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Genetic and Environmental Influences on ADHD Symptom Dimensions of Inattention and Hyperactivity: A Meta-Analysis

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Behavioral genetic investigations have consistently demonstrated large genetic influences for the core symptom dimensions of attention-deficit/hyperactivity disorder (ADHD), namely inattention (INATT) and hyperactivity (HYP). Yet little is known regarding potential similarities and differences in the *type* of genetic influence (i.e., additive vs. nonadditive) on INATT and HYP. As these symptom dimensions form the basis of the current *Diagnostic and Statistical Manual of Mental Disorders* subtype classification system, evidence of differential genetic influences would have important implications for research investigating causal mechanisms for ADHD. The current meta-analysis aimed to investigate the nature of etiological influences for INATT and HYP by comparing the type and magnitude of genetic and environmental influences each. A comprehensive literature search yielded 79 twin and adoption studies of INATT and/or HYP. Of these, 13 samples of INATT and 9 samples of HYP were retained for analysis. Results indicated that both dimensions were highly heritable (genetic factors accounted for 71% and 73% of the variance in INATT and HYP, respectively). However, the 2 dimensions were distinct as to the type of genetic influence. Dominant genetic effects were significantly larger for INATT than for HYP, whereas additive genetic effects were larger for HYP than for INATT. Estimates of unique environmental effects were small to moderate and shared environmental effects were negligible for both symptom dimensions. The pattern of results generally persisted across several moderating factors, including gender, age, informant, and measurement method. These findings highlight the need for future studies to disambiguate INATT and HYP when investigating the causal mechanisms, and particularly genetic influences, behind ADHD.

Keywords: inattention, hyperactivity, genetic, etiology

Attention-deficit/hyperactivity disorder (ADHD) is defined in the current diagnostic classification system as a behavioral syndrome composed of two correlated but distinct symptom dimensions: inattention–disorganization (INATT) and hyperactivity–impulsivity (HYP; American Psychiatric Association, 2000). These two symptom dimensions give rise to the three subtypes of ADHD: Primarily Inattentive (high inattention, low hyperactivity), Primarily Hyperactive (low inattention, high hyperactivity), and Combined (high on both symptom dimensions). Although questions regarding the validity of the categorical subtypes remain (see Lahey, Pelham, Loney, Lee, & Willcutt, 2005), the internal and external validity of the behavioral dimensions of INATT and HYP have generally been well supported (DuPaul, Power, Anastopoulos, & Reid, 1998; Milich, Ballentine, & Lynam, 2001). Factor analytic evidence generally suggests that ADHD is best understood as extremes along the INATT and HYP behavioral dimensions (DuPaul et al., 1998; Lahey et al., 2008). Moreover, there is emerging evidence that INATT and HYP may be linked to partially distinct neuropsychological mechanisms and temperament traits (Martel & Nigg, 2006; Sonuga-Barke, 2003). INATT and HYP also appear to be differentially predictive of later adolescent and adult outcomes. For example, INATT is a robust predictor of academic problems (Breslau, Lane, Sampson, & Kessler, 2008; Duncan et al., 2007), whereas HYP has been specifically related to substance abuse, even when controlling for conduct problems (Elkins, McGue, & Iacono, 2007).

The handful of twin and family studies examining the possibility of etiological differences between the ADHD symptom dimensions have offered additional, if inconsistent, support for distinct behavioral dimensions within ADHD. For example, family studies of subtype-specific inheritance have shown mixed results. One study found no familial coaggregation of ADHD categorical subtypes. This finding is consistent with the idea that the behavioral dimensions of INATT and HYP arise from a common genetic etiology, as there is no specificity of inheritance of any of the categorical subtypes (Smalley et al., 2000). However, other studies have demonstrated evidence of familial specificity for the Primarily Hyperactive–Impulsive subtype only using both *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) subtypes and empirically derived subtypes (Faraone, Biederman, & Friedman, 2000; Todd et al., 2001). Further, a recent meta-analysis of these family data demonstrated some subtype-specific inheritance, such that the subtypes are partially separable in families, although the transmission magnitude was small (Stawicki, Nigg, & von Eye,

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2006). Importantly, Stawicki et al. (2006) noted that the effect sizes tended to vary by the type of sample and data included (e.g., sibling studies showed smaller effect sizes than population twin studies). The authors also pointed out that these differences in sample composition may moderate the ways in which categorical subtype transmission is detected. Therefore, examination of behavioral dimensions as opposed to diagnostic subtype categories may provide a more clear and consistent answer as to potential etiological differences between INATT and HYP.

