A meta-analytic evaluation of the endophenotype hypothesis: Effects of measurement paradigm in the psychiatric genetics of impulsivity.

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Abstract

Recent transitions in psychiatric nosology have stimulated discussion about what constructs, and what level of analysis, are most appropriate for the study of psychopathology. The endophenotype hypothesis suggests that neurobiological and neuropsychological phenotypes will be superior to trait or diagnostic measures in elucidating the substrates of psychopathology, as the former are more proximal, and therefore more sensitive, to underlying etiology. This meta-analysis explores these issues by comparing the magnitude of genetic effects associated with phenotypes at different levels of analysis. Studies of three common polymorphisms—the short and long variants of the serotonin-transporter-linked polymorphic region (5-HTTLPR), the variable number tandem repeat polymorphism in the 3' untranslated region of the dopamine active transporter gene (DAT1 3' UTR VNTR), and the 48 base-pair VNTR in exon-3 of the dopamine D4 receptor gene (DRD4)—and their effects on phenotypes of impulsivity were examined. Consistent with endophenotype theory, level of phenotype moderated the magnitude of genetic effects. Diagnostic, trait and neuropsychological, then neurobiological phenotypes yielded successively larger effects. However, consistent with emerging meta-analytic findings, neurobiological phenotypes were most susceptible to bias and inflation, raising questions about the validity of reported effects.

Keywords: Attention-Deficit Hyperactivity Disorder, endophenotype, genetics, impulsivity, level of analysis, nosology, RDoc

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Recent transitions in psychiatric nosology—as manifested, for example, in the recent DSM revision (DSM-5; APA, 2013), ongoing draft revisions of ICD-11, and the National Institute of Mental Health's Research Domain Criteria (RDoC; Insel et al., 2010)—have amplified discussion about the nature of psychiatric disorders. Current diagnostic systems have been criticized for a lack of reliability and validity, which is partially attributable to the categorical nature of current nosologies (Haslam, Hollands, & Kuppens, 2011; Markon, Chmielewski, & Miller, 2011; Widiger & Clark, 2000), but also symptomatic of a system that distinguishes poorly between boundaries of psychopathology (e.g. Clark, Watson, & Reynolds, 1995; Kendler, Karkowski, & Prescott, 1999). Indeed, genetic vulnerabilities tend to predispose individuals to broad spectra of psychopathology, such as internalizing and externalizing, rather than particular diagnoses (Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Kendler, Prescott, Myers, & Neale, 2003). Consequently, it has been proposed—through the Research Domain Criteria and other platforms—that psychiatric research shift away from diagnostic categories, toward the study of transdiagnostic domains and constructs. If, for example, alcohol abuse, substance abuse, and Antisocial Personality Disorder are all manifestations of a latent externalizing factor, which is in turn driven by a genetic liability, the externalizing factor will be the more reliable and valid indicator of that genetic liability.

Another question is whether current diagnostic systems function at an appropriate level of analysis for the study of psychopathology. For example, while DSM-5 workgroups have focused on honing the behavioral and cognitive criteria of psychopathology, others have argued that this

diagnostic system fails to address what is known of the genetic and neurobiological correlates of mental disorders (Hyman, 2007; Insel & Wang, 2010; Sanislow et al., 2010). The proposed Research Domain Criteria is one well-known manifestation of this viewpoint. Although the RDoC framework proposes to integrate genetic, molecular, cellular, and systems neuroscience with behavioral and self-reported indicators of psychopathology, the model conceptualizes mental disorders as, fundamentally, brain disorders (Insel et al., 2010). If the behavioral and cognitive presentations of mental illness proceed from genetic and neurocircuit susceptibilities, focusing on these more basic levels of analysis will be more effective in predicting, diagnosing, and treating mental illness (Insel & Wang, 2010).

These two questions—what constructs should be the focus of study, and at what level—are particularly relevant to the study of psychiatric genetics. The first identification of a genetic polymorphism associated with a psychiatric diagnoses is often followed by a succession of contradictory replication attempts (c.f. Lusher, Chandler, & Ball, 2001), and while association studies have identified a number of common variants contributing to psychopathology, these variants explain a modest proportion of phenotypic variance. Narrow-sense heritability estimates of schizophrenia, for example, are approximately .64 (Lichtenstein et al., 2009), yet the aggregate effect of 37,655 common single-nucleotide polymorphisms (SNPs) explains just 3% of total phenotypic variance (Purcell, Wray, Stone, & Visscher, 2009).[1]

[1] However, heritability estimates may be inflated when interactive effects are ignored (e.g. Stoltenberg, Christ, & Highland, 2012), or when the probability of twin ascertainment is a function of the trait of interest (Martin & Wilson, 1982). For these and other reasons, heritability estimates may be a high benchmark against which to gauge variance explained by SNPs.

Progress in psychiatric genetics has been fitful, but phenotypes that are more sensitive to genetic variation may provide an inroad to this issue. Endophenotype theory proposes that a number of processes—e.g. neuro-anatomical, neuropsychological, or self-reported traits—mediate the relationship between genotype and diagnosis. Insofar as endophenotypes are closer to the genetic basis of psychopathology, they should be more heritable and more closely associated with genetic variation than symptom scores and diagnoses (Gottesman & Gould, 2003). Endophenotypes may improve measurement reliability, validity, and consequently, statistical power.

Attempts to identify endophenotypes of psychiatric disorders, however, have met with mixed success. Trait phenotypes mediate a significant portion of genetic-diagnostic covariance (Kendler, Neale, Kessler, Heath, & Eaves, 1993), but when linked to specific polymorphisms, the significance of intermediate phenotypes is less clear. Flint and Munafò's (2007) meta-analysis examined the relationship between the catechol-O-methyltransferase $Val^{158/108}$ Met polymorphism and three proposed endophenotypes of schizophrenia. In this analysis, the proposed endophenotypes did not yield larger genetic effects than a diagnosis of schizophrenia. Furthermore, the two neuropsychological measures were significantly—albeit weakly—associated with the polymorphism, while the neurobiological phenotype was not. Theory predicts the last would be most sensitive.

Gottesman and Gould's endophenotype theory depicts a relatively direct effect of genes on the endophenotype which, in turn, drives the disorder. Since the endophenotype mediates the relationship between the gene and diagnosis, the effect of the gene on the endophenotype should

therefore be larger than the gene's effect on diagnosis. There are, however, a number of alternatives to this model. For example, the endophenotype and diagnosis may both be epiphenomenal to the disorder (Walters & Owen, 2007). In this formulation, sometimes termed the "liability index" model, no claims are made regarding the relationship between the endophenotype and diagnosis. Genetic variation is hypothesized to be causal to both phenotypes, so no *a priori* hypotheses are made regarding the strength of their genetic associations. Interpretation of this model is particularly difficult when measurement error is taken into account – if two phenotypes are epiphenomenal to the genetic variant, the magnitude of the genetic association will be driven by both proximity and measurement error. In this case, a distal but reliable phenotype may be more strongly association with genetic factors than an unreliable, proximal indicator (Kendler & Neale, 2010).

Three other alternatives to the mediational model are possible. First, the endophenotype may partially mediate the relationship between gene and disorder. Second, the disorder may mediate the relationship between the gene and proposed endophenotype (Kendler & Neale, 2010). For example, an individual's performance on the Continuous Performance Task may be driven by ADHD, or by a combination of ADHD and genetic liabilities. Third, a disorder may reflect the cumulative effect of many endophenotypes. In any of these three scenarios, diagnosis may be a stronger indicator than any single endophenotype.

The Present Study

This meta-analysis examined how level of analysis—diagnostic, trait, neuropsychological, and neurobiological phenotypes of impulsivity—moderates the magnitude of genetic associations. Insofar as they reflect a relatively homogeneous dimension of

impulsivity, trait, neuropsychological, and neurobiological indicators are predicted to be superior to diagnostic phenotypes. In addition, the most proximal phenotypes were predicted to yield the largest estimates of genetic effects.

Methods

Phenotypes of impulsivity. To evaluate the effect of phenotype on the results of psychiatric genetic research, this meta-analysis focuses on genetic association studies in the domain of impulsivity in adults[2]. Because impulsivity is a common liability for a number of maladaptive behaviors (including those manifested in ADHD, Conduct Disorder, substance abuse, pathological gambling, Kleptomania, Trichotillomania, and Intermittent Explosive Disorder; Brewer & Potenza, 2008; Fineberg et al., 2010) research regarding the genetic bases of impulsivity has the potential to inform our understanding of a broad range of psychopathology. Heritability estimates of impulsivity-related constructs such as adult ADHD (h^2 = .30; Boomsma et al., 2010), Conscientiousness (H^2 = .44; Jang, Livesley & Vernon, 1996), and latent externalizing (h^2 = .81; Krueger et al., 2002) are relatively high, suggesting a significant portion of phenotypic variability within the domain is attributable to additive genetic factors (though see footnote 1).

[2] We focused on adult impulsivity, even though the literature regarding impulsivity in childhood is rich, in order to avoid confounding level of analysis with informant. In contrast to adults, child temperament is most often assessed via informant reports of observable behavior. Comparing diagnoses of childhood impulsivity with neuropsychological phenotypes would confound level of analysis with informant, making it difficult to know which factor is reflected in patterns of genetic effects. Furthermore, as is discussed in Footnote 2, we also conducted a preliminary analysis of the 5-HTTLPR polymorphism including children, finding that age was not a significant moderator of effect on impulsivity, either among children (p = .90), or children and adults combined (p = .39). For these reasons, only studies of adults were included.

Impulsivity itself is a heterogeneous construct. For example, the Personality Inventory for DSM-5 identifies Irresponsibility, Impulsivity, and Distractibility as facets of Disinhibition (Krueger, Derringer, Markon, Watson, & Skodol, 2012). Other subsets of the construct have also been proposed (Evenden, 1999). Factor- and primary-components analyses of impulsivity measures often identify three facets (Sharma, Markon, & Clark, 2014). The first reflects sensation seeking and positive emotionality, and is related to substance abuse and risky behavior as seen in mania. The second factor reflects Neuroticism and negative emotionality (others refer to this facet as urgency, i.e. Cyders & Smith, 2007; Smith et al., 2007), and is relevant to aggressive impulsivity and anti-social traits (i.e. Snowden & Gray; 2011). The third facet reflects disinhibition and a lack of Conscientiousness, or disconstraint. This facet appears to be most closely related to behavioral impulsivity and impulse control problems, especially Attention-Deficit Hyperactivity Disorder (Barkley, 1997; Nigg et al., 2002). Each facet of impulsivity predicts a significant range of psychopathology. However, for reasons of clarity and practicality, the present analysis focuses on those measures of impulsivity reflecting disinhibition and a lack of constraint.

Table S1 provides a list of included phenotypes, grouped by level of analysis. Phenotypes of impulsivity were grouped into one of four levels:

Diagnosis. Adult ADHD is associated with trait impulsivity, as well as various neuropsychological measures of impulse control (Malloy-Diniz, Fuentes, Leite, Correa, & Bechara, 2007). Among adolescents with ADHD, substance abuse, and Conduct Disorder, ADHD is the most closely related to a latent factor of disinhibition (Young, Stallings, Corley, Krauter, & Hewitt, 2000). Included studies had to report diagnoses based on current symptoms in

adulthood, rather than a retrospective report of childhood symptoms or diagnoses. Symptom inventories based on ADHD diagnostic criteria, such as the Adult ADHD Self-Report Rating Scale and the Swanson, Nolan, and Pelham Rating Scale (SNAP-IV, Inattention and Hyperactivity subscale) were also included in this category, as well as studies in which a diagnostic group was defined by scores above a given threshold on these scales.

Trait phenotypes. Impulsivity is also closely associated with basic personality traits such as conscientiousness, as well as major dimensions of psychopathology such as externalizing. Trait measures of impulsivity included, among others, the Barratt Impulsiveness Scale (BIS-10 & BIS-11), Eysenck Personality Inventory (EPI, neuroticism subscale), I7 (Impulsivity subscale), Psychopathy Checklist (PCL, Impulsiveness subscale), and the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ, Impulsive Sensation Seeking Subscale). Measures were included if they loaded primarily onto the "disinhibition versus constraint" factor described in a meta-analysis of impulsivity measures (Sharma, Markon, & Clark, 2014), or if they could be demonstrated to correlate closely with another measure that did (i.e. the Impulsiveness subscale of the PCL; Snowden & Gray, 2011).

Neuropsychological phenotypes. At the level of neuropsychological assessment, phenotypes of impulsivity, particularly disconstraint, often measure prepotent response inhibition (i.e. the Continuous Performance Task; for a review see Robbins, Gillan, Smith, Wit, & Ersche, 2011). Measures included the Continuous Performance Task, Delay Discounting, Go/No-Go, Iowa Gambling, Multiple-Source Interference, Stop-Signal Reaction Time, and Stroop tasks, among others. Many of these tasks produce multiple outcome measures. Conner's Continuous Performance Task, for example, provides data on examinees' commission errors, correct

responses, reaction time, reaction time variance, and response style. Where possible, outcome measures were included if they demonstrated convergence with other measures of disconstraint (as described by Sharma, Markon, & Clark; 2014), or prepotent response inhibition (as opposed to set shifting, monitoring, or resistance to proactive interference; Friedman & Miyake, 2004; Miyake et al., 2000). For measures not included in either of those analyses, variables were included if they reliably correlated with phenotypes that were (for instance, Iowa Gambling Task block scores were included based on their correlation with ADHD diagnoses and BIS-11 scores; Malloy-Diniz, Fuentes, Leite, Correa, & Bechara, 2007).

Neurobiological phenotypes. At a neurobiological level, impulsivity may be reflected in the function of the right inferior frontal cortex, supplementary motor area, anterior cingulate cortex, and subthalamic nucleus (Aron et al., 2007; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). The right inferior frontal gyrus may be particularly significant, as both temporary and permanent deactivation of this region—via transcranial magnetic stimulation and lesion, respectively—prevents response inhibition (Aron, Fletcher, Bullmore, Shakian, & Robbins; 2003; Chambers et al., 2006). Neurobiological effects were not excluded based on locus. Since the effects of genotype on these regions is inconsistent (Durston, 2010), it is difficult to establish empirically-based inclusion and exclusion criteria for loci. Alternatively, basing these criteria on the brain regions associated with neuropsychological or trait phenotypes would constrain neurobiological effects to those loci affected by other levels of analysis, and would not necessarily clarify which regions should be included (Horn, Dolan, Elliot, Deakin, & Woodruff, 2003; Simmonds, Pekar, & Mostofsky, 2008).

EEG, ERP, and fMRI studies were included if neurobiological effects were derived from participants performing a task of behavioral inhibition. To avoid pleiotropic effects not specific to impulsivity, volumetric studies were excluded. Table S1 reports the neurobiological loci included in this analysis.

Genotypes of interest

Much of the literature surrounding genetic association studies of impulsivity focuses on childhood ADHD (Doyle et al., 2005; Gizer, Ficks, & Waldman, 2009; Kebir & Joober, 2011; Waldman, 2005). A qualitative review of the genetic association literature suggest the same risk genes relevant to childhood ADHD may apply to the disorder in adults (Faraone, 2004), but the putative risk genes have not yet been examined via meta-analysis. Genetic association studies of adults are inconsistent, but estimates of the narrow-sense heritability of ADHD in adults (h^2 = .30; Boomsma et al., 2010) suggest promise for the identification of genetic correlates of the disorder.

This meta-analysis focuses on three well-studied polymorphisms and their relationship to impulsivity: the short and long variants of the serotonin-transporter-linked polymorphic region (5-HTTLPR), the dopamine active transporter gene variable number tandem repeat (DAT1 3' UTR VNTR), and the dopamine D4 receptor gene VNTR (DRD4 48 base-pair exon-3 VNTR) (Faraone et al., 2005; Gizer, Ficks, & Waldman, 2009; Swanson et al. 2000; Wallis, Russell, & Muenke, 2008). These polymorphisms were selected for meta-analysis based on their hypothesized associations with impulsivity and adult ADHD (Brewer & Potenza, 2008; Faraone, 2004), and also based on the feasibility of meta-analytic comparisons between phenotypes, given the extent of their coverage in the existing genetic association literature.

Brief descriptions of the three polymorphisms and their mechanisms of action follow:

The serotonin 5-HTTLPR polymorphism. The short variant of the 5-HTTLPR polymorphism reduces *in vitro* expression of the serotonin transporter (Heils et al., 1996), and reduces uptake of serotonin from the synapse (Lesch et al., 1996). Since serotonergic regulation in the prefrontal cortex is proposed to facilitate response inhibition (Pavlov, Chistiakov, & Checkonin, 2012), dysregulation of synaptic serotonin may prevent contingent response inhibition (Evenden, 1999). However, evidence of the 5-HTTLPR polymorphism's relationship to other phenotypes of impulsivity, such as trait impulsivity and ADHD, is mixed (Chamberlain & Sahakian, 2007).

A second polymorphism, the rs25531 single nucleotide polymorphism, occurs within the serotonin-transporter-linked promotor region. This polymorphism moderates the transcription of the 5-HTT gene, the G allele being similar in function to the short variant of the 5-HTTLPR polymorphism (Hu et al., 2006). Studies genotyping the rs25531 polymorphism in addition to the 5-HTTLPR polymorphism were included in the meta-analysis. In all cases, these studies considered the G-allele a risk genotype, grouped G-allele carriers with the 5-HTTLPR short allele carriers, and analyzed the combined risk genotype. Inclusion of the rs25531 polymorphisms was analyzed as a potential moderator of effect size.

