the meta-analysis are shown in Table 1.

Table 1 Citations, effect sizes, and respective weights for *MAOA-uVNTR*

Studies	Effect size (*OR*)	Study weight (random effects)
1. Manuck et al. (2000)	0.53	4.41
2. Caspi et al. 2002	1.02	8.02
3. Lawson et al. (2003)	1.68	4.79
4. Beitchman et al. (2004)	0.36	3.68
5. Jacob et al. (2005)	0.69	1.79
6. Huizinga et al. (2006)	0.7	5.03
7. Kim-Cohen et al. (2006)	0.7	9.28
8. Widom and Brzustowicz (2006)	1.01	7.91
9. Young et al. 2006)	0.9	6.82
10. Eisenberger et al. (2007)	9.94	1.2
11. Frazzetto et al. (2007)	0.8	6.72
12. Prichard et al. (2007)	0.94	9.84
13. Reif et al. (2007)	2.3	4.35
14. Ducci et al. (2008)	1.83	6.15
15. Guo et al. (2008)	1.19	10.12
16. Sjoberg et al. (2008)	1.14	5.75
17. Alia-Klein et al. (2009)	11.24	1.45
18. Guimaraes et al. (2009)	0.93	2.38
19. McDermott et al. (2009)	2.67	2.97
20. Prom-Wormley et al. (2009)	2.88	4.19
21. Qian et al. (2009)	0.89	4.62
22. Weder et al. (2009)	1.38	4.71
23. Williams et al. (2009)	2.42	6.1
24. Derringer et al. (2010)	1.32	9.22
25. Edwards et al. (2010)	1.39	5.7
26. Aslund et al. (2010)	1.02	9.71
27. Fergusson et al. (2011)	1.49	7.8
28. Cicchetti et al. (2012)	1.29	7.41
29. McGrath et al. (2012)	0.51	6.11
30. Gallardo-Pujol et al. (2012)	2.35	3.02
31. Verhoeven et al. (2012)	0.7	6.46
Total		
Fixed effects (FE)	1.08*	
Random effects (RE2)	**1.14***	

Larger weights reflect larger sample sizes; bold font indicates selected model

* $p = 0.035$ for FE model and $p = 1.37 \times 10^{-6}$ for RE2 model

Data from 18 studies were included in the meta-analysis for *5HTTLPR*. Of the initial pool of 50 studies, 17 were excluded because their samples overlapped with those in other studies, six studies were excluded due to participant referral for other psychiatric disorders. The remaining nine studies were excluded because appropriate effect sizes

Table 2 Citations, Effect Sizes, and Respective Weights for *5HTTLPR*

Studies	Effect size (*OR*)	Study weight (random effects)
1. Langley et al. (2003)	1.72	2.71
2. Liao et al. (2004)	4.54	2.2
3. Gerra et al. (2005)	6.99	3.68
4. Beitchman et al. (2006)	1.68	5.84
5. Haberstick et al. (2006)	1.19	4.54
6. Sakai et al. (2006)	2.06	6.72
7. Verona et al. (2006)	1.51	4.25
8. Grevet et al. (2007)	1.26	6.56
9. Lyons-Ruth et al. (2007)	2.7	3.84
10. Nobile et al. (2007)	1.13	7.11
11. Reif et al. (2007)	1	5.33
12. Brody et al. (2009)	1.16	6.83
13. Gonda et al. (2009)	1.9	4.98
14. Zimmerman et al. (2009)	2.08	3.69
15. Garcia et al. (2010)	1.32	5.12
16. Sakai et al. (2010)	0.72	5.55
17. Conway et al. (2012)	0.99	6.44
18. Sadeh et al. (2013)	1.89	5.78
Total		
Fixed effects	1.41*	
Random effects	**1.53***	

Larger weights reflect larger sample sizes. Bold font indicates selected model

* $p = 4.25 \times 10^{-9}$ for FE model and 7.59×10^{-11} for RE2 model

could not be extracted from the information provided. Citations and effect sizes for the studies included in the meta-analysis are shown in Table 2.

Analytic Method

The conversion of effect sizes to a common test statistic (the natural log of the Odds ratios, OR's) was conducted using Comprehensive Meta-Analysis Version 2 software (Borenstein et al. 2005), which can accommodate a wide range of effect size statistics and allows one to choose the statistic for conversion and output for all individual effect sizes. Converted effect sizes were then meta-analyzed using Metasoft (Han and Eskin 2011), which—in addition to the traditional fixed-effects (FE) and random-effects (RE) tests—provides an alternative random-effects (RE2) test that offers greater power than RE and FE to detect associations in the presence of heterogeneity. Fixed-effects models were initially used to evaluate the effects for each marker. The assumption of homogeneity of effect sizes was tested using the *Q*-statistic, which examines the weighted sum of squares of the individual studies around the mean effect size and uses a Chi square test to infer the presence of significant heterogeneity (Lipsey and Wilson 2001). If the *Q*-statistic was significant, the Han and Eskin's (2011) RE2 model was used to test the significance of the overall effect size and to distinguish the contribution of the mean effect (S_{FE}) and the heterogeneity (S_{Het}) to the test statistic for each marker. Finally, the I^2 index was utilized to quantify the magnitude of heterogeneity, given that it describes the proportion of total variation in study effect size estimates due to heterogeneity independently of both the number of studies included in the meta-analysis and the metric of effect sizes (Gizer et al. 2009; Higgins and Thompson 2002).