The first twin study to examine genetic and environmental contributions to INATT and HYP found that each symptom dimension was highly heritable and that they shared a significant proportion of their genes (Sherman, Iacono, & McGue, 1997). However, Willcutt, Pennington, and DeFries (2000) subsequently found that the heritability of INATT was high, regardless of the level of HYP, but that genetic influences for HYP increased linearly with levels of INATT. These results further suggest that different etiological influences may be operating for INATT and HYP. More recently, McLoughlin, Ronald, Kuntsi, Asherson, and Plomin (2007) examined genetic and environmental influences on INATT and HYP in a large-scale twin study. Their results again indicated substantial genetic influences for both INATT and HYP, as well as moderate to high genetic correlations between the two symptom domains. Even so, the genetic correlations between INATT and HYP (.57 for girls, .62 for boys) also indicated some etiological independence of the two symptom domains.

Overall, prior behavioral genetic studies have provided good evidence that (a) genetic factors make a substantial contribution to the variance in ADHD overall, and (b) the symptom dimensions of INATT and HYP and their covariance are also largely influenced by genetic factors. What is less clear is the degree of similarity or difference in the *types* of genetic effects (additive vs. nonadditive). Additive genetic effects represent the summed effects of genetic influences across multiple loci (e.g., height reflects additive genetic effects). In other words, additive genetic effects are cumulative and reflect the proportion of relevant alleles passed from parent to child (e.g., the height of the offspring is directly dependent upon the sum of "tall genetic markers" received from each biological parent). Given this, if additive genetic effects are operating for a trait, we would expect similarities between parents and their children across genetic loci related to that trait. In contrast, nonadditive or dominant genetic effects represent interactions among alleles both within and across loci. Nonadditive genetic influences are thus a function of multiplicative effects, in which the trait is influenced by interactions between alleles (e.g., the eye color of the offspring is dependent upon the interactions between the "eye color" alleles inherited from each parent). As each parent provides only one of the two alleles, nonadditive genetic effects typically do not result in parent–child similarity.

The type of genetic effects influencing ADHD and its symptom dimensions remains a fundamental question for research involving the genetic etiology of the disorder. Because of the different modes of inheritance operating for additive versus nonadditive genetic effects, differential patterns of phenotypic similarity are expected for parents and their offspring (i.e., additive genetic effects would result in similarity between parents and children, whereas nonadditive genetic effects would not). The presence of nonadditivity could then complicate the interpretation of family studies for ADHD, because potentially little parent–child phenotypic similarity would be observed. Further, the presence of nonadditive genetic effects remains an important consideration for molecular genetic research. Much of the work on ADHD to date has been explicitly testing for (or assuming) additive genetic effects. More recently, large-scale genetic studies have been testing both additive and dominant models of transmission using family-based association designs (see Brookes et al., 2006), however, this is not yet the norm. If nonadditive genetic influences are indeed contributing to ADHD via one or both of its core symptom domains, then it is unlikely they would be detected using the traditional single-locus parent–child transmission approach, as it primarily relies upon summing up alleles transmitted from heterozygote parents to their affected offspring across various genetic loci.

Regarding the type of genetic influences for ADHD, some studies have found that ADHD (and its constituent symptom dimensions of INATT and HYP) is influenced by predominately additive genetic effects (Eaves, Silberg, Meyer, & Maes, 1997; Kuntsi, Gayan, & Stevenson, 2000; Saudino, Ronald, & Plomin, 2005; van Beijsterveldt, Verhulst, Molenaar, & Boomsma, 2004), yet others have reported contributions from both additive and dominant genetic influences (Hudziak, Althoff, Derks, Faraone, & Boomsma, 2005; Rietveld, Hudziak, Bartels, Van Beijsterveldt, & Boomsma, 2003, 2004; Thapar, Harrington, Ross, & McGuffin, 2000). Confirming this mixed picture, a recent meta-analysis of the unidimensional ADHD phenotype indicated the presence of substantial additive and dominant genetic effects for ADHD (Burt, 2009). However, whether the type (and magnitude) of genetic effects influencing INATT is similar to that influencing HYP remains an important question to be answered.