The dopamine active transporter 3' UTR VNTR. The 10-repeat polymorphism of the DAT1 3' UTR VNTR is associated with increased *in vitro* transcription and expression of the transporter in an additive fashion, causing a reduction of synaptic dopamine (Fuke et al., 2001; Mill, Asherson, Browes, D'Souza, & Craig, 2002). Dopamine's role in reward and reinforcement suggests dysfunctional regulation of the neurotransmitter may influence reward seeking

behaviors and impulse control. Heightened DAT1 activity caused by the 10 repeat of the DAT 3'-UTR VNTR may reduce blood flow in areas of significant dopaminergic activity, including the frontal lobe and striatum, weakening response inhibition (Arnsten, 2006; da Silva et al., 2011; Durston et al., 2008).

The dopamine D4 receptor VNTR. The dopamine D4 receptor binds synaptic dopamine, and like the dopamine transporter, is linked to reward and reinforcement learning. The 7-repeat allele may inhibit the receptor's signaling functionality (Asghari et al., 1995). Evidence of the polymorphism's association with impulsivity is mixed. In 1996, the 7-repeat allele was found to be associated with Cloninger's Novelty Seeking (Ebstein et al., 1996), one of the first associations to be discovered between a common genetic variant and a personality trait. Subsequent attempts to replicate the effect were inconsistent in their findings (for a review, see Lusher, Chandler, & Ball, 2001). Munafò, Yalcin, Willis-Owen, and Flint (2008) found no evidence for an association of the DRD4 exon-3 VNTR polymorphism with impulsivity, though phenotypes included in this meta-analysis included measures of Extraversion and other approach-related traits.

Literature Search and Data Abstraction

PsycINFO and PubMed databases were searched for articles, abbreviated publications, and dissertations studying genetic correlates of impulsivity. Terms related to genetic analysis (gene, genetic, allele, DRD4, DAT1, 5-HTT, dopamine gene, serotonin gene) and terms related to impulsivity and measures of impulsivity (e.g. Attention Deficit Hyperactivity Disorder, behavior inhibition, BIS, disinhibition, go no-go, Multidimensional Personality Questionnaire,

NEO, stop signal) were queried in a pairwise fashion. Titles and abstracts were scanned to identify relevant publications.

Studies included in the meta-analysis are listed in the Supplementary Material. In cases where authors reported only that an effect was not statistically significant, or reported partial information (such as group means without standard deviations), we contacted the corresponding author and requested the necessary information. All data obtained prior to January 2014 was included. Two studies reported only effect sizes within genotype groups. In these two cases, population genotype frequencies within the same ethnic group were substituted for the purposes of calculating study weights (DRD4 frequencies reported in Chang, Kidd, Livak, Pakstis, & Kidd, 1996 used in Cummins et al., 2011; DAT1 frequencies reported in Cook et al., 1995 used in Forbes et al., 2009). One study reported the effect of the DRD4 polymorphism on ADHD, mediated by a latent novelty-seeking variable (Lynn et al., 2005). This study was excluded, as the analysis conflated the effects of genotype and phenotype.

Studies were coded for publication type (peer-reviewed article, dissertation, or abbreviated report), year of publication, and the total number of polymorphisms genotyped. Sample characteristics included ethnicity (Caucasian, Asian, or other), gender balance, average age, and whether the sample clinical versus non-clinical (a clinical sample was defined as any sample in which participants were included based on presence of a psychological diagnosis). Occasionally, multiple analyses of the same sample were reported in different publications (i.e. the effect of the DAT1 3' UTR VNTR on BIS-11 scores is reported in Congdon, Lesch, & Canli, 2008, while Stop Signal Reaction Times from the same sample are reported in Congdon, 2009). Therefore, effect sizes were coded for the sample from which they were derived.

In all three polymorphisms, the risk allele functions additively; that is, the heterozygous genotype is functionally intermediate between genotypes homozygous for the risk and non-risk alleles (Fuke et al., 2001; Heils et al., 1996; Mill, Asherson, Browes, D'Souza, & Craig, 2002; Schoots & van Tol, 2003; van Tol et al., 1992). However, studies that assumed the risk allele was either dominant or recessive were also included in the analysis. Studies were coded for the assumed pattern of dominance, which was analyzed as a potential moderator of effect size.

The Common Language Effect Size

The common language effect size was used to describe genetic effects in this analysis. Generally, effect sizes in genetic association studies take one of three forms: odds ratios, Cohen's d, or tests of homogeneity such as F- or Chi-squared tests. The common language effect size was used because it can compare three groups, obviating the need to assume the risk-alleles are either dominant or recessive, and can describe both continuous and categorical data.

McGraw & Wong (1992) first published the common language effect size for contrasts between two groups, and Vargha & Delaney (2000) generalized the statistic to multi-group cases. Vargha and Delaney termed it the "measure of stochastic superiority," denoted by the letter A. This statistic represents the probability that an individual selected from one group will score higher on a given measure than an individual from another group, and can describe group differences on both continuous and dichotomous measures.

As an example, a researcher studying the 5-HTTLPR polymorphism might calculate $A_{ss\text{-}sl}$, which would represent the probability that an individual with the short-short 5-HTTLPR genotypes scores higher on the BIS-11 than an individual with the short-long genotype. In the

case of dichotomous indicators such as ADHD diagnoses, $A_{ss\text{-}sl}$ is the probability that an individual with a short-short genotype is diagnosed with ADHD while an individual with a short-long genotype is not, minus one-half the probability that both individuals are of the same diagnostic status (i.e. a tie).

In multinomial cases, the weighted absolute difference between A and .5 is averaged over genotypes to calculate the average absolute deviance (AAD, the probability of stochastic homogeneity). This statistic reflects the extent to which the distributions of phenotypes differ across multiple groups. Notably, the multinomial form of the statistic is non-directional. The AAD is equivalent to the area under a receiver operating characteristic (ROC) curve, and can be interpreted in terms of a sensitivity analysis. A value of .5 indicates no sensitivity of the phenotype to differences in genotype. In continuous indicators, both A and AAD are linear transformations of Cohen's d. When transformed, Cohen's thresholds for small, medium, and large effects are equivalent to A and AAD values of .56, .64, and .71, respectively (Cohen, 1977; Vargha & Delaney, 2000).

Where available, AAD values were calculated from group means and standard errors, or diagnostic counts, within genotypes. When only an effect size such as a t- or F-value was reported, the common language effect size was calculated via transformations reported in Ruscio (2008). Weights for each study were calculated as the inverse sampling variance of the observed AAD statistic. As there are no published formulas for this sampling variance, the sampling variance was estimated via simulations for each study. In studies reporting continuous phenotypes, 1,000 effects were drawn from a normal distribution based on group means and

standard deviations. In diagnostic studies, effects were simulated from a binomial distribution. Among studies reporting only an effect size, effects were transformed to a d statistic, and simulations were drawn from a normal distribution with a mean of the d-value and unit variance. Simulated effects were transformed into an AAD value, and variances were calculated from the distribution of simulated effects.

Regression Analyses

Meta-analytic effect size estimates were calculated using mixed-effect regression models. Effects sizes were nested within samples, with samples modeled as random effects. Phenotypes were modeled as fixed-effects, as were other moderator variable such as publication type and sample ethnicity. Effects were weighted by their inverse variance. Regression models were fit using the "lme4" package for R (Bates & Sarkar, 2007; R Development Core Team, 2010).

For descriptive purposes, confidence intervals of meta-analytic effect sizes were calculated by bootstrap sampling (Efron & Tibshirani, 1993). Due to the skewed and truncated distribution of AAD values, bias corrected and accelerated bootstrap intervals were used (Ruscio & Mullen, 2012). One-thousand nine-hundred ninety-nine replications were drawn, in order that the 2.5th quantiles would fall on, rather than between replications, using the "boot" package for R (Canty & Ripley, 2012).

Formal hypothesis testing was performed via permutation tests, as these have lower type I and type II error than bootstrap methods (Corcoran & Mehta, 2002). Permutation tests were used to determine whether predictors significantly improved model fit as measured by changes in AIC, BIC, and log likelihood values. Fifteen hundred permutations were simulated for each test.

Estimating Publication Bias

To determine how publication bias may influence meta-analytic effect size estimates, a bias sensitivity analysis was performed, based on a method described by Copas (2013). This method models publication as a probit function of the reported effect size. The estimated parameters of the publication selection function are then used to calculate the maximum likelihood estimate of the observed effects for a given degree of publication bias. Parameters of the probit model were calculated in R using the "rootSolve" package (Soetaert, 2009).

In addition, bias was estimated as a function of study power based on simulated AAD statistics, described above. Power was estimated as the proportion of simulated effects surpassing the meta-analytic estimate.

Results

Study characteristics

Of the 106 studies which met inclusion criteria, 93 (~88%) were full-length articles published in peer-reviewed journals, ten (~10%) were brief reports, letters, or communications to journals, and three (~3%) were unpublished dissertations. Year of publication ranged from 1996 to 2013. A majority (76 studies; 73%) were performed in non-clinical samples of Caucasian ethnicity (67 studies; 65%). Sample sizes ranged from 21 to 3247 (mean = 270; SD = 366), with an average participant age of 30.6 (range: 18-71). Gender balance ranged from entirely female to entirely male, with the average sample being 51% male.

Neither the publication type ($p = .27$), nor the year of publication ($p = .74$) moderated effect size. Within those studies genotyping the 5-HTTLPR polymorphism, grouping carriers of the G-allele of the rs25531 polymorphism with carriers of the short allele of the 5-HTTLPR did not moderate reported effect ($p = .83$), nor did the total number of polymorphisms genotyped (p

= .39). Sample type (clinical or non-clinical; p = .63), ethnicity (p = .64), gender balance (p = .46), and age (p = .43) were also non-significant. Age did not moderate effect size (p = .43).

Table 1 provides the number of effect sizes and subjects observed for each combination of genotype and phenotype. Most publications reported more than one phenotype effect – the 106 studies included yielded a total of 192 effects. Trait measures were the most common phenotypes (95 effects; 49%), followed by neuropsychological tests (49 effects; 26%). Neurobiological studies made up 10% of reported effects (20 effects), and ADHD diagnoses 15% (28 effects). The median number of polymorphisms genotyped was 1 (range: 1-151), with the serotonin promoter polymorphism being the most common, followed by the DRD4 exon-3 VNTR and DAT1 3' UTR VNTR polymorphisms (92, 57, and 43 reported effects, respectively).

Previous research indicates that each of the included risk alleles function additively (Fuke et al., 2001; Heils et al., 1996; Mill, Asherson, Browes, D'Souza, & Craig, 2002; Schoots & van Tol, 2003; van Tol et al., 1992). However, nearly half of the included studies assumed dominance of the risk allele, and combined those homozygous and heterozygous for the risk allele into a single group. Despite this, the presumed dominance pattern (dominant, recessive, or incomplete dominance) did not moderate the effect size among studies genotyping 5-HTTLPR (p = .33), DAT1 3' UTR VNTR (p = .31), or DRD4 exon-3 VNTR (p = .29).

Phenotype Effects

Across-polymorphism analyses. Table 2 provides mean predicted effect sizes and 95% confidence intervals for the four phenotype levels, as well as mean genetic effects for the entire sample and for specific polymorphisms. The mean bootstrap estimate of the effect of genotype on phenotype was .614 (95% CI: .608 to .653), meaning that individuals with different genotypes

differ in phenotype in 61% of cases. According to the interpretive guidelines of Vargha & Delaney (2000), genotype accounted for a small to medium amount of total phenotype variance.

Figure 1 shows a box plot of AAD values for each phenotype collapsed across polymorphisms. Figure 2 presents the bootstrap means and confidence intervals of the AAD values in the entire sample and within polymorphisms. In the entire sample (i.e., collapsed across polymorphisms) the level of phenotype was a significant moderator of effect size ($p < .001$), and remained significant when polymorphism was included as a covariate ($p < .001$). The smallest genetic effects were observed in studies of ADHD (AAD: .527; 95% CI: .514 to .531). Dichotomization did not moderate this effect – symptom counts were not different from diagnostic phenotypes ($p = .41$). Trait measures of impulsivity were larger in magnitude, (AAD: .596; 95% CI: .585 to .619), as were neuropsychological measures (AAD: .621; 95% CI: .607 to .659). The largest effect sizes were derived from neurobiological phenotypes (AAD: .814; 95% CI: .717 to .838). Differences between all phenotypes were significant (diagnosis versus trait contrast $p = .01$, neuropsychological versus neurobiological contrast $p < .001$), except the contrast between trait and neuropsychological phenotypes ($p = .44$).

Within-polymorphism analyses. The three polymorphisms did not differ significantly in their effect on phenotypes of impulsivity ($p = .85$). The serotonin promoter polymorphism yielded an average AAD of .600 (95% CI: .593 to .635). The effect of the DAT1 3' UTR VNTR was .616 (95% CI: .579 to .671). Studies of the DRD4 exon-3 VNTR reported an average effect of .620 (95% CI: .590 to .648).

Serotonin transporter. Within studies reporting the effect of the 5-HTTLPR polymorphism, phenotype level was a significant predictor of effect size ($p =<.001$). The

diagnostic phenotype predicted an average AAD of .522 (95% CI: .508 to .523). Trait phenotypes (AAD: .585; 95% CI: .571 to .608) and neuropsychological phenotypes (mean AAD: .628; 95% CI: .599 to .690) yielded significantly greater effect sizes. Neurobiological phenotypes demonstrated the largest effects (AAD: .939; 95% CI: .783 to .997). Only pairwise contrasts between neurobiological measures and other phenotypes were significant.[3]

Dopamine transporter. Overall, the DAT1 3' UTR VNTR was associated with an average AAD of .528 (95% CI: .513 to .539). The AAD of trait phenotypes was .580 (95% CI: .546 to .615). A larger effect was found in neuropsychological phenotypes (AAD: .629; 95% CI: .530 to .650). Neurobiological phenotypes had the largest effects (AAD: .888; 95% CI: .761 to .991). Only pairwise contrasts between neurobiological measures and other phenotypes were significant.

Dopamine D4 receptor. Phenotype was a significant moderator of effect size among studies of the DRD4 exon-3 VNTR ($p < .001$). The effect of genotype in diagnosis of ADHD yielded an average AAD of .534 (95% CI: .524 to .569). Trait measures of impulsivity were associated an effect of .632 (95% CI: .599 to .688). Neuropsychological measures were less informative than trait measures (AAD: .594; 95% CI: .577 to .638). Neurobiological studies reported higher effect sizes (AAD: .717; 95% CI: .530 to .779). Among pairwise contrasts

[3] An extension of this analysis was performed, integrating literature on the 5-HTTLPR polymorphism in children (19 diagnostic effects, 6 trait effects, and 2 neuropsychological effects). No neurobiological studies of children were identified. Except for the two neuropsychological studies, all effects were by informant report. The pattern of effects in the combined child and adult studies was largely consistent with adult studies alone. Diagnostic and trait phenotypes remained equally informative ($p = .20$), and the contrast between neuropsychological and neurobiological effects remained significant ($p = .01$). Neuropsychological effects became significantly more informative than diagnoses and trait effects ($p < .001$ and .02). Informant was not a significant moderator of genetic effects ($p = .10$), although informant and age were entirely confounded. Age was not a significant moderator of the effects in the combined sample ($p = .39$).

between phenotypes, only the contrast between neuropsychological and neurobiological measures was significant.

Publication Bias

Selective publication of statistically significant effects can bias meta-analyses, resulting in effect size estimates that are larger than the true population effect. Furthermore, if there are systematic differences in the degree of publication bias between phenotypes, true differences between levels of analysis may be masked or exaggerated. For example, if publication bias is stronger in neuropsychological studies than studies of ADHD, the apparent advantage of neuropsychological phenotypes may be attributable to publication bias, rather than a true difference.

Neuroimaging studies, especially exploratory analyses, are particularly susceptible to bias (Ioannidis, 2011; Vul, Harris, Winkielman, & Pashler, 2009). Indeed, the results of neurobiological studies were heterogeneous (see Supplementary Table 1 for the location of effects included in this analysis). For instance, Brown and colleagues (2010) identified hypoactivity in the left anterior cingulate cortex among DAT1 risk allele carriers. This was an *a priori* region of interest, and is consistent with the meta-analytic findings of Hart, Radua, Nakao, Mataix-Cols, and Rubia (2013). In contrast, Passamonti et al. (2008) found the short allele of the 5-HTTLPR polymorphism was associated with greater activity in the right anterior cingulate cortex, in contrast to research showing that serotonin depletion results in poor response inhibition via attenuated activity in the ACC (Eagle, Bari, & Robbins, 2008). In other studies, effects were distributed through regions of the brain that were not *a priori* regions of interest. For example, Filbey, Claus, Morgan, Forester, and Hutchison (2011) identified three clusters of fMRI

hypoactivation among carriers of the DRD4 7 risk allele. The clusters were identified via whole-brain analysis, and included the left temporal region (BAs 3, 4, 5, 6, and 47), a bilateral posterior region (BA 31), and a left prefrontal region (BAs 9, 10, & 11). Only the last cluster is consistent with other reports of neurological activity associated with successful response inhibition (i.e. Tamm, Menon, & Reiss, 2002).

To assess the degree to which multiple testing may have impacted these findings, a likelihood-based bias sensitivity analysis was performed (Copas, 2013). In this analysis, the probability of publication is modeled as a function of effect size, with larger effects being more likely to be published. This function is used to estimate what the true population effect might be, given the observed effects and a hypothetical level of publication bias.

Supplementary Figure 1 shows, for each phenotype level, the estimated population effect at three levels of publication bias. In general, estimated population effects did not appear especially sensitive to publication bias. This may be due to the small amount of between-sample heterogeneity, on which the selection function parameters are dependent. At any one level of publication bias, the order of effect size magnitudes was consistent with the endophenotype theory.