Analysis of Moderators and Publication Bias

Given the presence of significant heterogeneity in effect sizes, potential moderators of the association between each variant and ASB were explored using meta-regression (Harbord and Higgins 2008). Meta-regression was conducted in STATA/SE 8.2 for Windows (STATA Statistical Software: Release 8 2003) using a revision of the *metareg* command (Harbord and Higgins 2008) that provides an overall *F*-statistic for models containing multiple predictors and estimates the proportion of variance in study effect sizes explained by moderators within the model (R^2). Putative moderators of the association between each genetic marker and ASB were entered as predictors within random-effects meta-regression analyses with individual effect sizes (i.e., the natural log of the OR's) for each marker entered as the dependent variable. We grouped moderators of interest into three a priori sets ("sample characteristics," "study characteristics," and "publication bias") for the following reasons: (1) we were interested in whether individual effect sizes were influenced by multiple moderators, and grouping predictors into sets that were tested using an omnibus *F*-statistic instead of conducting individual tests of each predictor greatly reduced the likelihood of Type I error; (2) there were too many moderators of interest to allow for simultaneous entry of all predictors within a single model, and (3) controlling for the correlations among predictor variables within each models allowed us to better examine the *unique* influences of hypothesized moderators. The moderators examined in the current study are discussed below.

Sample Characteristics

Age and Sex

Gender composition of the sample (% male) was included in order to determine whether sex differences in phenotypic liability contributed to variability in effect sizes. Further, as

the heritability of some antisocial phenotypes has been found to differ with age (Burt and Neiderhiser 2009), we coded the mean of the participants' ages in each study.

Ethnicity and Risk Allele Frequency

The ethnic composition of the sample (% European, % African, % Asian ancestry) was coded in order to test whether the presence of population stratification (ethnic differences in both allelic distribution and phenotypic levels) may have influenced differences in effect sizes across studies (Cardon and Palmer 2003). The frequency of the risk allele (% risk allele) in each sample was also included as an independent predictor.

Sample Type

The type of sample included in the current meta-analysis was also coded (0 = community-based, 1 = clinically- or forensically-referred). Phenotypic variability is likely to differ for community samples (in which participants may show a range of symptoms, but symptom levels are likely to cluster at the lower end of the range) in comparison to clinically-referred samples (who are more likely to show moderate to high symptom levels). As a result, the power to detect phenotypic differences by genotype in these respective samples may also differ.

Study Characteristics

Phenotype

Because antisocial and aggressive phenotypes may represent overlapping but nonidentical constructs with varying heritability (Burt and Neiderhiser 2009; Deater-Deckard and Plomin 1999; Rhee and Waldman 2002), each study was coded either 0 for examining more "pure" anger/aggression or 1 for using a broad conceptualization of ASB (a combination of aggressive and non-aggressive antisocial acts) as its primary outcome. If a study utilized more than one index of ASB, the broadest (i.e., most inclusive) index of ASB was selected for inclusion in the meta-analysis. If several indices within a single study appeared similar in this regard, the index providing the most evidence for reliability and validity was selected for inclusion.

Phenotypic Measurement

Two dummy variables indicated the source of phenotypic measurement ("objective": 0 = no, 1 = yes; and "self-report": 0 = no, 1 = yes). "Objective" instruments comprised at least some phenotypic scores that were not reporter-based (e.g., criminal records or laboratory observation) and "self-report" instruments comprised participant reports of their own symptoms. For an individual study to receive a coding of 1 on both of these variables, both forms of measurement had to have been included within a single composite phenotype that contributed to that study's overall effect size. In addition, because poor phenotypic measurement may reduce a study's power to detect significant associations and study authors may be more likely to withhold information on an instrument's reliability and validity when it is less than desirable, we included two additional dummy variables indicating whether the study provided information on the reliability and/or validity of the instrument utilized (0 = no, 1 = yes).

Allele Coding

Dummy coding was utilized to denote whether individual studies assigned heterozygous individuals to the low activity ("high risk") genotype group in the calculation of effect sizes for the *MAOA-uVNTR* and *5HTTLPR*. Studies that included heterozygous individuals in this group were coded as 1, and studies that did not were coded as 0.

For the *MAOA-uVNTR*, the inclusion of the 5-repeat allele was also coded (0 = no 5-repeat alleles present in sample, 1 = 5-repeats coded as "risk", 2 = 5-repeats coded as "nonrisk"). We then used orthogonal contrast coding to create two variables: 1) 5-repeat as "low activity" or "high activity" versus "no grouping" and 2) 5-repeat as "high activity" versus "low activity".

Publication Bias

Sample Size

Negative associations between effect size and sample size in a meta-analysis indicate a tendency for the selective publication of small studies with significant effects (Levine et al. 2009). We recorded the number of participants whose data were included in the calculation of the effect size for each study in order to provide one index of bias in the publication of studies for each gene.

Order of Publication

Initial studies of a phenomenon often produce stronger effect sizes than subsequent replication studies, which tend to report smaller, less consistent associations (Rothwell and Robertson 1997). As this may indicate temporally biased reporting, we included publication year as a potential moderator of effect sizes across studies.

Journal Impact

Studies published in more prestigious journals (as indicated by the journal's *impact factor*, the average number of citations per article in recent years) tend to report stronger effect sizes than those published in their less prestigious counterparts (Munafo et al. 2009), which may indicate systematic bias in journal acceptance and publication. We coded the most recent impact factor of the journal listed on each journal's website as a potential index of publication bias.

G x E Adversity Study

As noted earlier, many studies in the past decade have sought to replicate the findings of Caspi et al. (2002) by testing for the interactive effects of the *MAOA-uVNTR* and indices of adversity on ASB. In order to test whether these study designs have impacted the magnitude or significance of the reported main effects of the *MAOA-uVNTR*, we coded whether studies of this marker tested for such an interaction (yes = 1, no = 0).