The goal of this meta-analysis was thus to examine the extant behavioral genetic literature to determine whether there are meaningful differences in the genetic and environmental factors influencing INATT and HYP. Particular attention was given to evaluating any differences in the types of genetic effects for each dimension. We also investigated whether etiological similarities or differences persist across various moderators of etiologic effects, including gender, age, informant, and measurement method. Evidence for etiological separation of INATT and HYP could inform future empirical and theoretical work aimed at uncovering causal mechanisms underlying ADHD, as well as provide clues for molecular genetic investigations of ADHD.

Method

Search Strategy

To identify studies with relevant data (i.e., journal articles, published abstracts, and dissertations), a search was conducted of the PsycINFO and Medline databases in June and July of 2007. Search terms were used to identify studies regarding the phenotype of interest (i.e., inattention, hyperactivity, impulsivity, attention-deficit hyperactivity disorder, attention-deficit disorder, attention problems, overactivity) and then combined with each of the following genetically informative study terms: twin, twins, adoptee, adoptees, adoptive, genetic, environment. The reference section of each article was also examined in order to identify any additional relevant studies that may have been missed in the original search. To avoid bias associated with the "file drawer effect," we included all research examining genetic and environmental influences on

INATT and HYP, rather than just those that directly compared etiological influences on the two phenotypes. As a result, the majority of included studies were not motivated to explicitly confirm (or refute) differences in etiological influences on INATT and HYP, as this question was not the primary purpose of analyses in the majority of investigations.

The search yielded a total of 79 twin and adoption studies (e.g., separate articles). Inclusion criteria (i.e., construct requirements) are detailed below. Using these criteria, we retained 27 studies of INATT and 23 studies of HYP. After additionally accounting for nonindependence among the samples (as detailed below), 13 INATT and 9 HYP samples were ultimately included in analyses. Included and excluded studies are presented in the Appendix. Stem and leaf plots for all effect size data are presented for INATT and HYP in Tables 1 and 2, respectively.

Inclusion Criteria

Construct validity. Studies included in the analyses met at least one of the following criteria: (a) the study clearly distinguished between INATT and HYP and examined INATT and/or HYP (i.e., the items referenced explicit symptoms of INATT or HYP in *DSM–III–R* [American Psychiatric Association, 1987] or *DSM–IV* [American Psychiatric Association, 1994]), (b) there was empirical evidence that the measure successfully discriminated clinical and normative samples on either INATT or HYP (e.g., Connors Rating Scales, Achenbach Child Behavior Checklist [CBCL], or Teacher Report Form; see manuals for information; Achenbach & Rescorla, 2001; Connors, 1997), and/or (c) the measure was significantly associated with a validated measure of either INATT or HYP. Application of these criteria resulted in the inclusion of the Overactivity and Attention Problems scales on the Achenbach family of instruments (e.g., the Child Behavior Checklist, Teacher Report Form), the Cognitive Problems/Inattention and Hyperactivity/Impulsivity scales of the Connors Rating Scales, and *DSM* symptom counts of inattention and hyperactivity. Studies examining behavioral measures of inattention and impulsivity (e.g., via continuous performance tasks) were omitted ($n = 2$).

It is important to note that although measures of HYP were relatively "pure" (i.e., the items did not overlap with those assessing INATT), measures of INATT were not always as precise. Some measures included in the meta-analysis of INATT contained items that tapped hyperactive or impulsive behaviors (e.g., two of the seven items on the Attention Problems scale on the CBCL appeared to tap hyperactivity–impulsivity). Because most items tapped INATT behaviors, these studies were retained in the meta-analysis of INATT. However, to evaluate the robustness of our results, analyses were rerun limiting the data to those measures that uniquely assess INATT (e.g., *DSM* symptom counts, Connors Cognitive Problems/Inattention Scale).