A second assessment of publication bias was performed via power analyses. Bias is greatest among studies with poor statistical power, as low power increases the standard error of the effect, and consequently, the range from which published effects are sampled (Zollner & Pritchard, 2007). Non-parametric power simulations calculated the probability that—given their sample size—the observed studies would detect an effect of the same magnitude as the meta-analytic estimate. Power among trait and neuropsychological phenotypes was good (power

= .94, and .9, respectively). Diagnostic and neurobiological studies had less power (power = .71 and .64). Among neurobiological indicators, functional neuroimaging studies were underpowered (power = .55), consistent with other reports of power within the field of neuroscience (Button et al., 2013).

Discussion

Psychiatric nosologies are increasingly emphasizing constructs that span a broad range of psychopathology. This shift is based on the precept that transdiagnostic constructs—such as internalizing, externalizing, psychoticism, and impulsivity—are more reliable and valid than heterogeneous diagnostic categories. Second, it has been suggested that psychiatric diagnosis may be an inappropriate level of analysis for many areas of research. If traits, neuropsychological, and neurobiological phenotypes are more influenced by genetic variability than diagnoses, they may be more powerful indicators of genetic variants. This meta-analysis provides evidence consistent with both hypotheses.

In analyses of the three polymorphisms combined, the diagnostic phenotype was less sensitive to genetic variance than relatively homogeneous, transdiagnostic phenotypes. Two factors may limit the effectiveness of diagnostic phenotypes. First, dichotomous measures attenuate reliability and validity (Markon, Chmielewski, & Miller, 2011), though that phenomenon was not observed in this sample. Secondly, diagnostic heterogeneity may limit reliability. Genetic variance is associated with a diagnosis of ADHD, but to a lesser extent than it is associated with trait phenotypes. This may be because criteria of ADHD include symptoms of both inattention and hyperactivity, and are heterogeneous compared to the trait measures included in this analysis, which were selected based on their observed relationship to a particular

facet of impulsivity. Similar effects are observed in the domain of externalizing, in which the symptoms of four externalizing disorders are less robust indicators of genetic variability than the common variance described by a general externalizing component (Dick et al., 2008).

The observed results are consistent with the endophenotype hypothesis, too, in that the largest effects were observed in phenotypes that are thought to be most proximal to genetic etiologies. Among the combined polymorphisms, trait and neuropsychological measures are more robust indicators of genetic variance than diagnosis. Neurobiological measures are associated with the largest genetic effects. These results mirror those of another recent quantitative review of the schizophrenia literature, which found that neuroimaging studies are associated with larger effects than cognitive measures (Rose & Donohoe, 2013).

Two exceptions to the expected pattern were found. First, in combined polymorphism analyses, the magnitudes of genetic effects on trait and neuropsychological measures were not distinguishably different. In the analysis of DRD4 VNTR, the expected order of these two phenotypes was reversed. This may reflect a lack of sufficient statistical power to differentiate the two, or may indicate that neuropsychological and trait measures are equally informative. Secondly, the patterns observed in combined gene analyses were not observed in all single-gene analyses. This may also be a function of statistical power, or may be a function of the effect of each genotype on the domain in question.

Limitations

Bias. Meta-analytic effect size estimates can be biased, particularly when a large number of non-significant effects go unpublished. This concern is especially salient in psychiatric genetic research, as the published loci may be a small subset of those genotyped (Ioannidis, Ntzani,

Trikalinos, & Contopoulos-Ioannidis; 2001). The problem is compounded in neuroimaging research when only the largest effects from exploratory analyses are reported (Ioannidis, 2011; Vul, Harris, Winkielman, & Pashler, 2009). Neuroimaging effects may be large, but if the direction and location of those effects is unreliable, they may not inform our understanding of the etiology of psychopathology. Notably, neurobiological phenotypes were not excluded from this analysis on the basis of location. Furthermore, the limited number of effects prevented signed differential mapping, which would be sensitive to direction and location. The AAD statistic does not reflect the directionality of effects. More neuroimaging genetic research is necessary to validate these effects.

However, publication bias does not entirely explain the observed pattern of effects. When explicitly modeled, publication bias does not change the rank ordering of phenotypes. That is, even assuming the smallest 80% of effects are not published, the observed neurobiological effects are still larger in magnitude than neuropsychological and trait effects, which are in turn larger than diagnostic effects. Similar research based on power simulations has demonstrated that the potential for bias increases as power decreases (Zollner and Pritchard, 2007). By those simulations, the observed trait and neuropsychological effects are potentially unbiased, while diagnostic and neurobiological phenotypes may be biased by up to 10%. Within the subset of functional neuroimaging studies observed in this analysis, effects may be biased by 15% (all percentages estimated from Figure 2 of Zollner and Pritchard, 2007). In summary, formal analyses suggest that bias may skew the magnitude of the meta-analytic effect estimates, but does not disrupt their rank order.

Mediation versus epiphenomena. Although level of analysis moderates the magnitude of genetic effects, it is worth noting that this analysis did not test the mediational form of the endophenotype hypothesis, as too few studies in the dataset reported correlations among phenotypes. So, even though genotype has a stronger effect on neuropsychological phenotypes than diagnosis, the latter effect is not necessarily mediated by the former. While the observed trend of effect sizes is consistent with Gottesman and Gould's (2003) mediational model, it is possible that all phenotypes are either epiphenomena of genetic variation, or reflect both direct and mediated pathways between genotype and phenotype (i.e. as discussed by Kendler & Neale, 2010). If all phenotypes are epiphenomenal, the correlation between genotype and phenotype will be driven by measurement error, rather than proximity. Given the comparative reliabilities of some of the included phenotypes we examined (e.g., Markon, Chmielewski, & Miller, 2011 for a comparison of trait and dichotomous effects), this model is certainly plausible. However, as differences in reliabilities between neuropsychological tasks and neuroimaging effects are unclear (e.g., Aron, Gluck, and Poldrack, 2006; Freyer et al., 2009; Manoach, et al., 2001), an epiphenomenal model may not entirely account for the observed pattern. Further research is needed to understand the role of differential measurement error across paradigms.

Generalizability. Compared to other diagnoses, the literature on adult ADHD is relatively small. Furthermore, the diagnosis is atypical, in that the diagnostic criteria are based on the hypothesis of a specific neurodevelopmental trajectory.[4] It is unclear whether the same patterns would be observed in other diagnostic phenotypes associated with impulsivity, such as

[4] However, preliminary analyses within the 5-HTTLPR genotype, discussed in footnotes 2 and 3, suggest these findings extend to children.

substance use, anti-social behavior, or other externalizing phenomena. Similarly, the extent to which these results generalize to other domains of psychopathology, outside the domain of disconstraint or externalizing psychopathology, is somewhat unclear. Emerging research does support our findings with regards to psychosis (Rose & Donohoe, 2013), suggesting that this pattern will generalize to other domains. However, further research is clearly needed.

Utility. Level of analysis has a significant effect on the results of psychiatric genetic research. Regardless of how the pattern observed here is best explained—whether in terms of Gottesman and Gould's (2003) mediational model of endophenotypes or in terms of differential measurement error—the current results suggest that the endophenotype paradigm has certain practical utility in scientific inquiry.

Nevertheless, the best phenotypes may not always be the most proximal to genetic etiologies. The best level of analysis likely depends on the area of research, and the extent to which endophenotypes are associated with behaviors of clinical interest. In clinical studies, for example, trait measures or symptom counts may be more sensitive to therapeutic intervention than neuropsychological or neurobiological phenotypes, if the latter have weak relationships with the clinical constructs of interest. Even if the endophenotype has a strong, well-understood etiology, it may not mediate the etiology-psychopathology relationship if its association with psychopathology is weak.

Future directions for research

Emerging research supports the observed relationship between phenotype proximity and the magnitude of genetic effects (c.f. Rose & Donohoe, 2013). However, this literature is relatively new. Future research should explore whether the pattern of results is sensitive to the

diagnosis in question. Other diagnostic phenotypes may be more reliable than adult ADHD, and therefore demonstrate stronger associations with genetic variants.

Second, this analysis revealed a pattern of effects consistent with the endophenotype hypothesis. However, to discriminate between a mediational and epiphenomenal model, the proposed endophenotype must correlate not only with the genetic variant, but also with diagnostic phenotype. Future research should confirm these intermediate links.

Conclusions

Diagnostic, trait, neuropsychological, and neurobiological phenotypes reflect genetic liabilities of impulsivity in a manner consistent with endophenotype theory. Neuropsychological and trait measures of impulsivity were more sensitive diagnostic phenotypes. Genetic risk may be most clearly reflected in neurobiological phenotypes, though the accuracy of these effects remains in question. In addition, transdiagnostic phenotypes of impulsivity are more sensitive to genetic liabilities than diagnostic phenotypes. These results lend evidence to current shifts toward dimensional, transdiagnostic conceptualizations of psychopathology, particularly in psychiatric genetic research. Psychiatric genetics depends on the strength of its measures: phenotypes that are most sensitive to genetic liabilities are of practical significance to researchers, and may allow for more precise etiological research.

References

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th edition.). Washington, DC.

Arnsten, A. F. T. (2006). Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. *The Journal of Clinical Psychiatry*, *67 Suppl 8*, 7–12.

Aron, A. R., Durston, S., Eagle, D. M., Logan, G. D., Stinear, C. M., & Stuphorn, V. (2007). Converging Evidence for a Fronto-Basal-Ganglia Network for Inhibitory Control of Action and Cognition. *The Journal of Neuroscience*, *27*(44), 11860–11864. doi:10.1523/JNEUROSCI.3644-07.2007

Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakian, B. J., & Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience*, *6*(2), 115–116. doi:10.1038/nn1003

Aron, A. R., Gluck, M. A., & Poldrack, R. A. (2006). Long-term test-retest reliability of functional MRI in a classification learning task. *NeuroImage*, 29(3), 1000–1006. doi:10.1016/j.neuroimage.2005.08.010

Asghari, V., Sanyal, S., Buchwaldt, S., Paterson, A., Jovanovic, V., & Van Tol, H. H. M. (1995). Modulation of Intracellular Cyclic AMP Levels by Different Human Dopamine D4 Receptor Variants. *Journal of Neurochemistry*, *65*(3), 1157–1165. doi:10.1046/j.1471-4159.1995.65031157.x

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin*, *121*(1), 65–94. doi:10.1037/0033-2909.121.1.65

Bates, D., & Sarkar, D. (2007). *lme4: Linear mixed-effects models using S4 classes*.

Boomsma, D. I., Saviouk, V., Hottenga, J.-J., Distel, M. A., de Moor, M. H. M., Vink, J. M., … Willemsen, G. (2010). Genetic Epidemiology of Attention Deficit Hyperactivity Disorder (ADHD Index) in Adults. *PLoS ONE*, *5*(5), e10621. doi:10.1371/journal.pone.0010621

Brewer, J. A., & Potenza, M. N. (2008). The neurobiology and genetics of impulse control disorders: Relationships to drug addictions. *Biochemical Pharmacology*, *75*(1), 63–75.

Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, *14*(5), 365–376. doi:10.1038/nrn3475

Canty, A. & Ripley, B. (2012). boot: Bootstrap R (S-Plus) Functions. R package version 1.3-7.

Chamberlain, S. R., & Sahakian, B. J. (2007). The neuropsychiatry of impulsivity. *Current Opinion in Psychiatry*, *20*(3), 255–261. doi:10.1097/YCO.0b013e3280ba4989

Chambers, C. D., Bellgrove, M. A., Stokes, M. G., Henderson, T. R., Garavan, H., Robertson, I. H., … Mattingley, J. B. (2006). Executive "Brake Failure" following Deactivation of Human Frontal Lobe. *Journal of Cognitive Neuroscience*, *18*(3), 444–455. doi:10.1162/jocn.2006.18.3.444

Chang, F.-M., Kidd, J. R., Livak, K. J., Pakstis, A. J., & Kidd, K. K. (1996). The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. *Human Genetics*, *98*(1), 91–101. doi:10.1007/s004390050166

Clark, L. A., Watson, D., & Reynolds, S. (1995). Diagnosis and Classification of Psychopathology: Challenges to the Current System and Future Directions. *Annual Review of Psychology*, *46*(1), 121–153. doi:10.1146/annurev.ps.46.020195.001005

Cohen, J. (1977). *Statistical power analysis for the behavioral sciences* (Revised Edition.). New York: Academic Press.

Cook, E., Stein, M., Krasowski, C., Olkon, D., Kieffer, J., & Leventhal, B. (1995). Association of attention-deficit disorder and the dopamine transporter gene. *American Journal of Human Genetics*, *56*(4), 993.

Copas, J. B. (2013). A likelihood-based sensitivity analysis for publication bias in meta-analysis. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, *62*(1), 47–66. doi:10.1111/j.1467-9876.2012.01049.x

Corcoran, C. D., & Mehta, C. R. (2002). Exact level and power of permutation, bootstrap, and asymptotic tests of trend. *Journal of Modern Applied Statistical Methods*, 1, 42-51.

Cyders, M. A., & Smith, G. T. (2007). Mood-based rash action and its components: Positive and negative urgency. *Personality and Individual Differences*, *43*(4), 839–850. doi:10.1016/j.paid.2007.02.008

Dick, D., Fazil, A., Wang, J., Grucza, R., Schuckit, M., Kuperman, S., … Goate, A. (2008). Using dimensional models of externalizing psychopathology to aid in gene identification. *Archives of General Psychiatry*, *65*(3), 310–318.

Doyle, A. E., Faraone, S. V., Seidman, L. J., Willcutt, E. G., Nigg, J. T., Waldman, I. D., … Biederman, J. (2005). Are endophenotypes based on measures of executive functions useful for molecular genetic studies of ADHD? *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *46*(7), 774–803. doi:10.1111/j.1469-7610.2005.01476.x

Durston, S. (2010). Imaging genetics in ADHD. *NeuroImage, 53*(3), 832–838. doi:10.1016/j.neuroimage.2010.02.071

Durston, S., Fossella, J. A., Mulder, M. J., Casey, B. J., Ziermans, T. B., Vessaz, M. N., & Van Engeland, H. (2008). Dopamine transporter genotype conveys familial risk of attention-deficit/hyperactivity disorder through striatal activation. *Journal of the American Academy of Child and Adolescent Psychiatry, 47*(1), 61–67. doi:10.1097/chi.0b013e31815a5f17

Eagle, D. M., Bari, A., & Robbins, T. W. (2008). The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. *Psychopharmacology, 199*(3), 439–456. doi:10.1007/s00213-008-1127-6

Efron, B., & Tibshirani, R. (1993). *An Introduction to the Bootstrap*. CRC Press.

Evenden, J. L. (1999). Varieties of impulsivity. *Psychopharmacology, 146*(4), 348–361. doi:10.1007/PL00005481

Faraone, S. V. (2004). Genetics of adult attention-deficit/hyperactivity disorder. *Psychiatric Clinics of North America, 27*(2), 303–321. doi:10.1016/S0193-953X(03)00090-X

Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A., & Sklar, P. (2005). Molecular Genetics of Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry, 57*(11), 1313–1323. doi:10.1016/j.biopsych.2004.11.024

Fineberg, N. A., Potenza, M. N., Chamberlain, S. R., Berlin, H. A., Menzies, L., Bechara, A., … Hollander, E. (2010). Probing Compulsive and Impulsive Behaviors, from Animal Models to Endophenotypes: A Narrative Review. *Neuropsychopharmacology, 35*(3), 591–604. doi:10.1038/npp.2009.185

Flint, J., & Munafò, M. (2007). The Endophenotype Concept in Psychiatric Genetics. *Psychological Medicine*, *37*(02), 163–180. doi:10.1017/S0033291706008750

Freyer, T., Valerius, G., Kuelz, A. K., Speck, O., Glauche, V., Hull, M., & Voderholzer, U. (2009). Test–retest reliability of event-related functional MRI in a probabilistic reversal learning task. *Psychiatry Research: Neuroimaging*, *174*(1), 40-46.