Results

Main Effects

MAOA-uVNTR

The fixed-effects meta-analytic model yielded a modest, positive association between the low activity allele of the *MAOA-uVNTR* and ASB, $OR = 1.08$ 95 % CI (1.01–1.15), $p = 0.035$. Based on the presence of significant heterogeneity as indicated by the Q statistic ($\chi^2_{(30)} = 97.93$, $p < 0.001$, $I^2 = 69$ %), the RE2 model was selected as a more appropriate alternative. Results of the RE2 model revealed significant associations between the low activity allele of the *MAOA-uVNTR* and ASB, $S_{FE} = 4.43$, $S_{Het} = 20.53$, $OR = 1.14$, 95 % CI (0.98–1.32), $p = 1.37 \times 10^{-6}$. It is important to note here that the 95 % confidence interval for the meta-analytic effect size was calculated using the traditional RE approach, which is more stringent than the RE2 approach used in the calculation of the p value for the effects. This difference accounts for why the significance test suggests there is an effect present whereas the confidence interval does not. We will elaborate on this finding in the "Discussion" Section. The forest plot for the *MAOA-uVNTR* is given in Fig. 1. Egger's test of asymmetry (Egger et al. 1997), which examines abnormalities in the distribution of standardized effect size plotted as a function of study precision (1/standard error) was nonsignificant, $t = 1.35$, $p = 0.19$, suggesting that there was not an oversampling of statistically significant effects in the pool of studies.

5HTTLPR

The fixed-effects model yielded a moderate, positive association between the short allele of the *5HTTLPR* and ASB, $OR = 1.41$, 95 % CI (1.26–1.59), $p = 4.25 \times 10^{-9}$. Significant heterogeneity also was present in the effect sizes for *5HTTLPR* ($\chi^2_{(17)} = 47.71$, $p < 0.001$, $I^2 = 64$ %),

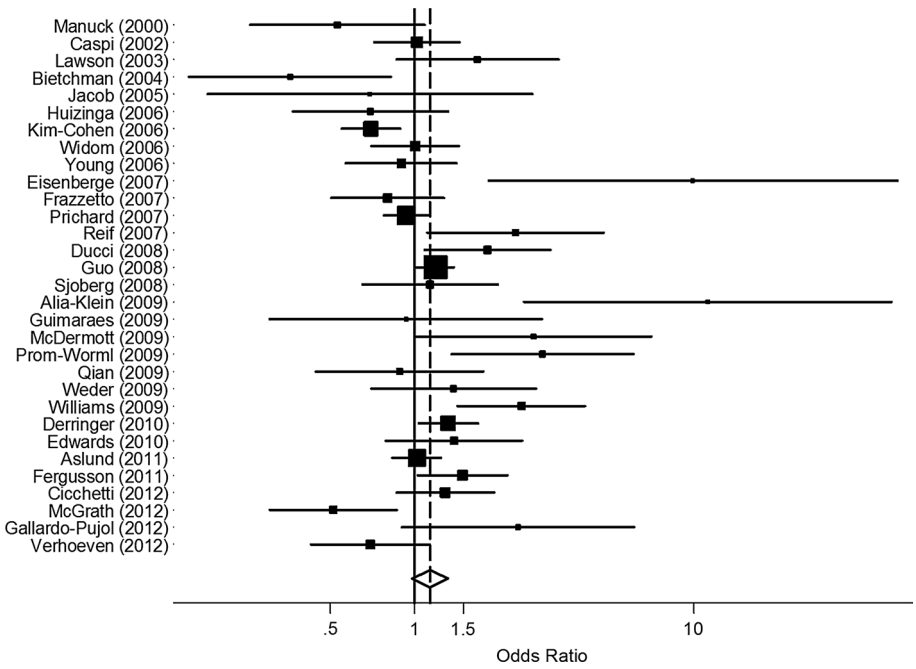

Fig. 1 Forest plot of MAOA-uVNTR effect sizes (random-effects model). Individual study effects (in odds ratios) are indicated by the horizontal placement of the corresponding squares, and individual study weights are indicated by the area of each *square*. The 95 % confidence interval for each study effect is indicated by a *horizontal line*. The overall random-effects meta-analytic effect size is indicated by an open diamond and the *dashed vertical line*, which can be compared to the *solid line* representing the meta-analytic effect under the null hypothesis (odds ratio = 1)