Nonindependent samples. The final justification for study exclusion was nonindependent sampling (a relatively common phenomenon in these data). Studies had nonindependent data for several reasons, including more than one dependent measure of the phenotype (e.g., INATT or HYP) in their sample (either within publications and/or across multiple publications) or longitudinal follow-up data on the same set of subjects. These multiple measures could take several forms, including multiple informants examined separately and/or data for more than one relevant measure examined separately.

Hierarchical linear modeling (HLM) meta-analytic approaches can easily accommodate this sort of nonindependence. However, it is not currently possible to estimate genetic and environmental influences within these designs (to our knowledge). Instead, one common approach to handling nonindependence in meta-analyses of (primarily adult) twin data is to choose the largest sample and omit the others (Rhee & Waldman, 2002). In child and adolescent twin samples, however, this approach is potentially problematic. First, because of attrition over time in many longitudinal investigations, the first wave (or youngest) nonindependent sample is typically the largest. Second, because mothers are more likely than fathers to attend assessments and are more reliable than children as informants, maternal reports are typically available for all or nearly all participants, whereas other informant reports are not. Given this association between sample size and sample characteristics, the current meta-analysis implemented the following strategy: When nonindependent samples varied across age, informant report, and/or dependent measure, weighted averages were used to compute the study effect size (i.e., the sample size is used to weight the

Table 1
Stem and Leaf Plot of Effect Sizes (Correlations) for Twin and Adoption Studies of Inattention

	Leaf		
Stem	MZ twin pairs ($r = a^2 + c^2$)	DZ twin pairs/FS ($r = .5a^2 + c^2$)	Unrelated sibling pairs ($r = c^2$)
.9	022		
.8	00011133556778		
.7	000000111112222333556889		
.6	112244556688999	0014	
.5	379	00378	
.4	1	44555777	
.3	13339	001112223478899	
.2	1	00111222233333444556666788899999	
.1		014579	0
.0		003	899
−.0		237	3
−.1		7	

Note. MZ = monozygotic; DZ = dizygotic; FS = full siblings. Unrelated sibling pairs include step siblings and adoptive siblings.

Table 2
Stem and Leaf Plot of Effect Sizes (Correlations) for Twin and Adoption Studies of Hyperactivity

	Leaf		
Stem	MZ twin pairs ($r = a^2 + c^2$)	DZ twin pairs/FS ($r = .5a^2 + c^2$)	Unrelated sibling pairs ($r = c^2$)
.9	01234		
.8	014567778		
.7	01123358	09	
.6	11112333566999		
.5	00125778	002234679	
.4	06779	2357	
.3	01223778		
.2	158	113344557789	
.1	9	0001113456	
.0		113778	
−.0		1234569	
−.1		16	

Note. MZ = monozygotic; DZ = dizygotic; FS = full siblings. Unrelated sibling pairs include step siblings and adoptive siblings.

contribution of the given effect size to the average effect size). If nonindependent samples contained multiple assessments but did not vary by sample size, simple averages were computed. If nonindependent samples did not vary by age or informant report, the largest sample was chosen. If sample sizes were equal, the sample with more information on gender, age, or informant was included. The results of this strategy are indicated in the inclusion columns listed in the Appendix.

Analyses

Behavioral genetic analyses make use of the differences in the proportion of segregating genes that are shared between family members. Monozygotic twins (MZ, or identical twins) result from the splitting of a single fertilized zygote and as such, share 100% of their segregating genetic material. Dizygotic (DZ, or fraternal) twins are the result of two separately fertilized zygotes and so, like all full siblings, share an average of 50% of their segregating genes. Because half siblings share only one biological parent, they share an average of 25% of their segregating genes, whereas adoptive siblings and step-siblings are biologically unrelated and thus do not share any of their segregating genetic material.