Friedman, N. P., & Miyake, A. (2004). The Relations Among Inhibition and Interference Control Functions: A Latent-Variable Analysis. *Journal of Experimental Psychology: General*, *133*(1), 101–135. doi:10.1037/0096-3445.133.1.101

Fuke, S., Suo, S., Takahashi, N., Koike, H., Sasagawa, N., & Ishiura, S. (2001). The VNTR polymorphism of the human dopamine transporter (DAT1) gene affects gene expression. *The Pharmacogenomics Journal*, *1*(2), 152–156. doi:10.1038/sj.tpj.6500026

Gizer, I. R., Ficks, C., & Waldman, I. D. (2009). Candidate gene studies of ADHD: a meta-analytic review. *Human Genetics*, *126*(1), 51–90. doi:10.1007/s00439-009-0694-x

Gottesman, I. I., & Gould, T. D. (2003). The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. *American Journal of Psychiatry*, *160*(4), 636–645. doi:10.1176/appi.ajp.160.4.636

Hart, H., Radua, J., Nakao, T., Mataix-Cols, D., & Rubia, K. (2013). Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: Exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry*, *70*(2), 185–198. doi:10.1001/jamapsychiatry.2013.277

Haslam, N., Holland, E., & Kuppens, P. (2011). Categorical versus dimensions in personality and psychopathology: a quantitative review of taxometric research. *Psychological Medicine*, *41*(11), 1–18. doi:10.1017/S0033291711001966

Heils, A., Teufel, A., Petri, S., Stöber, G., Riederer, P., Bengel, D., & Lesch, K. P. (1996). Allelic Variation of Human Serotonin Transporter Gene Expression. *Journal of Neurochemistry*, *66*(6), 2621–2624. doi:10.1046/j.1471-4159.1996.66062621.x

Hicks, B. M., Krueger, R. F., Iacono, W., McGue, M., & Patrick, C. J. (2004). Family transmission and heritability of externalizing disorders: A twin-family study. *Archives of General Psychiatry*, *61*(9), 922–928. doi:10.1001/archpsyc.61.9.922

Horn, N. R., Dolan, M., Elliott, R., Deakin, J. F. W., & Woodruff, P. W. R. (2003). Response inhibition and impulsivity: an fMRI study. *Neuropsychologia*, 41(14), 1959–1966. doi:10.1016/S0028-3932(03)00077-0

Hu, X.-Z., Lipsky, R. H., Zhu, G., Akhtar, L. A., Taubman, J., Greenberg, B. D., … Goldman, D. (2006). Serotonin Transporter Promoter Gain-of-Function Genotypes Are Linked to Obsessive-Compulsive Disorder. *The American Journal of Human Genetics*, *78*(5), 815–826. doi:10.1086/503850

Hyman, S. E. (2007). Can neuroscience be integrated into the DSM-V? *Nature Reviews Neuroscience*, *8*(9), 725–732. doi:10.1038/nrn2218

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., … Wang, P. (2010). Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. *American Journal of Psychiatry*, *167*(7), 748–751. doi:10.1176/appi.ajp.2010.09091379

Insel, T., & Wang, P. (2010). Rethinking mental illness. *JAMA*, *303*(19), 1970–1971. doi:10.1001/jama.2010.555

Ioannidis, J. P. A. (2011). Excess significance bias in the literature on brain volume abnormalities. *Archives of General Psychiatry*, *68*(8), 773–780. doi:10.1001/archgenpsychiatry.2011.28

Ioannidis, J. P. A., Ntzani, E. E., Trikalinos, T. A., & Contopoulos-Ioannidis, D. G. (2001). Replication validity of genetic association studies. *Nature Genetics*, *29*(3), 306–309. doi:10.1038/ng749

Jang, K. L., Livesley, W. J., & Vemon, P. A. (1996). Heritability of the Big Five Personality Dimensions and Their Facets: A Twin Study. *Journal of Personality*, *64*(3), 577–592. doi:10.1111/j.1467-6494.1996.tb00522.x

Kebir, O., & Joober, R. (2011). Neuropsychological endophenotypes in attention-deficit/hyperactivity disorder: a review of genetic association studies. *European Archives of Psychiatry and Clinical Neuroscience*, *261*(8), 583–594. doi:10.1007/s00406-011-0207-5

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Fears and phobias: reliability and heritability. *Psychological Medicine*, *29*(03), 539–553.

Kendler, K. S., & Neale, M. C. (2010). Endophenotype: a conceptual analysis. *Molecular Psychiatry*, *15*(8), 789–797. doi:10.1038/mp.2010.8

Kendler, K., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. (1993). A longitudinal twin study of personality and major depression in women. *Archives of General Psychiatry*, *50*(11), 853–862. doi:10.1001/archpsyc.1993.01820230023002

Kendler, K. S., Prescott, C. A., Myers, J. M., & Neale, M. C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry*, *60*, 929–937.

Krueger, R. F., Hicks, B. M., Patrick, C. J., Carlson, S. R., Iacono, W. G., & McGue, M. (2002). Etiologic connections among substance dependence, antisocial behavior and personality: Modeling the externalizing spectrum. *Journal of Abnormal Psychology*, *111*(3), 411–424. doi:10.1037/0021-843X.111.3.411

Krueger, R. F., Derringer, J., Markon, K. E., Watson, D., & Skodol, A. E. (2012). Initial construction of a maladaptive personality trait model and inventory for DSM-5. *Psychological Medicine*, 42, 1879-1890.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., … Murphy, D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science (New York, N.Y.)*, *274*(5292), 1527–1531.

Lichtenstein, P., Yip, B., Bjork, C., Pawitan, Y., Cannon, T., Sullivan, P., & Hultman, C. (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *The Lancet*, *373*(9659), 234–239. doi:10.1016/S0140-6736(09)60072-6

Lusher, J., Chandler, C., & Ball, D. (2001). Dopamine D4 receptor gene (DRD4) is associated with Novelty Seeking (NS) and substance abuse: the saga continues . . . *Molecular Psychiatry*, *6*(5). doi:10.1038/sj.mp.4000918

Lynn, D. E., Lubke, G., Yang, M., McCracken, J. T., McGough, J. J., Ishii, J., … Smalley, S. L. (2005). Temperament and character profiles and the dopamine D4 receptor gene in

ADHD. *The American Journal of Psychiatry*, *162*(5), 906–913. doi:10.1176/appi.ajp.162.5.906

Malloy-Diniz, L., Fuentes, D., Leite, W. B., Correa, H., & Bechara, A. (2007). Impulsive behavior in adults with attention deficit/ hyperactivity disorder: Characterization of attentional, motor and cognitive impulsiveness. *Journal of the International Neuropsychological Society*, *13*(04), 693–698. doi:10.1017/S1355617707070889

Manoach, D. S., Halpern, E. F., Kramer, T. S., Chang, Y., Goff, D. C., Rauch, S. L., ... & Gollub, R. L. (2001). Test-retest reliability of a functional MRI working memory paradigm in normal and schizophrenic subjects. *American Journal of Psychiatry*, *158*(6), 955-958.

Markon, K. E., Chmielewski, M., & Miller, C. J. (2011). The reliability and validity of discrete and continuous measures of psychopathology: A quantitative review. *Psychological Bulletin*, *137*(5), 856–879. doi:10.1037/a0023678

Martin, N. G., & Wilson, S. R. (1982). Bias in the estimation of heritability from truncated samples of twins. Behavior Genetics, 12(4), 467–472. doi:10.1007/BF01065638

McGraw, K. O., & Wong, P. S., (1992). A common language effect size statistic. *Psychological Bulletin*, *111*(2), 361–365. doi:10.1037/0033-2909.111.2.361

Mill, J., Asherson, P., Browes, C., D'Souza, U., & Craig, I. (2002). Expression of the dopamine transporter gene is regulated by the 3′ UTR VNTR: Evidence from brain and lymphocytes using quantitative RT-PCR. *American Journal of Medical Genetics*, *114*(8), 975–979. doi:10.1002/ajmg.b.10948

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex

"Frontal Lobe" tasks: a latent variable analysis. *Cognitive Psychology*, *41*(1), 49–100. doi:10.1006/cogp.1999.0734

Munafò, M. R., Yalcin, B., Willis-Owen, S. A., & Flint, J. (2008). Association of the dopamine D4 receptor (DRD4) gene and approach-related personality traits: meta-analysis and new data. *Biological Psychiatry*, *63*(2), 197–206. doi:10.1016/j.biopsych.2007.04.006

Nigg, J. T., John, O. P., Blaskey, L. G., Huang-Pollock, C. L., Willicut, E. G., Hinshaw, S. P., & Pennington, B. (2002). Big Five dimensions and ADHD symptoms: Links between personality traits and clinical symptoms. *Journal of Personality and Social Psychology*, *83*(2), 451–469. doi:10.1037/0022-3514.83.2.451

Pavlov, K. A., Chistiakov, D. A., & Chekhonin, V. P. (2012). Genetic determinants of aggression and impulsivity in humans. *Journal of Applied Genetics*, *53*(1), 61–82. doi:10.1007/s13353-011-0069-6

Purcell, S. M., Wray, N. R., Stone, J. L., & Visscher, PM. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, *460*(7256), 748–752. doi:10.1038/nature08185

R Development Core Team. (2010). *R: A Language and Environment for Statistical Computing*. Vienna, Austria. Retrieved from http://www.R-project.org

Robbins, T. W., Gillan, C. M., Smith, D. G., De Wit, S., & Ersche, K. D. (2012). Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends in Cognitive Sciences*, *16*(1), 81–91. doi:10.1016/j.tics.2011.11.009

Rose, E. J., & Donohoe, G. (2013). Brain vs Behavior: An Effect Size Comparison of Neuroimaging and Cognitive Studies of Genetic Risk for Schizophrenia. *Schizophrenia Bulletin*, *39*(3), 518–526. doi:10.1093/schbul/sbs056

Ruscio, J. (2008). A probability-based measure of effect size: Robustness to base rates and other factors. *Psychological Methods*, *13*(1), 19–30. doi:10.1037/1082-989X.13.1.19

Ruscio, J., & Mullen, T. (2012). Confidence Intervals for the Probability of Superiority Effect Size Measure and the Area under a Receiver Operating Characteristic Curve. *Multivariate Behavioral Research*, *47*(2), 201–223.

Sanislow, C. A., Pine, D. S., Quinn, K. J., Kozak, M. J., Garvey, M. A., Heinssen, R. K., … Cuthbert, B. N. (2010). Developing constructs for psychopathology research: Research domain criteria. *Journal of Abnormal Psychology*, *119*(4), 631–639. doi:10.1037/a0020909

Schoots, O., & Van Tol, H. H. M. (2003). The human dopamine D4 receptor repeat sequences modulate expression. *The Pharmacogenomics Journal*, *3*(6), 343–348. doi:10.1038/sj.tpj.6500208

Sharma, L., Markon, K. E., & Clark, L. A. (2014). Toward a theory of distinct types of "impulsive" behaviors: A meta-analysis of self-report and behavioral measures. Psychological Bulletin, 140(2), 374–408. doi:10.1037/a0034418

Simmonds, D. J., Pekar, J. J., & Mostofsky, S. H. (2008). Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia*, 46(1), 224–232. doi:10.1016/j.neuropsychologia.2007.07.015

Smith, G. T., Fischer, S., Cyders, M. A., Annus, A. M., Spillane, N. S., & McCarthy, D. M. (2007). On the Validity and Utility of Discriminating Among Impulsivity-Like Traits. *Assessment*, *14*(2), 155–170. doi:10.1177/1073191106295527

Snowden, R. J., & Gray, N. S. (2011). Impulsivity and psychopathy: Associations between the Barrett Impulsivity Scale and the Psychopathy Checklist revised. *Psychiatry Research*, *187*(3), 414–417. doi:10.1016/j.psychres.2011.02.003

Soetaert K. (2009). rootSolve: Nonlinear root finding, equilibrium and steady-state analysis of ordinary differential equations. R-package version 1.6

Stoltenberg, S. F., Christ, C. C., & Highland, K. B. (2012). Serotonin system gene polymorphisms are associated with impulsivity in a context dependent manner. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 39(1), 182–191. doi:10.1016/j.pnpbp.2012.06.012

Swanson, J. ., Flodman, P., Kennedy, J., Spence, M. A., Moyzis, R., Schuck, S., … Posner, M. (2000). Dopamine genes and ADHD. *Neuroscience & Biobehavioral Reviews*, *24*(1), 21–25. doi:10.1016/S0149-7634(99)00062-7

Tamm, L., Menon, V., & Reiss, A. L. (2002). Maturation of Brain Function Associated With Response Inhibition. *Journal of the American Academy of Child & Adolescent Psychiatry*, *41*(10), 1231–1238. doi:10.1097/00004583-200210000-00013

Van Tol, H. H. M., Wu, C. M., Guan, H.-C., Ohara, K., Bunzow, J. R., Civelli, O., … Jovanovic, V. (1992). Multiple dopamine D4 receptor variants in the human population. *Published online: 09 July 1992; | doi:10.1038/358149a0*, *358*(6382), 149–152. doi:10.1038/358149a0

Vargha, A., & Delaney, H. D. (2000). A Critique and Improvement of the "CL" Common Language Effect Size Statistics of McGraw and Wong. *Journal of Educational and Behavioral Statistics*, *25*(2), 101–132. doi:10.2307/1165329

Vul, E., Harris, C., Winkielman, P., & Pashler, H. (2009). Puzzlingly High Correlations in fMRI Studies of Emotion, Personality, and Social Cognition. *Perspectives on Psychological Science*, *4*(3), 274–290. doi:10.1111/j.1745-6924.2009.01125.x

Waldman, I. D. (2005). Statistical Approaches to Complex Phenotypes: Evaluating Neuropsychological Endophenotypes for Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*, *57*(11), 1347–1356. doi:10.1016/j.biopsych.2005.03.002

Wallis, D., Russell, H. F., & Muenke, M. (2008). Review: Genetics of Attention Deficit/Hyperactivity Disorder. *Journal of Pediatric Psychology*, *33*(10), 1085–1099. doi:10.1093/jpepsy/jsn049

Walters, J. T. R., & Owen, M. J. (2007). Endophenotypes in psychiatric genetics. *Molecular Psychiatry*, *12*(10), 886–890. doi:10.1038/sj.mp.4002068

Widiger, T. A., & Clark, L. A. (2000). Toward DSM--V and the classification of psychopathology. *Psychological Bulletin*, *126*(6), 946–963. doi:10.1037/0033-2909.126.6.946

Young, S. E., Stallings, M. C., Corley, R. P., Krauter, K. S., & Hewitt, J. K. (2000). Genetic and environmental influences on behavioral disinhibition. *American Journal of Medical Genetics*, *96*(5), 684–695.

Zollner, S., & Pritchard, J. K. (2007). Overcoming the Winner's Curse: Estimating Penetrance Parameters from Case-Control Data. *American Journal of Human Genetics*, *80*(4), 605–615.

Table 1
Number of reported effects and total sample size by phenotype and polymorphism

	ADHD Diagnosis	Trait Impulsivity	Neuropsychological Tasks	Neurobiological Measures
	N (effects)	N (effects)	N (effects)	N (effects)
5-HTTLPR	21916 (13)	11438 (54)	3399 (23)	58 (2)
DAT1 3' UTR VNTR	2561 (9)	2871 (14)	1916 (12)	568 (8)
DRD4 exon 3 VNTR	4524 (6)	6972 (27)	3085 (14)	1600 (10)

Table 2

Mean AAD and confidence intervals predicted by mixed-effect regression of effect size on phenotype

Total Sample

		95% Confidence Interval	
	AAD	Lower limit	Upper limit
Mean effect	.614	.608	.653
ADHD Diagnosis	.527	.514	.531
Trait Impulsivity	.596	.585	.619
Neuropsychological Tasks	.621	.607	.659
Neurobiological Measures	.814	.717	.838

5-HTTLPR

		95% Confidence Interval	
	AAD	Lower limit	Upper limit
Mean effect	.600	.593	.635
ADHD Diagnosis	.522	.508	.523
Trait Impulsivity	.585	.571	.608
Neuropsychological Tasks	.628	.599	.690
Neurobiological Measures	.939	.783	.997

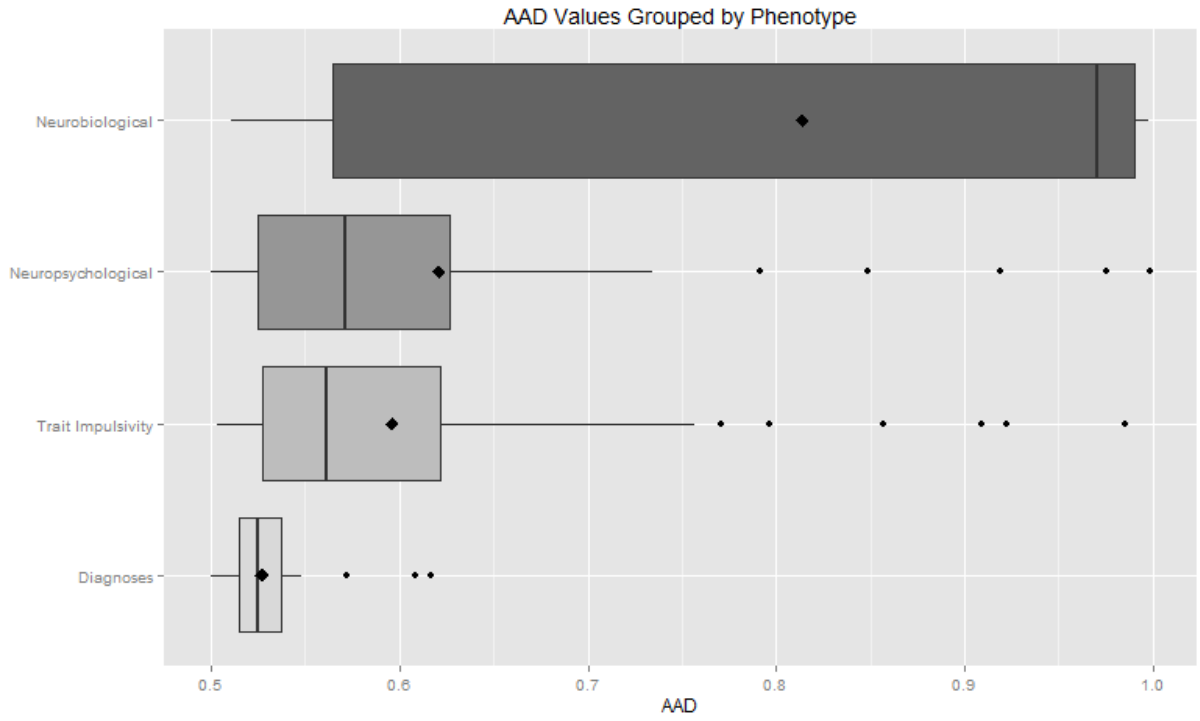
DAT1 3' UTR VNTR

		95% Confidence Interval	
	AAD	Lower limit	Upper limit
Mean effect	.616	.579	.671
ADHD Diagnosis	.528	.513	.539
Trait Impulsivity	.580	.546	.615
Neuropsychological Tasks	.629	.530	.650
Neurobiological Measures	.888	.761	.991