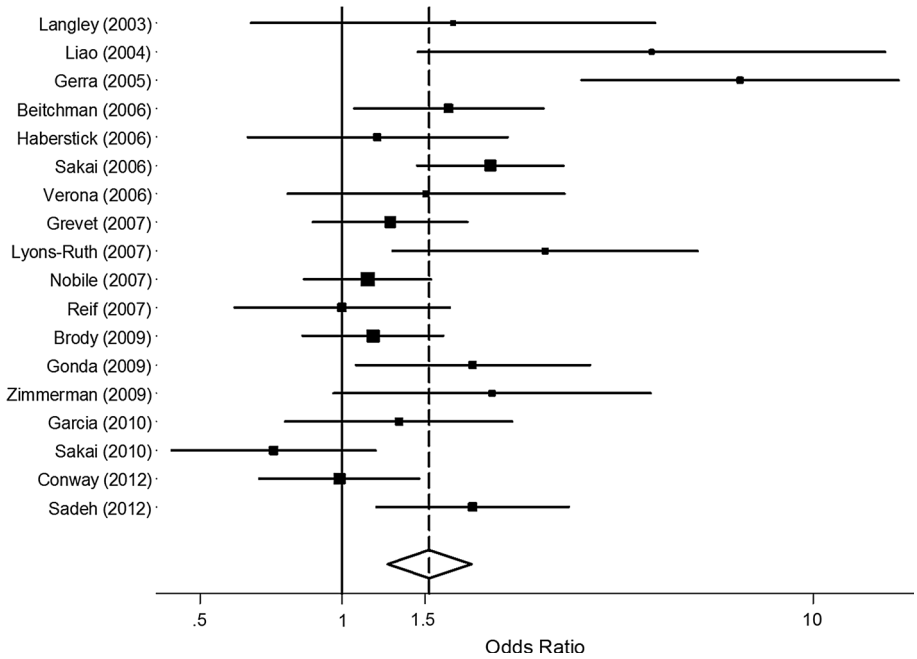

Fig. 2 Forest plot of 5HTTLPR effect sizes (random-effects model). Individual study effects (in odds ratios) are indicated by the horizontal placement of the corresponding *squares*, and individual study weights are indicated by the area of each square. The 95 % confidence interval for each study effect is indicated by a *horizontal line*. The overall random-effects meta-analytic effect size is indicated by an open diamond and the *dashed vertical line*, which can be compared to the *solid line* representing the meta-analytic effect under the null hypothesis (odds ratio = 1)

and consequently the RE2 model was again deemed more appropriate. The RE2 model revealed a moderate and significant association between the short allele of *5HTTLPR* and ASB, $S_{FE} = 34.50$, $S_{Het} = 9.33$, $OR = 1.53$, 95 % CI (1.25–1.88), $p = 7.59 \times 10^{-11}$. The forest plot for *5HTTLPR* is given in Fig. 2. Egger's test of publication bias was significant ($t = 2.29$, $p = 0.036$); the intercept of the regression line in the association between study precision and standardized effect was significantly greater than zero, indicating a tendency for studies with little precision (i.e., small samples) to report larger effects (Egger et al. 1997). This may suggest an oversampling of statistically significant effect sizes in the extant literature for *5HTTLPR*.

Moderation Tests

Information regarding the moderator coding for studies of the *MAOA-uVNTR* and *5HTTLPR* is given in Tables 3 and 4, respectively. Study samples were predominantly male and of European ethnicity. Participants sampled for studies of each variant were similar in age ($M = 24.94$ and 22.66, respectively). The risk (short) allele of *5HTTLPR* appeared to be more common across samples than the risk (low-activity) allele of *MAOA-uVNTR*. For the *MAOA-uVNTR*, although males have only one copy and females have two, the *distribution* of risk alleles appeared to be similar across both sexes (as would be expected). Interestingly, it appeared that studies of the *MAOA-uVNTR* on average appeared in more high-impact journals and had larger samples than studies of the *5HTTLPR*.

Studies for both markers utilized population-based samples more frequently than psychiatrically- or forensically-referred samples. In addition, studies more frequently utilized self-report measures of ASB than objective measures such as laboratory behavior or criminal records. Although a higher percentage of studies of the *MAOA-uVNTR* reported information on the reliability of the phenotypic measures (45 vs. 28 % for studies of the *5HTTLPR*), fewer reported information on the validity of these measures (10 % for *MAOA-uVNTR* versus 28 % for *5HTTLPR*). For the *5HTTLPR*, it was fairly common for studies to group individuals with heterozygous genotypes with individuals with the low-activity homozygous genotype, but for the *MAOA-uVNTR*, most studies did not group heterozygous individuals with homozygotes (likely because males are hemizygous and many of these studies excluded females).

MAOA-uVNTR

Correlations among moderator variables for the *MAOA-uVNTR* and *5HTTLPR* are provided in Tables 5, 6, and 7. Separate correlation matrices were computed for each moderator group in order to maximize visual clarity and interpretability. Small to moderate correlations indicated

Table 3 Study moderators (*MAOA-uVNTR*)

First author/year	Impact	Case Control[a]	Psychiatric[b]	*N*	Age	Broad ASB[c]	Objective Measure[d]	Self-Report[e]	% Male	% European	5R Coding[f]	Prop. Risk Allele Males	Prop. Risk Allele Females	Heterozygous Coding[g]	Reliability[h]	Validity[i]	GxE Study[j]
1. Manuck (2000)	2.80	0	0	110	45.20	0	0	1	100	88	1	0.35	NA	0	1	0	0
2. Caspi (2002)	31.36	0	0	442	26.00	1	1	1	100	100	1	0.37	NA	0	0	0	1
3. Lawson (2003)	3.48	1	1	172	NA	1	0	1	100	100	2	0.43	NA	0	0	0	0
4. Beitchman (2004)	15.47	1	1	100	9.50	0	0	0	100	80	0	0.40	NA	0	0	0	0
5. Jacob (2005)	6.69	1	1	506	31.15	1	0	1	36	99	2	0.39	0.40	2	0	0	0
6. Huizinga (2006)	8.67	0	0	277	NA	1	1	1	100	100	2	0.38	NA	0	0	0	1
7. Kim-Cohen (2006)	15.47	0	0	975	7.00	1	0	0	100	100	1	0.34	NA	0	1	0	1
8. Widom (2006)	8.67	0	0	409	41.00	1	1	1	51	63	0	0.41	0.35	0	0	0	1
9. Young (2006)	12.76	0	1	247	NA	1	0	1	100	47	0	0.29	NA	0	0	0	1
10. Eisenberger (2007)	9.44	0	0	22	20.59	0	0	1	41	28	1	0.00	NA	0	1	0	0
11. Frazzetto (2007)	4.41	0	0	145	29.59	0	0	1	31	100	1	0.44	0.56	1	1	1	1
12. Prichard (2007)	2.06	0	0	1682	NA	1	1	1	60	100	1	0.38	0.38	0	0	1	0
13. Reif (2007)	6.69	0	1	169	34.10	0	1	0	100	100	2	0.33	NA	0	1	0	1
14. Ducci (2008)	15.47	1	1	326	37.80	1	0	1	0	0	0	0.00	0.38	0	1	0	1
15. Guo (2008)	4.40	0	0	2524	15.55	1	0	1	48	57	1	0.43	NA	2	1	0	0
16. Sjoberg (2008)	6.69	0	1	136	NA	1	0	1	100	100	0	0.40	NA	0	0	0	0
17. Alia-Klein (2009)	3.03	0	0	27	30.36	0	0	1	100	42	1	0.48	NA	0	1	0	0
18. Guimaraes (2009)	4.70	1	1	85	9.83	1	0	1	100	100	2	0.39	NA	0	0	0	0
19. McDermott (2009)	9.68	0	0	78	22.00	0	1	0	100	61	NA	0.27	NA	0	0	0	0
20. Prom-Wormley (2009)	5.20	0	0	730	NA	1	0	1	0	100	1	0.00	0.34	2	0	0	1
21. Qian (2009)	2.31	1	1	171	10.30	1	0	0	100	0	0	0.70	NA	0	1	1	0
22. Weder (2009)	8.67	0	0	114	9.70	0	0	0	66	24	1	0.00	NA	0	1	0	1
23. Williams (2009)	6.69	0	0	208	36.19	1	0	1	67	100	0	0.39	0.26	0	1	0	0
24. Derringer (2010)	3.00	0	0	841	NA	1	0	1	71	98	1	0.35	0.25	0	0	0	1
25. Edwards (2010)	4.28	0	0	186	NA	1	0	0	100	100	1	0.31	NA	0	1	0	1
26. Aslund (2010)	2.52	0	0	1427	NA	1	0	1	66		2	0.38	0.37	0	1	0	1
27. Fergusson (2011)	5.95	0	0	398	15.00	1	0	1	100	88	2	0.38	NA	0	0	0	1
28. Cicchetti (2012)	4.40	0	0	627	11.27	1	0	1	50	11	1	0.51	NA	0	0	0	1
29. McGrath (2012)	2.06	0	0	192	42.90	1	0	1	0	100	1	0.00	0.32	1	1	0	1
30. Gallardo-Pujol (2012)	3.48	0	0	57	22.77	0	1	0	100	100	1	0.37	NA	0	0	0	0

Table 3 continued

First author/year	Impact	Case Control[a]	Psychiatric[b]	*N*	Age	Broad ASB[c]	Objective Measure[d]	Self-Report[e]	% Male	% European	5R Coding[f]	Prop. Risk Allele Males	Prop. Risk Allele Females	Heterozygous Coding[g]	Reliability[h]	Validity[i]	GxE Study[j]
31. Verhoeven (2012)	NA	0	0	276	20.16	0	0	1	23	100	1	0.35	0.35	0	0	0	1

Refer to Table 1 for citation corresponding with study number

[a] Coding of 1 indicates case control study

[b] Coding of 1 indicates psychiatric sample

[c] Coding of 1 indicates a broadly defined phenotype (i.e., inclusion of both aggressive and non-aggressive behavior), and coding of 0 indicates phenotype was limited to aggression

[d] Coding of 1 indicates at least 1 objective measure was used in calculation of effect size

[e] Coding of 1 indicates at least 1 self-report measure was used in calculation of effect size

[f] Coding of 0 indicates study did not include the 5-repeat allele; coding of 1 indicates the 5-repeat allele was coded as low activity; coding of 2 indicates the 5-repeat allele was coded as high activity (two contrast terms were created from this variable, as described in text)

[g] Coding of 0 indicates study did not group heterozygous genotypes with homozygous genotypes; coding of 1 indicates heterozygous genotypes were grouped with low activity genotypes; coding of 2 indicates heterozygous genotypes were grouped with high activity genotypes

[h] Coding of 1 indicates study discussed/provided statistical support for reliability of the phenotypic measurement utilized

[i] Coding of 1 indicates study discussed/provided statistical support for the validity of the phenotypic measurement utilized

[j] Coding of 1 indicates the study purpose was to replicate the interaction of the MAOA-uVNTR (Caspi et al. 2002) with an index of childhood adversity (e.g. maltreatment)

overlap among many putative moderators, supporting the use of meta-regression to determine the unique contribution of each variable to the heterogeneity in effect sizes.

As previously described, associations between hypothesized moderators and effect sizes were examined using several meta-regression models (see Tables 5, 6, and 7 for moderator groupings). In the first model, we examined the role of sample characteristics in study effect sizes. Because there was a high level of redundancy between several variables describing the ethnic composition of the sample ("Percent Caucasian," "Percent African," and "Percent Asian") and the most observations were available for "Percent Caucasian," we chose not to include "Percent Asian" or "Percent African" in the model. In addition, because many studies of this marker did not utilize female samples, very few observations were available describing the proportion of the risk allele in females. As a result, this variable was also excluded from the analyses. The meta-regression of *MAOA-uVNTR* effect sizes on sample characteristics yielded a nonsignficant omnibus F-statistic, $F(5,16) = 0.96$, $p = 0.47$, indicating that the coded sample characteristics did not contribute significantly to heterogeneity in effect sizes for the *MAOA-uVNTR*. The omnibus F-statistic was also nonsignificant in the second model, indicating that the coded study characteristics also did not significantly contribute to explaining the observed heterogeneity, $F(7,14) = 0.76$, $p = 0.63$. Lastly, we examined the contribution of publication bias to the variability in reported effect sizes. The omnibus F-statistic in this model was also nonsignificant, $F(4,25) = 1.26$, $p = 0.31$.