DRD4 exon 3 VNTR

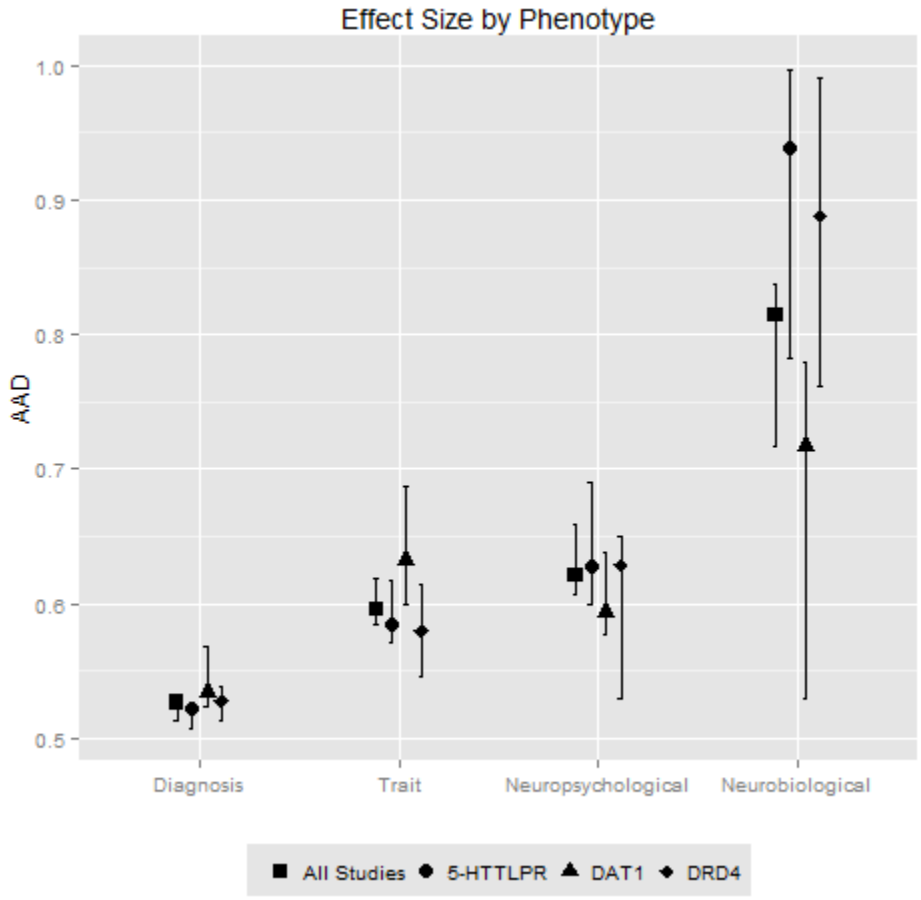
		95% Confidence Interval	
	AAD	Lower limit	Upper limit
Mean effect	.620	.590	.648
ADHD Diagnosis	.534	.524	.569
Trait Impulsivity	.632	.599	.688
Neuropsychological Tasks	.594	.577	.638
Neurobiological Measures	.717	.530	.779

Figure 1



Note: Boxplot endpoints represent upper and lower quartiles of the observed distribution of effect sizes. Whisker limits indicate maximum and minimum values, minus outliers (small diamonds). Bold lines indicate the median observed effect within groups. Large diamonds indicate group means.

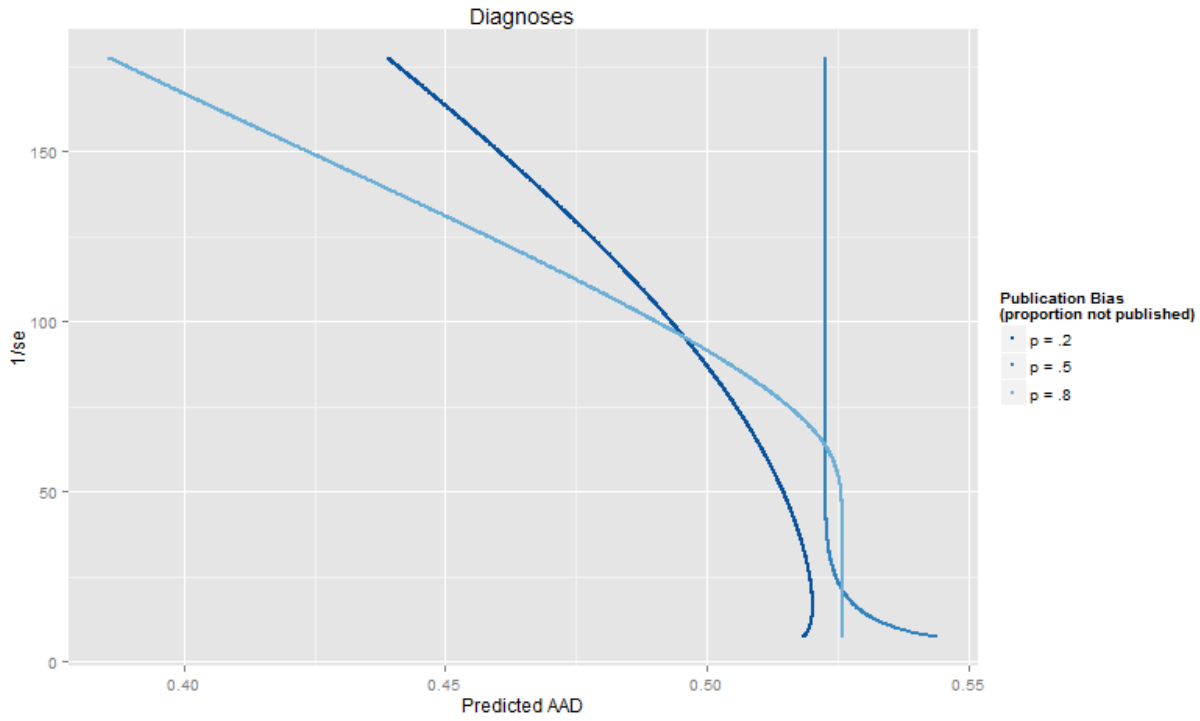
Figure 2



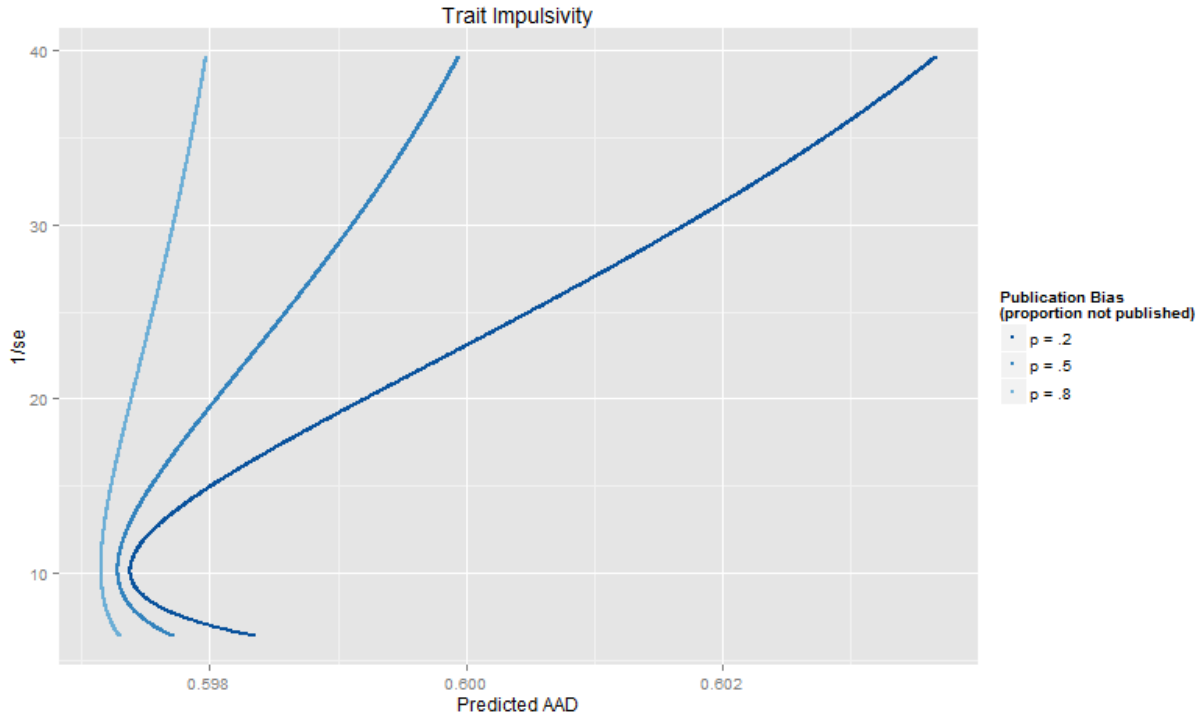
Note: Circles represent the mean effect predicted by bootstrap estimates of regression parameters. Bars indicated 95% bias-corrected and accelerated bootstrap confidence intervals.

Supplemental Material

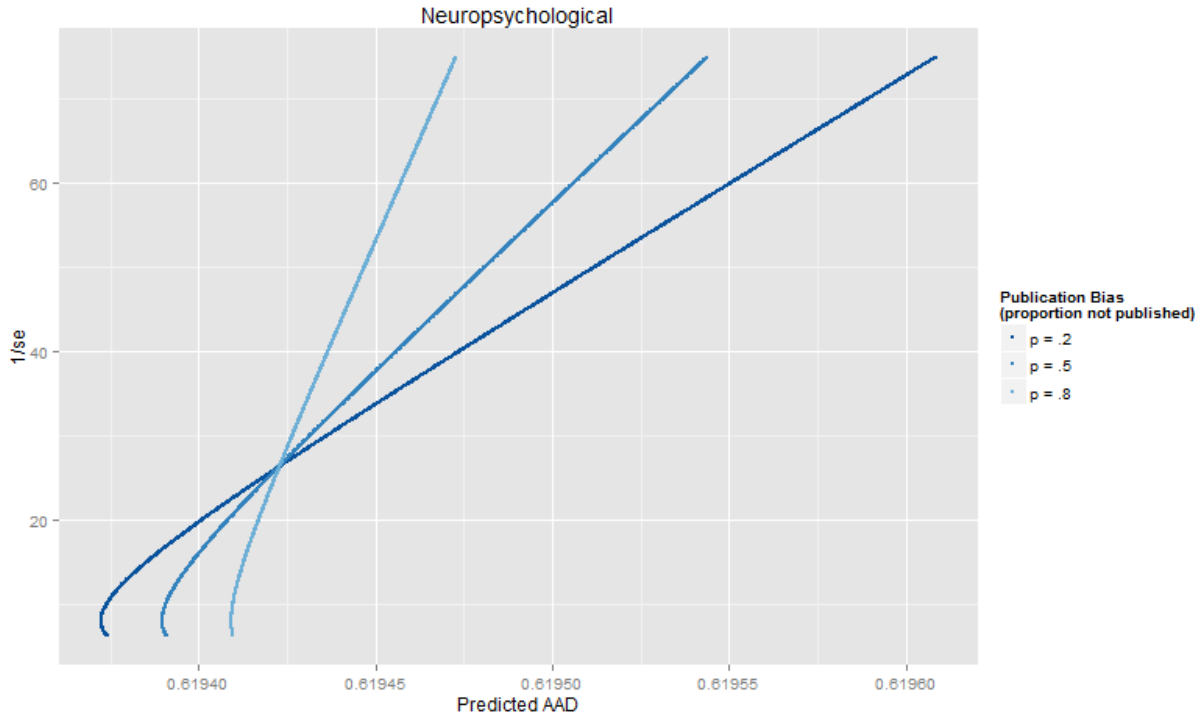
Supplemental Figure 1a



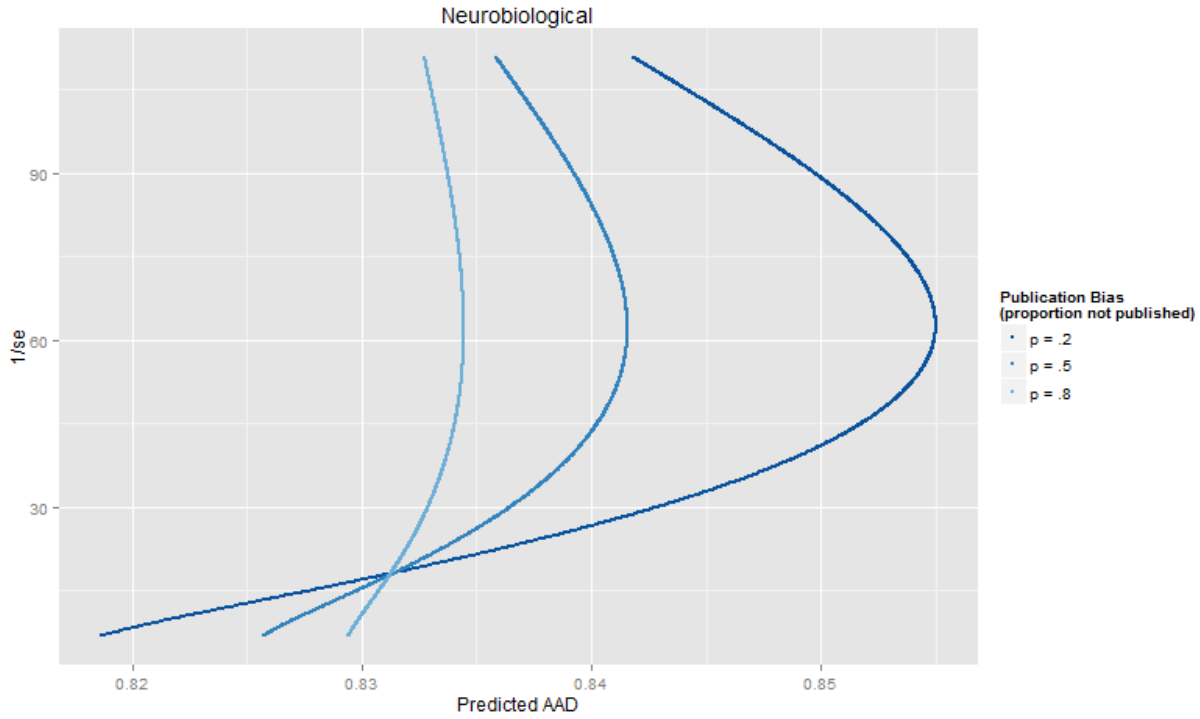
Supplemental Figure 1b



Supplemental Figure 1c



Supplemental Figure 1d



Note: Curves represent predicted meta-analytic effect sizes given a hypothetical degree of publication bias. The range of the y-axis is derived from the range of standard errors observed within each phenotype.

Supplemental Table 1

Author	Year	Polymorphism	Indicator	AAD
Brown, AB	2010	DAT1	SCID - Hyperactive symptoms count	0.534
Brown, AB	2010	DAT1	SCID - Inattentive symptoms count	0.525
Carpentier, PJ	2012	DRD4	ADHD diagnosis via DSM-IV-based clinical interview	0.527
da Silva, MA	2011	DAT1	ADHD diagnosis via DSM-IV-based clinical interview	0.528
Dawes, MA	2009	5-HTTLPR	ADHD diagnosis via Children's Interview for Psychiatric Syndromes†	0.572
Dresler, T	2010	DAT1	ADHD diagnosis via DSM-IV-based clinical interview	0.501
Ettinger, U	2006	DAT1	ASRS - Total score	0.513
Ettinger, U	2006	DRD4	ASRS - Total score	0.522
Franke, B	2008	DAT1	ASRS - Total score	0.538
Gordon, EM	2012	DAT1	ASRS - Inattention score	0.616
Gordon, EM	2012	DAT1	ASRS - Hyperactive/Impulsive score	0.527
Grevet, EH	2007	5-HTTLPR	ADHD diagnosis via KSADS†	0.517
Grevet, EH	2007	5-HTTLPR	SNAP - Inattention	0.548
Grevet, EH	2007	5-HTTLPR	SNAP - Hyperactivity	0.532
Heinzel, S	2012	DRD4	ADHD diagnosis via SCID	0.525
Johann, M	2003	5-HTTLPR	ADHD diagnosis via DSM-IV-based clinical interview	0.5
Johansson, S	2008	DAT1	ADHD diagnosis via ASRS	0.512
Kiive, E	2013	5-HTTLPR	ASRS - Hyperactivity/Impulsivity score	0.52
Kiive, E	2013	5-HTTLPR	ASRS - Inattention score	0.504
Kim, J-W	2006	5-HTTLPR	ADHD diagnosis via DISC-IV†	0.546
Landaas, ET	2010	5-HTTLPR	ADHD diagnosis via DSM-IV-based clinical interview	0.516
Landaas, ET	2010	5-HTTLPR	ADHD diagnosis via DSM-IV-based clinical interview	0.509
Landaas, ET	2010	5-HTTLPR	ADHD diagnosis via ASRS	0.541
Landaas, ET	2010	5-HTTLPR	ADHD diagnosis via DSM-IV-based clinical interview	0.517
Landaas, ET	2010	5-HTTLPR	ADHD diagnosis via DSM-IV-based clinical interview	0.522
Monuteaux, MC	2008	DRD4	ADHD diagnosis via SCID and KSADS†	0.501
Muglia, P	2000	DRD4	ADHD diagnosis via DSM-IV-based clinical interview	0.608
Sanchez-Mora, C	2011	DRD4	ADHD diagnosis via SCID-II	0.537
Akkerman, K	2010	5-HTTLPR	BIS-11 - Total score	0.723