5HTTLPR

Correlations among continuous and binary moderator variables for the *5HTTLPR* are shown in Table 5. Again, overlap was present among many putative moderators, supporting the use of meta-regression to examine the unique contributions to the heterogeneity observed across studies. "Percent Asian" and "Percent African" were once again removed prior to analysis due to substantial overlap with "Percent Caucasian." None of the three models testing putative moderators of *5HTTLPR* effect sizes emerged as significant [sample characteristics, $F(5,7) = 0.34$, $p = 0.87$; study characteristics, $F(6,11) = 0.70$, $p = 0.66$; publication bias, $F(3,12) = 1.71$, $p = 0.22$].

Discussion

The first aim of the current study was to conduct a comprehensive meta-analysis of the main effects of two serotonergic polymorphisms on antisocial phenotypes. For

Table 4 Study moderators (*5-HTTLPR*)

Study	Impact	Case control[a]	Psychiatric[b]	*N*	Age	Broad ASB[c]	Objective measure[c]	Self-report[e]	% Male	% European	Prop. risk allele	Heterozygous coding[f]	Reliability[g]	Validity[h]
1. Langley et al. (2003)	2.06	0	1	54	NA	1	0	0	0	100	0.44	0	0	0
2. Liao et al. (2004)	2.57	0	1	250	34.70	1	1	0	100	0	0.72	1	0	0
3. Gerra et al. (2005)	2.60	0	0	106	16.74	0	0	1	60	100	0.42	0	0	0
4. Beitchman et al. (2006)	12.54	1	1	154	9.54	0	0	0	85	100	0.39	0	0	0
5. Haberstick et al. (2006)	3.35	0	0	NA	NA	0	0	0	49	90	0.45	0	0	1
6. Sakai et al. (2006)	4.16	1	1	390	15.58	1	0	1	85	48	0.41	0	0	0
7. Verona et al. (2006)	3.35	0	0	111	21.00	0	1	0	50	82	0.72	2	0	0
8. Grevet et al. (2007)	2.60	1	1	312	34.10	1	0	1	53	100	0.48	0	0	0
9. Lyons-Ruth et al. (2007)	2.06	0	0	NA	NA	1	0	1	0	73	0.41	0	0	1
10. Nobile et al. (2007)	4.95	0	0	589	12.11	0	0	0	51	99	0.42	1	0	0
11. Reif et al. (2007)	7.99	0	1	184	34.10	0	1	0	100	100	NA	1	1	0
12. Brody et al. (2009)	4.72	0	0	440	11.00	1	0	1	47	0	0.24	1	0	0
13. Gonda et al. (2009)	3.64	0	0	86	32.13	0	0	1	0	100	0.39	0	0	0
14. Zimmerman et al. (2009)	4.36	0	0	91	12.00	0	0	0	49	100	0.42	1	0	1
15. Garcia et al. (2010)	2.80	0	1	147	33.31	1	0	1	1	100	0.45	1	1	1
16. Sakai et al. (2010)	2.06	0	0	224	NA	1	0	1	46	100	NA	0	1	1
17. Conway et al. (2012)	1.92	0	0	203	20.00	0	0	1	39	93	0.49	0	1	0
18. Sadeh et al. (2013)	4.86	0	1	237	30.90	1	0	1	100	29	0.33	0	1	0

Refer to Table 2 for citation corresponding with study number

[a] Coding of 1 indicates case control study

[b] Coding of 1 indicates Psychiatric Sample

[c] Coding of 1 indicates a broadly defined phenotype (i.e., inclusion of both aggressive and non-aggressive behavior), and coding of 0 indicates phenotype was limited to aggression

[d] Coding of 1 indicates at least 1 objective measure was used in calculation of effect size

[e] Coding of 1 indicates at least 1 self-report measure was used in calculation of effect size

[f] Coding of 0 indicates study did not group heterozygous genotypes with homozygous genotypes; coding of 1 indicates heterozygous genotypes were grouped with s/s genotypes; coding of 2 indicates heterozygous genotypes were grouped with l/l genotypes

[g] Coding of 1 indicates study discussed/provided statistical support for reliability of the phenotypic measurement utilized

[h] Coding of 1 indicates study discussed/provided statistical support for the validity of the phenotypic measurement utilized

Table 5 Sample characteristics: Pearson and point-biserial correlations among moderators of the *MAOA-uVNTR* and *5HTTLPR*

	1	2	3	4	5	6	7	8
1. Age (*M*)	1	−0.02	−0.04	−0.21	0.36	0.37		0.50
2. % Male	−0.36	1	−0.41	−0.10	0.44	0.15		0.39
3. % European	0.22	0.15	1	−0.73**	−0.66*	0.00		−0.17
4. % African	−0.27	−0.06	−0.66**	1	−0.10	−0.54		−0.14
5. % Asian	−0.33	0.10	−0.75**	−0.04	1	0.61*		0.32
6. Proportion of risk alleles (MAOA males)[a]	−0.24	0.54**	0.08	0.08	0.31	1		0.09
7. Proportion of risk alleles (MAOA females)[b]	−0.31	−0.25	−0.07	NA	NA	0.20	1	
8. Psychiatric sample	−0.10	0.20	−0.11	−0.11	0.30	0.16	0.18	1

Correlations for *MAOA-uVNTR* moderators are displayed below the diagonal; correlations for *5HTTLPR* moderators are displayed above the diagonal

NA indicates correlation could not be computed from the number of available data points

* indicates significance at $p < 0.05$; ** indicates significance at $p < 0.01$. Due to small numbers of studies for particular moderators, small and moderate associations did not achieve significance at $p < 0.05$

[a] Proportion of risk alleles (MAOA males) indicates the proportion of alleles within the sample considered "high risk" for the gene of interest within the full sample for 5HTTLPR or males only for MAOA-uVNTR

[b] Proportion of risk alleles (MAOA females) indicates the proportion of alleles within the sample considered "high risk" for the gene of interest and was only coded for the MAOA-uVNTR