Aluja, A	2009	5-HTTLPR	ZKPQ - Impulsive Sensation Seeking	0.551
Aluja, A	2009	5-HTTLPR	SPSRQ - Sensitivity to Reward	0.567
Anghelescu, I	2010	DAT1	NEO FFI - Conscientiousness	0.506
Anghelescu, I	2010	DAT1	TCI - Novelty Seeking	0.53
Baca-Garcia, E	2004	5-HTTLPR	BIS-11 - Total score	0.531
Bayle, FJ	2003	5-HTTLPR	BIS-10 - Total score	0.545
Benjamin, J	1996	DRD4	TPQ - Novelty Seeking	0.59
Blanchard, MM	2011	DAT1	BIS-11 - Total score	0.507
Brummett, BH	2003	5-HTTLPR	NEO PI-R - Conscientiousness	0.517
Burt, SA	2002	DRD4	MPQ - Constraint	0.515
Colzato, LS	2010	DAT1	Dickman's Impulsivity Inventory - Dysfunctional Impulsivity	0.581
Colzato, LS	2010	DRD4	Dickman's Impulsivity Inventory - Dysfunctional Impulsivity	0.653
Congdon, EJ	2008	DAT1	BIS-11 - Total score	0.857
Congdon, EJ	2008	DAT1	BIS-11 - Total score	0.564
Congdon, EJ	2008	DRD4	BIS-11 - Total score	0.523
Courtet, P	2004	5-HTTLPR	BIS-11 - Total score	0.6
Dawes, MA	2009	5-HTTLPR	BIS-11 - Total score	0.757
Dragan, WL	2006	5-HTTLPR	NEO-FFI - Conscientiousness	0.521
Dragan, WL	2007	DRD4	NEO-FFI - Conscientiousness	0.985
Du, L	2001	5-HTTLPR	NEO-FFI - Conscientiousness	0.534
Ebstein, RP	1996	DRD4	TPQ - Novelty Seeking	0.985
Ebstein, RP	1997	5-HTTLPR	TPQ - Novelty Seeking	0.688
Eisenberg, DT	2007	DRD4	BIS-11 - Total score	0.645
Eisenberg, DT	2007	DRD4	EIQ - Impulsiveness	0.629
Eisenberg, DT	2007	DRD4	Sensation Seeking Scale	0.622
Eisenegger, C	2010	DRD4	BIS-11 - Motor Impulsivity	0.503
Flory, JD	1999	5-HTTLPR	TPQ - Conscientiousness	0.539
Forbes, EE	2009	DAT1	BIS-11 - Total score	0.645
Gebhardt, C	2000	DRD4	TCI - Novelty Seeking	0.573
Gillihan, SJ	2009	5-HTTLPR	I7 Impulsivity	0.623
Gonda, X	2009	5-HTTLPR	TCI - Novelty Seeking	0.719
Gordon, EM	2012	DAT1	BIS-11 - Total score	0.612

Greenberg, BD	2000	5-HTTLPR	NEO-FFI - Conscientiousness	0.537
Grevet, EH	2007	5-HTTLPR	TCI - Novelty Seeking	0.559
Hahn, T	2011	DAT1	SPSRQ - Sensitivity to Reward	0.506
Hahn, T	2013	5-HTTLPR	SPSRQ - Sensitivity to Reward	0.52
Hamer, DH	1999	5-HTTLPR	TCI - Novelty Seeking	0.531
Joo, YH	2007	5-HTTLPR	TCI - Novelty Seeking	0.507
Katsuragi, S	1999	5-HTTLPR	TCI - Novelty Seeking	0.797
Kazantseva, AV	2009	DAT1	TCI - Novelty Seeking	0.528
Kazantseva, AV	2009	DAT1	TCI - Novelty Seeking	0.53
Kazantseva, AV	2011	DAT1	TCI - Novelty Seeking	0.527
Kim, S-J	2006	5-HTTLPR	TCI - Novelty Seeking	0.504
Kim, S-J	2006	DAT1	TCI - Novelty Seeking	0.561
Kumakiri, C	1999	5-HTTLPR	NEO PI-R – Conscientiousness	0.542
Kumakiri, C	1999	5-HTTLPR	TCI - Novelty Seeking	0.518
Lang, UE	2004	5-HTTLPR	NEO FFI - Conscientiousness	0.566
Lemarquande, DG	2000	DRD4	Sensation Seeking Scale - Disinhibition	0.636
Lerman, C	2000	5-HTTLPR	EPI - Neuroticism	0.506
Malhotra, AK	1996	DRD4	TPQ - Novelty Seeking	0.922
Mill, JS	2002	DRD4	BFI - Conscientiousness	0.516
Mill, JS	2002	DRD4	MPQ - Constraint	0.535
Moukaddam, NJ	2008	5-HTTLPR	BIS-11 - Total score	0.91
Muller, DJ	2010	DAT1	TCI - Novelty Seeking	0.594
Muller, DJ	2010	DRD4	TCI - Novelty Seeking	0.514
Must, A	2007	5-HTTLPR	TCI - Novelty Seeking	0.534
Nakamura, T	1997	5-HTTLPR	TCI - Novelty Seeking	0.619
Nakamura, T	1997	5-HTTLPR	NEO-PI - Conscientiousness	0.568
Osher, Y	2000	5-HTTLPR	TCI - Novelty Seeking	0.568
Osher, Y	2000	5-HTTLPR	NEO-PI-R - Conscientiousness	0.547
Passamonti, L	2008	5-HTTLPR	BIS-11 - Total score	0.771
Patkar, AA	2002	5-HTTLPR	BIS-11 - Total score	0.562
Patkar, AA	2002	5-HTTLPR	Sensation Seeking Scale - Disinhibition	0.61
Pogue-Geile, MP	1998	DRD4	NEO-PI - Conscientiousness	0.531

Pogue-Geile, MP	1998	DRD4	TPQ - Novelty Seeking	0.511
Pogue-Geile, MP	1998	DRD4	Sensation Seeking Scale - Disinhibition	0.509
Pooley, EC	2003	5-HTTLPR	Plutchik Impulsivity Scale	0.509
Racine, SE	2009	5-HTTLPR	BIS-11 - Total score	0.554
Roussos, P	2009	DRD4	TCI - Novelty Seeking	0.659
Roussos, P	2010	DRD4	TCI - Novelty Seeking	0.598
Sadeh, N	2012	5-HTTLPR	PCL - Impulsivity/Antisociality Subscale	0.562
Sakado, K	2003	5-HTTLPR	BIS-11 - Total score	0.672
Samochowiec, J	2004	5-HTTLPR	NEO-FFI - Conscientiousness	0.555
Samochowiec, J	2004	5-HTTLPR	TCI - Novelty Seeking	0.509
Sen, S	2004	5-HTTLPR	NEO-PI - Conscientiousness	0.626
Soyka, M	2002	DRD4	TCI - Novelty Seeking	0.622
Soyka, M	2002	DRD4	Sensation Seeking Scale - Disinhibition	0.52
Soyka, M	2002	DRD4	NEO-FFI - Conscientiousness	0.626
Steiger, H	2005	5-HTTLPR	BIS-11 - Total score	0.596
Stoltenberg, SF	2002	5-HTTLPR	NEO-FFI - Conscientiousness	0.608
Stoltenberg, SF	2012	5-HTTLPR	BIS-11 - Total score	0.518
Strobel, A	2003	DRD4	NEO-FFI - Conscientiousness	0.541
Surguladze, SA	2008	5-HTTLPR	NEO PI-R - Conscientiousness	0.6
Surguladze, SA	2008	5-HTTLPR	TCI - Novelty Seeking	0.621
Suzuki, A	2008	5-HTTLPR	TCI - Novelty Seeking	0.514
Szekely, A	2004	DRD4	TCI - Novelty Seeking	0.741
Umekage, T	2003	5-HTTLPR	NEO PI-R - Conscientiousness	0.537
Varga, G	2012	5-HTTLPR	BIS-11 - Total score	0.523
Varga, G	2012	DRD4	BIS-11 - Total score	0.567
Vormfelde, SV	2006	5-HTTLPR	NEO PI-R - Conscientiousness	0.557
Vormfelde, SV	2006	5-HTTLPR	TCI - Novelty Seeking	0.552
Wagner, S	2009	5-HTTLPR	BIS-5 - Total score	0.566
Wiesbeck, GA	2004	5-HTTLPR	TCI - Novelty Seeking	0.532
Zalsman, G	2001	5-HTTLPR	Plutchik Impulsivity Scale	0.585
Ariza, M	2012	DRD4	Stroop - Interference Score	0.515
Boonstra, AM	2008	DAT1	Stop Signal Task - SSRT	0.71

Bosia, M	2010	5-HTTLPR	CPT - Hits	0.999
Bosia, M	2010	5-HTTLPR	CPT - Commissions	0.6
Brown, AB	2010	DAT1	MSIT - Percent correct inhibitions	0.66
Brown, AB	2010	DAT1	MSIT - Reaction time on interference trials	0.543
Clark, L	2005	5-HTTLPR	Stop Signal Task - SSRT	0.614
Clark, L	2005	5-HTTLPR	Stop Signal Task - Errors	0.535
Colzato, LS	2010	DAT1	Stop Signal Task - SSRT	0.553
Colzato, LS	2010	DRD4	Stop Signal Task - SSRT	0.58
Congdon, EJ	2008	DAT1	Stop-Signal Task - Percent correct inhibition	0.975
Congdon, EJ	2008	DAT1	Stop-Signal Task - SSRT	0.538
Congdon, EJ	2008	DRD4	Stop-Signal Task - SSRT	0.621
Congdon, EJ	2009	DAT1	Stop-Signal Task - SSRT	0.919
Cummins, TDR	2012	DAT1	Stop-Signal Task - SSRT	0.524
Cummins, TDR	2012	DRD4	Stop-Signal Task - SSRT	0.507
da Rocha, FF	2008	5-HTTLPR	CPT II - Commissions	0.627
da Rocha, FF	2008	5-HTTLPR	Iowa Gambling Task - Net score	0.791
Dresler, T	2010	DAT1	CPT (OX version) - Commissions following primers	0.574
Dresler, T	2010	DAT1	CPT (OX version) - Commissions following distractors	0.536
Dresler, T	2010	DAT1	CPT (OX version) - Reaction time	0.511
Dresler, T	2010	DAT1	CPT (OX version) - Reaction time standard deviation	0.513
Eisenberg, DT	2007	DRD4	Delay Discounting Task - Coefficient of discounting	0.623
Fallgatter, AJ	1999	5-HTTLPR	CPT - Reaction time	0.571
Fallgatter, AJ	1999	5-HTTLPR	CPT - Total errors	0.583
Filbey, FM	2011	DRD4	Go/No-Go - Commissions	0.71
Filbey, FM	2011	DRD4	Go/No-Go - Successful No-Go trials	0.661
Ha, RY	2009	5-HTTLPR	Iowa Gambling Task - Net score	0.53
He, Q	2010	5-HTTLPR	Iowa Gambling Task - Net score (trials 1-40)	0.849
He, Q	2010	5-HTTLPR	Iowa Gambling Task - Net score (trials 40-100)	0.716
Heinzel, S	2012	DRD4	Go/No-Go - Commissions	0.549
Heinzel, S	2012	DRD4	Go/No-Go - Successful No-Go trials	0.533
Heinzel, S	2012	DRD4	Go/No-Go - Go reaction time	0.5
Heinzel, S	2012	DRD4	Go/No-Go - Go reaction time standard deviation	0.536

Jollant, F	2007	5-HTTLPR	Iowa Gambling Task - Net score (trials 1-50)	0.572
Jollant, F	2007	5-HTTLPR	Iowa Gambling Task - Net score (trials 50-100)	0.524
Lage, GM	2011	5-HTTLPR	CPT - Commissions	0.518
Lage, GM	2011	5-HTTLPR	Iowa Gambling Task - Net score	0.501
O'Hara, R	2007	5-HTTLPR	Stroop - Interference score	0.551
Passamonti, L	2008	5-HTTLPR	Go-No/Go - Total errors	0.508
Passamonti, L	2008	5-HTTLPR	Go-No/Go - Go reaction time	0.617
Roussos, P	2009	DRD4	Iowa Gambling Task - Net score	0.734
Roussos, P	2010	DRD4	Iowa Gambling Task - Net score	0.624
Steiger, H	2005	5-HTTLPR	Go/No-Go task - Commissions	0.694
Stoltenberg, SF	2011	5-HTTLPR	Iowa Gambling Task - Net score	0.516
Strobel, A	2007	5-HTTLPR	CPT - Hit rate	0.5
Strobel, A	2007	5-HTTLPR	CPT - False Alarms	0.553
Sweitzer, MM	2012	DRD4	Delay Discounting - Coefficient of discounting	0.514
Walderhaug, E	2010	5-HTTLPR	CPT – Beta	0.623
Brown, AB	2010	DAT1	fMRI (MSIT interference - control) L dorsal anterior cingulate cortex (ROI)	0.99
Brown, AB	2010	DAT1	fMRI (MSIT interference - control) R lateral prefrontal cortex (exploratory)	0.989
Brown, AB	2010	DAT1	fMRI (MSIT interference - control) R cerebellar vermis (exploratory)	0.998
Congdon, EJ	2009	DAT1	fMRI (SSRT inhibit - go trials) inferior frontal gyrus (ROI)	0.967
Congdon, EJ	2009	DAT1	fMRI (SSRT inhibit - go trials) subthalamic nucleus (ROI)	0.974
Congdon, EJ	2009	DAT1	fMRI (SSRT inhibit - go trials) pre-supplementary motor area (ROI)	0.982
Congdon, EJ	2009	DAT1	fMRI (SSRT inhibit - go trials) globus pallidus (ROI)	0.988
Dresler, T	2010	DAT1	EEG (go - no-go trials) centroid anteriorization	0.546
Fallgatter, AJ	1999	5-HTTLPR	EEG (CPT inhibition trials) centroid anteriorization	0.783
Filbey, FM	2011	DRD4	fMRI (successful no-go trials) left superior temporal gyrus (exploratory)	0.996
Filbey, FM	2011	DRD4	fMRI (successful no-go trials) right cingulate gyrus (exploratory)	0.991
Filbey, FM	2011	DRD4	fMRI (successful no-go trials) left medial frontal gyrus (exploratory)	0.996
Heinzel, S	2012	DRD4	EEG (successful no-go trials) centroid anteriorization	0.511
Loo, SK	2010	DRD4	EEG (CPT) frontal beta2 power	0.586
Loo, SK	2010	DRD4	EEG (CPT) central beta2 power	0.56
Loo, SK	2010	DRD4	EEG (CPT) parietal beta2 power	0.568
Loo, SK	2010	DRD4	EEG (CPT) frontal theta power	0.566

Loo, SK	2010	DRD4	EEG (CPT) central theta power	0.557
Loo, SK	2010	DRD4	EEG (CPT) parietal theta power	0.534
Passamonti, L	2008	5-HTTLPR	fMRI (go – no-go trials) right ventral anterior cingulate cortex (ROI)	0.997

ASRS: ADHD Symptom Rating Scale; BIS: Behavioral Avoidance System scale; BFI: Big Five Inventory; CPT: Continuous Performance Task; DISC: Diagnostic Interview Schedule for Children; EEG: Electroencephalography; EIQ: Eysenck's Impulsivity Questionnaire; EPI: Eysenck Personality Inventory; ERP: Event-Related Potential; I7: Impulsiveness-Venturesomeness-Empathy questionnaire; KSADS: Schedule for Affective Disorders and Schizophrenia for School-Age Children; MPQ: Multidimensional Personality Questionnaire; MSIT: Multiple-Source Interference Task; NEO FFI: Neuroticism-Extroversion-Openness Five-Factor Inventory, NEO PI-R: Neuroticism-Extroversion-Openness Personality Inventory, Revised; PCL: Psychopathy Checklist; SCID: Structured Clinical Interview for DSM-IV; SNAP: Swanson, Nolan and Pelham Scale; SPSRQ: Sensitivity to Punishment and Sensitivity to Reward Questionnaire; TCI: Temperament and Character Inventory; TPQ: Tridimensional Personality Questionnaire; ZKPQ: Zuckerman-Kuhlman Personality Questionnaire. † Effects derived from current symptoms in adulthood.

Studies included in meta-analysis

Akkermann, K., Nordquist, N., Oreland, L., & Harro, J. (2010). Serotonin transporter gene promoter polymorphism affects the severity of binge eating in general population. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *34*(1), 111–114. doi:10.1016/j.pnpbp.2009.10.008

Aluja, A., Garcia, L. F., Blanch, A., De Lorenzo, D., & Fibla, J. (2009). Impulsive-disinhibited personality and serotonin transporter gene polymorphisms: Association study in an inmate's sample. *Journal of Psychiatric Research*, *43*(10), 906–914. doi:10.1016/j.jpsychires.2008.11.008

Anghelescu, I., Klawe, C., Singer, P., Fehr, C., Hiemke, C., Quante, A., … Szegedi, A. (2010). Low novelty seeking and high self directedness scores in alcohol-dependent patients without comorbid psychiatric disorders homozygous for the A10 allele of the dopamine transporter gene. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *11*(2 Pt 2), 382–389. doi:10.1080/15622970701775058

Ariza, M., Garolera, M., Jurado, M. A., Garcia-Garcia, I., Hernan, I., Sánchez-Garre, C., … Narberhaus, A. (2012). Dopamine Genes (DRD2/ANKK1-TaqA1 and DRD4-7R) and Executive Function: Their Interaction with Obesity. *PloS one*, *7*(7), e41482. doi:10.1371/journal.pone.0041482Arnsten, A. F. T. (2006). Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. *The Journal of Clinical Psychiatry*, *67 Suppl 8*, 7–12.

Baca-Garcia, E., Vaquero, C., Diaz-Sastre, C., García-Resa, E., Saiz-Ruiz, J., Fernández-Piqueras, J., & De Leon, J. (2004). Lack of association between the serotonin transporter promoter gene polymorphism and impulsivity or aggressive behavior among suicide attempters and healthy volunteers. *Psychiatry Research*, *126*(2), 99–106. doi:10.1016/j.psychres.2003.10.007

Bayle, F. j., Leroy, S., Gourion, D., Millet, B., Olié, J. p., Poirier, M. f., & Krebs, M. o. (2003). 5HTTLPR polymorphism in schizophrenic patients: Further support for association with violent suicide attempts. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *119B*(1), 13–17. doi:10.1002/ajmg.b.10037

Benjamin, J., Li, L., Patterson, C., Greenberg, B. D., Murphy, D. L., & Hamer, D. H. (1996). Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nature Genetics*, *12*(1), 81–84. doi:10.1038/ng0196-81

Blanchard, M. M., Chamberlain, S. R., Roiser, J., Robbins, T. W., & Müller, U. (2011). Effects of two dopamine-modulating genes (DAT1 9/10 and COMT Val/Met) on n-back working memory performance in healthy volunteers. *Psychological Medicine*, *41*(3), 611–618. doi:10.1017/S003329171000098X

Boonstra, A. M., Kooij, J. J. S., Buitelaar, J. K., Oosterlaan, J., Sergeant, J. A., Heister, J. G. A. M. A., & Franke, B. (2008). An exploratory study of the relationship between four candidate genes and neurocognitive performance in adult ADHD. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *147B*(3), 397–402. doi:10.1002/ajmg.b.30595

Bosia, M., Anselmetti, S., Pirovano, A., Ermoli, E., Marino, E., Bramanti, P., … Cavallaro, R. (2010). HTTLPR functional polymorphism in schizophrenia: executive functions vs. sustained attention dissociation. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *34*(1), 81–85. doi:10.1016/j.pnpbp.2009.10.001

Brown, A. B., Biederman, J., Valera, E. M., Doyle, A. E., Bush, G., Spencer, T., … Seidman, L. J. (2010). Effect of dopamine transporter gene (SLC6A3) variation on dorsal anterior cingulate function in attention-deficit/hyperactivity disorder. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*, *153B*(2), 365–375. doi:10.1002/ajmg.b.31022

Brummett, B. H., Siegler, I. C., McQuoid, D. R., Svenson, I. K., Marchuk, D. A., & Steffens, D. C. (2003). Associations among the NEO Personality Inventory, Revised and the serotonin transporter gene-linked polymorphic region in elders: effects of depression and gender. *Psychiatric Genetics*, *13*(1), 13–18. doi:10.1097/01.ypg.0000051093.88669.85

Burt, S. A., McGue, M., Iacono, W., Comings, D., & MacMurray, J. (2002). An examination of the association between DRD4 and DRD2 polymorphisms and personality traits. *Personality and Individual Differences*, *33*(6), 849–859. doi:10.1016/S0191-8869(01)00194-5. doi:10.1016/j.bcp.2007.06.043

Carpentier, P. J., Arias Vasquez, A., Hoogman, M., Onnink, M., Kan, C. C., Kooij, J. J. S., … Buitelaar, J. K. (2012). Shared and unique genetic contributions to attention deficit/hyperactivity disorder and substance use disorders: A pilot study of six candidate

genes. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*. doi:10.1016/j.euroneuro.2012.07.003

Clark, L., Roiser, J., Cools, R., Rubinsztein, D., Sahakian, B., & Robbins, T. (2005). Stop signal response inhibition is not modulated by tryptophan depletion or the serotonin transporter polymorphism in healthy volunteers: implications for the 5-HT theory of impulsivity. *Psychopharmacology, 182*(4), 570–578. doi:10.1007/s00213-005-0104-6

Colzato, L. S., Van den Wildenberg, W. P. M., Van der Does, A. J. W., & Hommel, B. (2010). Genetic markers of striatal dopamine predict individual differences in dysfunctional, but not functional impulsivity. *Neuroscience, 170*(3), 782–788. doi:10.1016/j.neuroscience.2010.07.050

Congdon, E. J. (2008). *The neurogenetic basis of behavioral inhibition*. (Doctoral Dissertation). Retrieved from ProQuest Dissertations and Theses. (Accession Order No. AAT 3338156)

Congdon, E., Constable, R. T., Lesch, K. P., & Canli, T. (2009). Influence of SLC6A3 and COMT Variation on Neural Activation During Response Inhibition. *Biological Psychology, 81*(3), 144–152. doi:10.1016/j.biopsycho.2009.03.005

Congdon, E., Lesch, K. P., & Canli, T. (2008). Analysis of DRD4 and DAT polymorphisms and behavioral inhibition in healthy adults: implications for impulsivity. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics, 147B*(1), 27–32. doi:10.1002/ajmg.b.30557

Courtet, P., Picot, M.-C., Bellivier, F., Torres, S., Jollant, F., Michelon, C., … Malafosse, A. (2004). Serotonin transporter gene may be involved in short-term risk of subsequent suicide attempts. *Biological Psychiatry, 55*(1), 46–51.

Cummins, T. D. R., Hawi, Z., Hocking, J., Strudwick, M., Hester, R., Garavan, H., … Bellgrove, M. A. (2011). Dopamine transporter genotype predicts behavioural and neural measures of response inhibition. *Molecular Psychiatry*. doi:10.1038/mp.2011.104

Da Rocha, F. F., Malloy-Diniz, L., Lage, N. V., Romano-Silva, M. A., De Marco, L. A., & Correa, H. (2008). Decision-making impairment is related to serotonin transporter promoter polymorphism in a sample of patients with obsessive-compulsive disorder. *Behavioural Brain Research*, *195*(1), 159–163. doi:10.1016/j.bbr.2008.05.015

Da Silva, M. A., Cordeiro, Q., Louzã, M., & Vallada, H. (2011). Lack of association between a 3'UTR VNTR polymorphism of dopamine transporter gene (SLC6A3) and ADHD in a Brazilian sample of adult patients. *Journal of Attention Disorders*, *15*(4), 305–309. doi:10.1177/1087054710365989

Dawes, M. A., Roache, J. D., Javors, M., Bergeson, S. E., Richard, D. M., Mathias, C. W., … Johnson, B. A. (2009). Drinking Histories in Alcohol-Use-Disordered Youth: Preliminary Findings on Relationships to Platelet Serotonin Transporter Expression With Genotypes of the Serotonin Transporter. *Journal of Studies on Alcohol and Drugs*, *70*(6), 899–907.

Dragan, W. Ł., & Oniszczenko, W. (2006). Association of a functional polymorphism in the serotonin transporter gene with personality traits in females in a Polish population. *Neuropsychobiology*, *54*(1), 45–50. doi:10.1159/000095741

Dragan, W. Ł., & Oniszczenko, W. (2007). An association between dopamine D4 receptor and transporter gene polymorphisms and personality traits, assessed using NEO-FFI in a Polish female population. *Personality and Individual Differences*, *43*(3), 531–540. doi:10.1016/j.paid.2007.01.001

Dresler, T., Ehlis, A.-C., Heinzel, S., Renner, T. J., Reif, A., Baehne, C. G., … Fallgatter, A. J. (2010). Dopamine transporter (SLC6A3) genotype impacts neurophysiological correlates of cognitive response control in an adult sample of patients with ADHD. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *35*(11), 2193–2202. doi:10.1038/npp.2010.91

Du, L., Bakish, D., & Hrdina, P. D. (2000). Gender differences in association between serotonin transporter gene polymorphism and personality traits. *Psychiatric Genetics*, *10*(4), 159–164.Da Silva, N., Jr, Szobot, C. M., Anselmi, C. E., Jackowski, A. P., Chi, S. M., Hoexter, M. Q., … Rohde, L. A. (2011). Attention deficit/hyperactivity disorder: is there a correlation between dopamine transporter density and cerebral blood flow? *Clinical Nuclear Medicine*, *36*(8), 656–660. doi:10.1097/RLU.0b013e318219b49d

Ebstein, R P, Gritsenko, I., Nemanov, L., Frisch, A., Osher, Y., & Belmaker, R. H. (1997). No association between the serotonin transporter gene regulatory region polymorphism and the Tridimensional Personality Questionnaire (TPQ) temperament of harm avoidance. *Molecular Psychiatry*, *2*(3), 224–226.

Ebstein, Richard P., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., … Belmaker, R. H. (1996). Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. *Nature Genetics*, *12*(1), 78–80. doi:10.1038/ng0196-78

Eisenberg, D. T. A., Mackillop, J., Modi, M., Beauchemin, J., Dang, D., Lisman, S. A., … Wilson, D. S. (2007). Examining impulsivity as an endophenotype using a behavioral

approach: a DRD2 TaqI A and DRD4 48-bp VNTR association study. *Behavioral and Brain Functions: BBF*, *3*, 2. doi:10.1186/1744-9081-3-2

Ettinger, U., Joober, R., DE Guzman, R., & O'driscoll, G. A. (2006). Schizotypy, attention deficit hyperactivity disorder, and dopamine genes. *Psychiatry and Clinical Neurosciences*, *60*(6), 764–767. doi:10.1111/j.1440-1819.2006.01594.x

Fallgatter, A. J., Jatzke, S., Bartsch, A. J., Hamelbeck, B., & Lesch, K. P. (1999). Serotonin transporter promoter polymorphism influences topography of inhibitory motor control. *The International Journal of Neuropsychopharmacology*, *2*(02), 115–120.

Filbey, F. M., Claus, E. D., Morgan, M., Forester, G. R., & Hutchison, K. (2011). Dopaminergic genes modulate response inhibition in alcohol abusing adults. *Addiction Biology*. doi:10.1111/j.1369-1600.2011.00328.x

Flory, J. D., Manuck, S. B., Ferrell, R. E., Dent, K. M., Peters, D. G., & Muldoon, M. F. (1999). Neuroticism is not associated with the serotonin transporter (5-HTTLPR) polymorphism. *Molecular Psychiatry*, *4*(1), 93–96.

Forbes, E. E., Brown, S. M., Kimak, M., Ferrell, R. E., Manuck, S. B., & Hariri, A. R. (2009). Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. *Molecular Psychiatry*, *14*(1), 60–70. doi:10.1038/sj.mp.4002086

Franke, B., Hoogman, M., Arias Vasquez, A., Heister, J. G. A. M., Savelkoul, P. J., Naber, M., … Buitelaar, J. K. (2008). Association of the dopamine transporter (SLC6A3/DAT1) gene 9-6 haplotype with adult ADHD. *American Journal of Medical Genetics. Part B,*

Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics, *147B*(8), 1576–1579. doi:10.1002/ajmg.b.30861

Gebhardt, C., Leisch, F., Schüssler, P., Fuchs, K., Stompe, T., Sieghart, W., … Aschauer, H. N. (2000). Non-association of dopamine D4 and D2 receptor genes with personality in healthy individuals. *Psychiatric Genetics*, *10*(3), 131–137.

Gillihan, S. J., Sankoorikal, G. M. V., Brodkin, E. S., & Farah, M. J. (2009). Effect of serotonin transporter genotype on impulsivity and venturesomeness: A preliminary investigation. *Journal of Evolutionary Psychology*, *7*(4), 331–340. doi:10.1556/JEP.7.2009.4.3

Gonda, X., Fountoulakis, K. N., Juhasz, G., Rihmer, Z., Lazary, J., Laszik, A., … Bagdy, G. (2009). Association of the s allele of the 5-HTTLPR with neuroticism-related traits and temperaments in a psychiatrically healthy population. *European Archives of Psychiatry and Clinical Neuroscience*, *259*(2), 106–113. doi:10.1007/s00406-008-0842-7

Gordon, E. M., Stollstorff, M., Devaney, J. M., Bean, S., & Vaidya, C. J. (2011). Effect of Dopamine Transporter Genotype on Intrinsic Functional Connectivity Depends on Cognitive State. *Cerebral Cortex*. doi:10.1093/cercor/bhr305

Greenberg, B. D., Li, Q., Lucas, F. R., Hu, S., Sirota, L. A., Benjamin, J., … Murphy, D. L. (2000). Association between the serotonin transporter promoter polymorphism and personality traits in a primarily female population sample. *American Journal of Medical Genetics*, *96*(2), 202–216. doi:10.1002/(SICI)1096-8628(20000403)96:2<202::AID-AJMG16>3.0.CO;2-J

Grevet, E. H., Marques, F. Z. C., Salgado, C. A. I., Fischer, A. G., Kalil, K. L., Victor, M. M., … Bau, C. H. D. (2007). Serotonin transporter gene polymorphism and the phenotypic

heterogeneity of adult ADHD. *Journal of Neural Transmission*, *114*(12), 1631–1636. doi:10.1007/s00702-007-0797-2

Groleau, P., Steiger, H., Joober, R., Bruce, K. R., Israel, M., Badawi, G., … Sycz, L. (2012). Dopamine-system genes, childhood abuse, and clinical manifestations in women with Bulimia-spectrum Disorders. *Journal of Psychiatric Research*, *46*(9), 1139–1145. doi:10.1016/j.jpsychires.2012.05.018

Ha, R. Y., Namkoong, K., Kang, J. I., Kim, Y. T., & Kim, S. J. (2009). Interaction between serotonin transporter promoter and dopamine receptor D4 polymorphisms on decision making. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *33*(7), 1217–1222. doi:10.1016/j.pnpbp.2009.07.009

Hahn, T., Heinzel, S., Dresler, T., Plichta, M. M., Renner, T. J., Markulin, F., … Fallgatter, A. J. (2011). Association between reward-related activation in the ventral striatum and trait reward sensitivity is moderated by dopamine transporter genotype. *Human Brain Mapping*, *32*(10), 1557–1565. doi:10.1002/hbm.21127

Hahn, T., Heinzel, S., Notebaert, K., Dresler, T., Reif, A., Lesch, K.-P., … Fallgatter, A. J. (2013). The tricks of the trait: Neural implementation of personality varies with genotype-dependent serotonin levels. *NeuroImage*, *81*, 393–399. doi:10.1016/j.neuroimage.2013.05.037

Hamer, D. H., Greenberg, B. D., Sabol, S. Z., & Murphy, D. L. (1999). Role of the Serotonin Transporter Gene in Temperament and Character. *Journal of Personality Disorders*, *13*(4), 312–328. doi:10.1521/pedi.1999.13.4.312

He, Q., Xue, G., Chen, C., Lu, Z., Dong, Q., Lei, X., … Bechara, A. (2010). Serotonin transporter gene-linked polymorphic region (5-HTTLPR) influences decision making under ambiguity and risk in a large Chinese sample. *Neuropharmacology, 59*(6), 518–526. doi:10.1016/j.neuropharm.2010.07.008

Heinzel, S., Dresler, T., Baehne, C. G., Heine, M., Boreatti-Hümmer, A., Jacob, C. P., … Ehlis, A.-C. (2012). COMT × DRD4 Epistasis Impacts Prefrontal Cortex Function Underlying Response Control. *Cerebral Cortex*. doi:10.1093/cercor/bhs132

Johann, M., Bobbe, G., Putzhammer, A., & Wodarz, N. (2003). Comorbidity of Alcohol Dependence With Attention-Deficit Hyperactivity Disorder: Differences in Phenotype With Increased Severity of the Substance Disorder, but Not in Genotype (Serotonin Transporter and 5-Hydroxytryptamine-2c Receptor). *Alcoholism: Clinical and Experimental Research, 27*(10), 1527–1534. doi:10.1097/01.ALC.0000090143.00703.07

Johansson, S., Halleland, H., Halmøy, A., Jacobsen, K. K., Landaas, E. T., Dramsdahl, M., … Haavik, J. (2008). Genetic analyses of dopamine related genes in adult ADHD patients suggest an association with the DRD5-microsatellite repeat, but not with DRD4 or SLC6A3 VNTRs. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics, 147B*(8), 1470–1475. doi:10.1002/ajmg.b.30662

Jollant, F., Buresi, C., Guillaume, S., Jaussent, I., Bellivier, F., Leboyer, M., … Courtet, P. (2007). The influence of four serotonin-related genes on decision-making in suicide attempters. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics:*

The Official Publication of the International Society of Psychiatric Genetics, *144B*(5), 615–624. doi:10.1002/ajmg.b.30467

Joo, Y. H., Oh, H. B., Kim, B., Jung, S. H., Chung, J. K., Hong, J. P., & Kim, C. Y. (2007). No association between 5-HTTLPR and harm avoidance in Korean college students. *Journal of Korean Medical Science*, *22*(1), 138–141.

Katsuragi, S., Kunugi, H., Sano, A., Tsutsumi, T., Isogawa, K., Shinichiro, N., & Akiyoshi, J. (1999). Association between serotonin transporter gene polymorphism and anxiety-related traits. *Biological Psychiatry*, *45*(3), 368–370. doi:http://dx.doi.org/10.1016/S0006-3223(98)00090-0

Kazantseva, A. V., Gaĭsina, D. A., Malykh, S. B., & Khusnutdinova, E. K. (2009). [Role of dopamine transporter gene (DAT1) polymorphisms in personality traits variation]. *Genetika*, *45*(8), 1110–1117.