Table 6 Study characteristics: Pearson and point-Biserial correlations among moderators of the MAOA-uVNTR and 5HTTLPR

	1	2	3	4	5	6	7	8
1. Broad ASB	1	−0.15	0.45			0.00	0.12	0.12
2. Objective measure	−0.12	1	−0.50*			0.32	0.06	−0.28
3. Self-report measure	0.38*	−0.21	1			−0.32	0.31	0.06
4. 5-Repeat contrast 1[a]	0.26	0.10	0.14	1				
5. 5-Repeat contrast 2[a]	−0.17	0.09	0.06	NA	1			
6. Heterozygous coding[b]	−0.10	−0.14	0.16	−0.22	0.15	1	0.09	0.09
7. Reliability	−0.21	−0.34	−0.21	−0.29	0.06	0.29	1	0.17
8. Validity	−0.01	0.08	−0.06	−0.22	−0.07	0.36	0.14	1

Correlations for *MAOA-uVNTR* moderators are displayed below the diagonal; correlations for *5HTTLPR* moderators are displayed above the diagonal; the risk allele for the *MAOA-uVNTR* = low activity allele

NA indicates correlation could not be computed from the number of available data points

* indicates significance at $p < 0.05$; ** indicates significance at $p < 0.01$; point-biserial correlations were used for dichotomous moderators. Due to small numbers of studies for particular moderators, small and moderate associations did not achieve significance at $p < 0.05$

[a] 5-repeat contrast 1 indicates contrast term for 5 repeat allele coded as low vs. high activity; 5-repeat contrast 2 indicates contrast term for 5-repeat grouped with low/high vs. ungrouped

[b] Heterozygous Coding indicates heterozygous individuals were included in the low activity group (coded as 1) or not included in the low activity group (coded as 0) for each allele

both polymorphisms, individuals with high-risk genotypes showed significant elevations in ASB, providing empirical support for the role of common serotonergic system variants in these phenotypes. Specifically, the genetic variants that resulted in increased availability of synaptic serotonin were associated with increased risk for ASB and aggression. Although the low activity alleles of these markers both appear to confer some risk, the magnitude of their effects suggest that each plays only a modest role in ASB phenotypes. Findings from recent genome-wide association studies of complex traits indicate that genetic effects of this size or smaller are likely to be the norm for individual loci, and that hundreds or thousands of genes may contribute to variation in complex traits such as aggression and ASB (Plomin and Davis 2009). Although the serotonergic markers examined in this study represent those most commonly studied with respect to ASB, more comprehensive coverage of common and rare variants within *5HTT* and *MAOA* as well as other serotonergic genes may explain additional variance in antisocial phenotypes.

Table 7 Publication bias: Pearson and point-biserial correlations among moderators of the *MAOA-uVNTR* and *5HTTLPR*

	1	2	3
1. Sample size	1	0.08	0.06
2. Order of publication	0.07	1	−0.06
3. Journal impact	−0.12	−0.46*	1
4. G × E adversity study[a]	0.04	0.24	0.25

Correlations for *MAOA-uVNTR* moderators are displayed below the diagonal; correlations for *5HTTLPR* moderators are displayed above the diagonal

* indicates significance at $p < 0.05$; ** indicates significance at $p < 0.01$. Due to small numbers of studies for particular moderators, small and moderate associations did not achieve significance at $p < 0.05$

[a] G × E adversity study indicates whether the study's purpose was to test for an interaction of the *MAOA-uVNTR* and an index of adversity on antisocial behavior ("yes" coded as 1, "no" coded as 0)

The notion that common variation within serotonergic genes may influence variation in ASB has been hypothesized for some time given previous findings that serotonergic variation has been associated with elevations in these behaviors (Brunner et al. 1993; Coccaro 1989; Nordquist and Oreland 2010) and psychotropic medications affecting serotonergic functioning can impact socio-emotional information processing (Harmer et al. 2004; Merens et al. 2007). It is plausible that serotonergic variants produce the emotional and behavioral characteristics associated with ASB by influencing structural and functional variation across neural regions such as the prefrontal cortex (Firk et al. 2013; Payer et al. 2012) and the amygdala (Murphy et al. 2013), which have been previously implicated in aggression and threat reactivity (Blair 2010; Gregg and Siegel 2001; Hariri et al. 2002). Future imaging genetics studies should focus on serotonin neurotransmission during tasks designed to elicit responses relevant to aggression (e.g., potential endophenotypes such as social information processing, threat reactivity) in order to provide us with a better understanding of the functional impact of these genes on ASB phenotypes. Given the heterogeneity found for the associations between serotonergic genes and ASB in the present investigation, it will also be important for us to determine whether the effects of serotonergic polymorphisms on these phenotypes are contingent upon the presence of other sources of genetic variation that have been found to impact serotonergic neurotransmission, for instance, the integrin beta 3 (*ITGB3*) gene recently found to impact serotonergic uptake in mice (Whyte et al. 2013).

Two additional aims concerned the presence of heterogeneity in effect sizes across studies. First, we sought to determine the extent of heterogeneity in effect sizes across studies for the *5HTTLPR* and *MAOA-uVNTR*. Substantial between-study heterogeneity was present for both markers, suggesting that the role of the high-risk genotypes for ASB may depend on various contextual factors. Second, we examined the roles of potential moderators of the heterogeneity across studies. Using a meta-regression strategy, we found that none of the coded sample characteristics (e.g., gender composition, ethnic composition, and age) nor study characteristics (e.g., ASB phenotypes examined, analytic strategy) were significantly associated with the effect sizes for either marker. Thus, we found little support for the notion that sample or methodological differences explain inconsistent genetic effects across studies, and it remains to be determined whether such inconsistencies may be characterized by other known factors. We encourage future investigators to provide more consistent information on additional study-level factors, including genotyping and quality control indices (e.g. Hardy–Weinberg equilibrium) in order to better inform the consistency and validity of individual study findings.