Kazantseva, A. V., Gaĭsina, D., Malykh, S., & Khusnutdinova, E. (2011). The role of dopamine transporter (SLC6A3) and dopamine D2 receptor/ankyrin repeat and kinase domain containing 1 (DRD2/ANKK1) gene polymorphisms in personality traits. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(4), 1033–1040. doi:10.1016/j.pnpbp.2011.02.013

Kiive, E., & Harro, J. (n.d.). The effect of serotonin transporter gene promoter polymorphism on adolescent and adult ADHD symptoms and educational attainment: A longitudinal study. *European Psychiatry*, (0). doi:10.1016/j.eurpsy.2012.04.004

Kim, J.-W., Park, C.-S., Hwang, J.-W., Shin, M.-S., Hong, K.-E., Cho, S.-C., & Kim, B.-N. (2006). Clinical and genetic characteristics of Korean male alcoholics with and without

attention deficit hyperactivity disorder. *Alcohol and Alcoholism (Oxford, Oxfordshire)*, *41*(4), 407–411. doi:10.1093/alcalc/agl034

Kim, S. J., Kim, Y. S., Lee, H. S., Kim, S. Y., & Kim, C.-H. (2006). An interaction between the serotonin transporter promoter region and dopamine transporter polymorphisms contributes to harm avoidance and reward dependence traits in normal healthy subjects. *Journal of Neural Transmission*, *113*(7), 877–886. doi:10.1007/s00702-006-0444-3

Kumakiri, C., Kodama, K., Shimizu, E., Yamanouchi, N., Okada, S., Noda, S., … Shirasawa, H. (1999). Study of the association between the serotonin transporter gene regulatory region polymorphism and personality traits in a Japanese population. *Neuroscience Letters*, *263*(2-3), 205–207.

Lage, G. M., Malloy-Diniz, L. F., Matos, L. O., Bastos, M. A. R., Abrantes, S. S. C., & Corrêa, H. (2011). Impulsivity and the 5-HTTLPR polymorphism in a non-clinical sample. *PloS One*, *6*(2), e16927. doi:10.1371/journal.pone.0016927

Landaas, E. T., Johansson, S., Jacobsen, K. K., Ribasés, M., Bosch, R., Sánchez-Mora, C., … Haavik, J. (2010). An international multicenter association study of the serotonin transporter gene in persistent ADHD. *Genes, Brain, and Behavior*, *9*(5), 449–458. doi:10.1111/j.1601-183X.2010.00567.x

Lang, U. E., Bajbouj, M., Wernicke, C., Rommelspacher, H., Danker-Hopfe, H., & Gallinat, J. (2004). No association of a functional polymorphism in the serotonin transporter gene promoter and anxiety-related personality traits. *Neuropsychobiology*, *49*(4), 182–184. doi:10.1159/000077363

LeMarquand, D. G. (1997). *Serotonin and disorders of human disinhibition : alcohol abuse and dependence, aggression and impulsivity*. Pihl, Robert O. (advisor). Retrieved from http://digitool.Library.McGill.CA:8881/R/?func=dbin-jump-full&object_id=34998

Lerman, C., Caporaso, N. E., Audrain, J., Main, D., Boyd, N. R., & Shields, P. G. (2000). Interacting effects of the serotonin transporter gene and neuroticism in smoking practices and nicotine dependence. *Molecular Psychiatry*, *5*(2), 189–192. doi:10.1038/sj.mp.4000672

Loo, S. K., Hale, S. T., Hanada, G., Macion, J., Shrestha, A., McGough, J. J., … Smalley, S. L. (2010). Familial clustering and DRD4 effects on electroencephalogram measures in multiplex families with attention deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(4), 368–377.

Malloy-Diniz, L. F., Neves, F. S., de Moraes, P. H. P., De Marco, L. A., Romano-Silva, M. A., Krebs, M.-O., & Corrêa, H. (2011). The 5-HTTLPR polymorphism, impulsivity and suicide behavior in euthymic bipolar patients. *Journal of Affective Disorders*, 133(1-2), 221–226. doi:10.1016/j.jad.2011.03.051

Malhotra, A. K., Virkkunen, M., Rooney, W., Eggert, M., Linnoila, M., & Goldman, D. (1996). The association between the dopamine D4 receptor (D4DR) 16 amino acid repeat polymorphism and novelty seeking. *Molecular Psychiatry*, *1*(5), 388–391.

Mill, J., Asherson, P., Browes, C., D'Souza, U., & Craig, I. (2002). Expression of the dopamine transporter gene is regulated by the 3′ UTR VNTR: Evidence from brain and lymphocytes using quantitative RT-PCR. *American Journal of Medical Genetics*, *114*(8), 975–979. doi:10.1002/ajmg.b.10948

Monuteaux, M. C., Seidman, L. J., Faraone, S. V., Makris, N., Spencer, T., Valera, E., … Biederman, J. (2008). A preliminary study of dopamine D4 receptor genotype and structural brain alterations in adults with ADHD. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *147B*(8), 1436–1441. doi:10.1002/ajmg.b.30870

Moukaddam, N. J. (2010). *Impact of genetic variability in the serotonin transporter, tryptophan hydroxylase-2, and serotonin 2A receptors on MDMA use and impulsivity*. (Doctoral dissertation). Retrieved from ProQuest Dissertations and Theses. (Accession Order No. AAT 3367483)

Muglia, P., Jain, U., Macciardi, F., & Kennedy, J. L. (2000). Adult attention deficit hyperactivity disorder and the dopamine D4 receptor gene. *American Journal of Medical Genetics*, *96*(3), 273–277.

Müller, D. J., Chiesa, A., Mandelli, L., De Luca, V., De Ronchi, D., Jain, U., … Kennedy, J. L. (2010). Correlation of a set of gene variants, life events and personality features on adult ADHD severity. *Journal of Psychiatric Research*, *44*(9), 598–604. doi:10.1016/j.jpsychires.2009.11.011

Must, A., Juhász, A., Rimanóczy, A., Szabó, Z., Kéri, S., & Janka, Z. (2007). Major depressive disorder, serotonin transporter, and personality traits: why patients use suboptimal decision-making strategies? *Journal of Affective Disorders*, *103*(1-3), 273–276. doi:10.1016/j.jad.2007.02.001

Nakamura, T., Muramatsu, T., Ono, Y., Matsushita, S., Higuchi, S., Mizushima, H., … Asai, M. (1997). Serotonin Transporter Gene Regulatory Region Polymorphism and

Anxiety-Related Traits in the Japanese. *American Journal of Medical Genetics (Neuropsychiatric Genetics), 74*, 544–545.

O'Hara, R., Schröder, C. M., Mahadevan, R., Schatzberg, A. F., Lindley, S., Fox, S., … Hallmayer, J. F. (2007). Serotonin transporter polymorphism, memory and hippocampal volume in the elderly: association and interaction with cortisol. *Molecular Psychiatry*, *12*(6), 544–555. doi:10.1038/sj.mp.4001978

Osher, Y., Hamer, D., & Benjamin, J. (2000). Association and linkage of anxiety-related traits with a functional polymorphism of the serotonin transporter gene regulatory region in Israeli sibling pairs. *Molecular Psychiatry, 5*(2), 216–219.

Passamonti, L., Cerasa, A., Gioia, M. C., Magariello, A., Muglia, M., Quattrone, A., & Fera, F. (2008). Genetically dependent modulation of serotonergic inactivation in the human prefrontal cortex. *NeuroImage*, *40*(3), 1264–1273. doi:10.1016/j.neuroimage.2007.12.028

Patkar, A. A., Berrettini, W. H., Hoehe, M., Thornton, C. C., Gottheil, E., Hill, K., & Weinstein, S. P. (2002). Serotonin transporter polymorphisms and measures of impulsivity, aggression, and sensation seeking among African-American cocaine-dependent individuals. *Psychiatry Research*, *110*(2), 103–115. doi:10.1016/S0165-1781(02)00098-7

Pogue-Geile, M., Ferrell, R., Deka, R., Debski, T., & Manuck, S. (1998). Human novelty-seeking personality traits and dopamine D4 receptor polymorphisms: a twin and genetic association study. *American Journal of Medical Genetics*, *81*(1), 44–48. doi:10.1002/(SICI)1096-8628(19980207)81:1<44::AID-AJMG9>3.0.CO;2-N

Pooley, E. C., Houston, K., Hawton, K., & Harrison, P. J. (2003). Deliberate self-harm is associated with allelic variation in the tryptophan hydroxylase gene (TPH A779C), but

not with polymorphisms in five other serotonergic genes. *Psychological Medicine*, *33*(5), 775–783.

Racine, S. E., Culbert, K. M., Larson, C. L., & Klump, K. L. (2009). The possible influence of impulsivity and dietary restraint on associations between serotonin genes and binge eating. *Journal of Psychiatric Research*, *43*(16), 1278–1286. doi:10.1016/j.jpsychires.2009.05.002

Ricketts, M. H., Hamer, R. M., Manowitz, P., Feng, F., Sage, J. I., Paola, R. D., & Menza, M. A. (1998). Association of long variants of the dopamine D4 receptor exon 3 repeat polymorphism with Parkinson's disease. *Clinical Genetics*, 54(1), 33–38. doi:10.1111/j.1399-0004.1998.tb03690.x

Roussos, P., Giakoumaki, S. G., & Bitsios, P. (2009). Cognitive and emotional processing in high novelty seeking associated with the L-DRD4 genotype. *Neuropsychologia*, *47*(7), 1654–1659. doi:10.1016/j.neuropsychologia.2009.02.005

Roussos, P., Giakoumaki, S. G., & Bitsios, P. (2010). Cognitive and emotional processing associated with the Season of Birth and dopamine D4 receptor gene. *Neuropsychologia*, *48*(13), 3926–3933. doi:10.1016/j.neuropsychologia.2010.09.021

Rybakowski, F., Samochowiec, J., Zakrzewska, M., Czerski, P., Stepień, G., Pelka-Wysiecka, J., … Rybakowski, J. K. (2002). Interaction of monoamine transporter genes and personality dimensions. *Archives of Psychiatry and Psychotherapy*, 4(2), 17–24.

Sadeh, N., Javdani, S., & Verona, E. (2012). Analysis of Monoaminergic Genes, Childhood Abuse, and Dimensions of Psychopathy. *Journal of Abnormal Psychology*. doi:10.1037/a0029866

Sakado, K., Sakado, M., Muratake, T., Mundt, C., & Someya, T. (2003). A psychometrically derived impulsive trait related to a polymorphism in the serotonin transporter gene-linked polymorphic region (5-HTTLPR) in a Japanese nonclinical population: assessment by the Barratt impulsiveness scale (BIS). *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*, *121B*(1), 71–75. doi:10.1002/ajmg.b.20063

Samochowiec, J., Syrek, S., Michał, P., Ryżewska-Wódecka, A., Samochowiec, A., Horodnicki, J., … Kucharska-Mazur, J. (2004). Polymorphisms in the Serotonin Transporter and Monoamine Oxidase A Genes and Their Relationship to Personality Traits Measured by the Temperament and Character Inventory and NEO Five-Factor Inventory in Healthy Volunteers. *Neuropsychobiology*, *50*(2), 174–181. doi:10.1159/000079111

Sánchez-Mora, C., Ribasés, M., Casas, M., Bayés, M., Bosch, R., Fernàndez-Castillo, N., … Cormand, B. (2011). Exploring DRD4 and its interaction with SLC6A3 as possible risk factors for adult ADHD: a meta-analysis in four European populations. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*, *156B*(5), 600–612. doi:10.1002/ajmg.b.31202

Sen, S., Villafuerte, S., Nesse, R., Stoltenberg, S. F., Hopcian, J., Gleiberman, L., … Burmeister, M. (2004). Serotonin transporter and GABA(A) alpha 6 receptor variants are associated with neuroticism. *Biological Psychiatry*, *55*(3), 244–249. doi:10.1016/j.biopsych.2003.08.006

Soyka, M., Preuss, U. W., Koller, G., Zill, P., & Bondy, B. (2002). Dopamine D 4 receptor gene polymorphism and extraversion revisited: results from the Munich gene bank project for alcoholism. *Journal of Psychiatric Research*, *36*(6), 429–435.

Steiger, H., Joober, R., Israël, M., Young, S. N., Ng Ying Kin, N. M. K., Gauvin, L., … Torkaman-Zehi, A. (2005). The 5HTTLPR polymorphism, psychopathologic symptoms, and platelet [3H-] paroxetine binding in bulimic syndromes. *International Journal of Eating Disorders*, *37*(1), 57–60. doi:10.1002/eat.20073

Stoltenberg, S. F., Christ, C. C., & Highland, K. B. (2012). Serotonin system gene polymorphisms are associated with impulsivity in a context dependent manner. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *39*(1), 182–191. doi:10.1016/j.pnpbp.2012.06.012

Stoltenberg, S. F., Lehmann, M. K., Anderson, C., Nag, P., & Anagnopoulos, C. (2011). Serotonin Transporter (5-HTTLPR) Genotype and Childhood Trauma are Associated with Individual Differences in Decision Making. *Frontiers in Genetics*, *2*, 33. doi:10.3389/fgene.2011.00033

Stoltenberg, S. F., Twitchell, G. R., Hanna, G. L., Cook, E. H., Fitzgerald, H. E., Zucker, R. A., & Little, K. Y. (2002). Serotonin transporter promoter polymorphism, peripheral indexes of serotonin function, and personality measures in families with alcoholism. *American Journal of Medical Genetics*, *114*(2), 230–234.

Stoltenberg, S. F., & Vandever, J. M. (2010). Gender moderates the association between 5-HTTLPR and decision-making under ambiguity but not under risk. *Neuropharmacology*, *58*(2), 423–428. doi:10.1016/j.neuropharm.2009.09.010

Strobel, A., Dreisbach, G., Müller, J., Goschke, T., Brocke, B., & Lesch, K.-P. (2007). Genetic Variation of Serotonin Function and Cognitive Control. *Journal of Cognitive Neuroscience*, *19*(12), 1923–1931. doi:10.1162/jocn.2007.19.12.1923

Strobel, A., Spinath, F. M., Angleitner, A., Riemann, R., & Lesch, K.-P. (2003). Lack of association between polymorphisms of the dopamine D4 receptor gene and personality. *Neuropsychobiology*, *47*(1), 52–56. doi:10.1159/000068876

Surguladze, S. A., Elkin, A., Ecker, C., Kalidindi, S., Corsico, A., Giampietro, V., … Phillips, M. L. (2008). Genetic variation in the serotonin transporter modulates neural system-wide response to fearful faces. *Genes, Brain and Behavior*, *7*(5), 543–551. doi:10.1111/j.1601-183X.2008.00390.x

Suzuki, A., Matsumoto, Y., Oshino, S., Kamata, M., Goto, K., & Otani, K. (2008). Combination of the serotonin transporter and norepinephrine transporter gene promoter polymorphisms might influence harm avoidance and novelty seeking in healthy females. *Neuroscience Letters*, *439*(1), 52–55. doi:10.1016/j.neulet.2008.04.088

Sweitzer, M. M., Halder, I., Flory, J. D., Craig, A. E., Gianaros, P. J., Ferrell, R. E., & Manuck, S. B. (2012). Polymorphic variation in the dopamine D4 receptor predicts delay discounting as a function of childhood socioeconomic status: evidence for differential susceptibility. *Social Cognitive and Affective Neuroscience*. doi:10.1093/scan/nss020

Szekely, A., Ronai, Z., Nemoda, Z., Kolmann, G., Gervai, J., & Sasvari-Szekely, M. (2004). Human personality dimensions of persistence and harm avoidance associated with DRD4 and 5-HTTLPR polymorphisms. *American Journal of Medical Genetics. Part B,*

Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics, *126B*(1), 106–110. doi:10.1002/ajmg.b.20134

Umekage, T., Tochigi, M., Marui, T., Kato, C., Hibino, H., Otani, T., … Sasaki, T. (2003). Serotonin transporter-linked promoter region polymorphism and personality traits in a Japanese population. *Neuroscience Letters*, *337*(1), 13–16.

Varga, G., Szekely, A., Antal, P., Sarkozy, P., Nemoda, Z., Demetrovics, Z., & Sasvari-Szekely, M. (2012). Additive effects of serotonergic and dopaminergic polymorphisms on trait impulsivity. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *159B*(3), 281–288. doi:10.1002/ajmg.b.32025

Vormfelde, S. V., Hoell, I., Tzvetkov, M., Jamrozinski, K., Sehrt, D., Brockmöller, J., & Leibing, E. (2006). Anxiety- and novelty seeking-related personality traits and serotonin transporter gene polymorphisms. *Journal of Psychiatric Research*, *40*(6), 568–576. doi:10.1016/j.jpsychires.2005.10.002

Wagner, S., Baskaya, O., Lieb, K., Dahmen, N., & Tadić, A. (2009). The 5-HTTLPR polymorphism modulates the association of serious life events (SLE) and impulsivity in patients with Borderline Personality Disorder. *Journal of Psychiatric Research*, *43*(13), 1067–1072. doi:10.1016/j.jpsychires.2009.03.004

Walderhaug, E., Herman, A. I., Magnusson, A., Morgan, M. J., & Landrø, N. I. (2010). The short (S) allele of the serotonin transporter polymorphism and acute tryptophan depletion both increase impulsivity in men. *Neuroscience Letters*, *473*(3), 208–211. doi:10.1016/j.neulet.2010.02.048

Wiesbeck, G. A., Weijers, H.-G., Wodarz, N., Keller, H. K., Michel, T. M., Herrmann, M. J., & Boening, J. (2004). Serotonin transporter gene polymorphism and personality traits in primary alcohol dependence. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *5*(1), 45–48.

Zalsman, G., Frisch, A., Bromberg, M., Gelernter, J., Michaelovsky, E., Campino, A., … Weizman, A. (2001). Family-based association study of serotonin transporter promoter in suicidal adolescents: No association with suicidality but possible role in violence traits. *American Journal of Medical Genetics*, *105*(3), 239–245. doi:10.1002/ajmg.1261