Several of our findings are of broad relevance to the etiology of ASB. First, effect sizes for these genetic variants did not differ by ASB phenotype, suggesting that broadly-defined ASB is affected by these serotonergic genes in much the same way as more specific traits such as aggression. These findings further support previous reports that putatively different ASB phenotypes such as CD, aggression, and delinquency share a common genetic basis (Baker et al. 2007). Nonetheless, our coding of sample and study characteristics was limited to the information that we could gather from the included studies. We were able to test in a very broad sense whether there were differences in the effect sizes of studies that used broad conceptualizations of ASB or more narrowly defined aggression, but there are more fine-grained distinctions in the measurement of antisocial and aggressive phenotypes that may serve to moderate study effects but for which information could not be gleaned (e.g., aggressive vs. non-aggressive ASB). Second, effect sizes for the serotonergic markers did not differ for community-based or clinically-referred samples. Consequently, it seems that these serotonergic genes influence variation in ASB in the general population just as they differentiate individuals with clinically significant levels of ASB from non-referred controls. Because each of these study designs assessed ASB using different instruments, we were unable to make any distributional comparisons regarding the symptom levels of those who were classified as community-based or clinically-referred. Thus, it is plausible that phenotypic heterogeneity within each of these samples due to differences in sampling strategies may have resulted in a large degree of overlap between the two, reducing our ability to detect meaningful differences. Finally, the finding that publication bias was present in studies of the *5HTTLPR* (with an apparent oversampling of

statistically significant effect sizes in the literature) should serve to caution investigators and reviewers alike against dismissing null findings in future studies. Publication bias continues to be a serious concern in clinical research, as the tendency to favor significant over null findings has inundated the field with reports of "false positive" associations (Simmons et al. 2011).

This study had several limitations. Primarily, because there were studies within the current meta-analysis that failed to report data across all the examined moderators, the pool of studies analyzed within each meta-regression model was limited to those containing information across all moderators. In order to determine whether examining each putative moderator separately (and thus increasing our N for some models) may have altered our findings, we conducted supplementary meta-regressions between each individual moderator and study effect sizes (see Supplementary Table 8). The pattern of nonsignificant results yielded for each individual moderator was similar to that which emerged in our previous meta-regression models (which accounted for the overlap among the moderators and utilized far fewer statistical tests) with the exception of two individual moderators that showed *marginally significant* negative associations with effect sizes for the *5HTTLPR*: order of publication and study reliability ($R^2 = 0.15$ and 0.12, respectively). According to these associations, studies that were published earlier and/or did not report information regarding the reliability of their phenotypic measurement tended to report larger effect sizes, a finding that would appear consistent with our earlier observation of significant publication bias for *5HTTLPR*. Notwithstanding, these associations were only marginally significant and were found in the context of multiple statistical tests, and these circumstances should be considered carefully when interpreting these findings. Consistent reporting of sample characteristics and methodology in future studies will permit greater power to detect moderators of genetic effects on ASB.

Another limitation of the current study is that we were unable to examine whether variation in rs25531 moderated associations between *5HTTLPR* and ASB. This A/G SNP within *5HTTLPR* has been reported to reduce the expression of *5-HTTLPR* for l-allele carriers to be similar to that of s-allele carriers (Wendland et al. 2006). Although some studies have differentiated between A and G allele carriers (L_A vs. L_G) in their analysis of the *5HTTLPR* (e.g., Beitchman et al. 2006; Butovskaya et al. 2012), the majority of studies included in the present meta-analysis did not. Thus, we were unable to determine whether differentiating between L_A and L_G genotypes impacted the effect sizes for this marker. Because it is plausible that rs25531 genotype is an important factor in the association between *5HTTLPR* and ASB, future studies of this marker should separate l-allele carriers into L_A and L_G subgroups prior to the examination of genotypic effects.

Finally, although we detected significant effects for the *MAOA-uVNTR* under the RE2 model ($p = 1.37 \times 10^{-6}$), the confidence interval for the meta-analytic OR (0.98–1.32) suggested only nominal significance. This occurred because Metasoft (Han and Eskin 2011) first utilizes the traditional random effects (RE) approach for estimating the meta-analytic effect size and confidence interval for a set of observed effects (taking heterogeneity—variation in the "true" effect size across studies—into account) then utilizes an alternative random-effects (RE2) model to determine the probability of the observed effects under the null hypothesis (Han and Eskin 2011). The RE2 model utilizes a likelihood ratio test instead of the traditional *z*-test, the rationale being that the traditional significance test for RE paradoxically assumes heterogeneity in effect sizes under the null hypothesis (Han and Eskin 2011). Please refer to Han and Eskin (2011) for a more in-depth discussion of this model and the underlying rationale. Because the RE2 model relaxes this assumption, it provides a more powerful test of the meta-analytic effects than the traditional RE method (Han and Eskin 2011). Consequently, as the effects of this marker appear to be particularly small and heterogeneous across studies, it is important that we exercise restraint in making inferences about the role of the *MAOA-uVNTR* in ASB.

In conclusion, the current meta-analysis provided evidence for main effects of the *5HTTLPR* and the *MAOA-uVNTR* on antisocial phenotypes. There was considerable heterogeneity in effect sizes across studies for both markers, which was not significantly associated with sample or study characteristics. Despite some limitations, the current investigation provides a comprehensive statistical analysis of the main effects of the two most commonly studied serotonergic genetic markers on ASB in children and adults.

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Conflict of Interest The authors declare that they have no conflict of interest.

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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