Behavioral genetic analyses use these differences in degree of genetic relatedness to parse the variance within observed behaviors or characteristics (i.e., phenotypes) into four components. The additive genetic (a^2) variance component represents the effect of individual genes summed across loci. Additive genetic effects, if acting alone, would effectively create MZ correlations that are approximately twice those of DZ/full sibling correlations. The dominant genetic variance component (d^2) is an index of interactive genetic effects across multiple loci and, if acting alone, would produce MZ correlations that are more than twice as large as those for DZ/full siblings. The shared environmental variance component (c^2) captures the part of the environment that is common to both members of a sibling pair and serve to make siblings within a pair more similar to each other. Shared environmental factors do not differ by degree of genetic relatedness, and if acting alone, would serve to make all sibling correlations similar in magnitude. The nonshared environment (e^2) represents those environmental factors that make sibling pairs dissimilar to one another and also does not differ by degree of genetic relatedness. Nonshared environmental effects, which also include measurement error, thus reduce all sibling correlations to the same degree.

A critical assumption of twin analyses is the *equal environments assumption*, which supposes that the environmental factors that are etiologically relevant to the phenotype in question are no more likely to be shared among MZ twin pairs than among DZ twin pairs. Thus, any differences in the correlations between MZ and DZ correlations are thought to be due to differences in their degree of genetic similarity. The equal environments assumption has been demonstrated to be valid for numerous phenotypes (see Plomin, DeFries, McClearn, & McGruffin, 2008, for review). For their part, adoption studies may be influenced by environmental range restriction, as adoptive parents are more likely to be better educated, more affluent, and show less vulnerability to psychopathology. However, a recent examination of the effects of environmental range restriction demonstrated that it had no effect on the adoptive-sibling correlations for several behavioral measures (McGue et al., 2007).

One common approach to testing causal influences within the field of behavioral genetics is to fit a series of alternative biometric models and then compare their fit to the observed data. In the current meta-analysis, two models were fitted: the ACE and the ADE models. The first estimates additive genetic (A), shared environment (C), and nonshared environmental contributions (E) to the symptom dimensions (ACE). The second estimates additive genetic (A), dominant genetic (D), and nonshared environmental influences (E) for INATT and HYP (ADE). It is not possible to simultaneously estimate c^2 and d^2 in these analyses, because these parameters are estimated using the same information (e.g., differences in sibling similarity with genetic relatedness). Mx (Neale, 1997), a structural equation modeling program, was used to perform the model-fitting analyses. Mx uses maximum-likelihood model-fitting techniques to fit models to observed correlation matrices. Goodness of fit was estimated using the chi-squared test statistic. The chi-squared values were then converted to the Akaike's Information Criterion (AIC; $AIC = \chi^2 - (2 \times df)$; Akaike, 1987) and the Bayesian Information Criterion (BIC; $BIC = \chi^2 - [\ln(N) \times df]$; $N = 30{,}947$ pairs; Raftery, 1995). In the current study, AIC and BIC were used to determine the best-fitting model, with the lowest or most negative values considered best. These two fit indices are the most commonly used fit indices within the field of behavioral genetics (Markon & Krueger, 2004). Both indices measure model fit relative to parsimony; however, BIC weights parsimony somewhat more heavily than does AIC.

Specific analyses. Parameter estimates for INATT and HYP across all available (but independent) data were computed, and the fit indices of the constrained and unconstrained ACE and ADE models were compared. The constrained model forces the genetic and environmental parameter estimates to be equal across the two phenotypes, whereas the unconstrained model allows these estimates to vary. The best-fitting model, as indicated by the lowest AIC and BIC, was then presented and discussed. Confidence intervals that do not overlap with zero indicated that the parameter was significantly greater than zero. Further, individual parameters were constrained across INATT and HYP (e.g., a^2 for INATT and

a^2 for HYP) to determine whether equalizing the estimates resulted in a reduction in model fit. A reduction in model fit (as indexed by a significant change in chi-squared) indicates that the magnitude of explained variance differed across the two phenotypes.

We next examined a series of possible moderators in order to evaluate the persistence of any observed etiological differences between INATT and HYP. The paths in question were equated across INATT and HYP within different categories of the moderator, and subsequent changes in model fit were examined. Because the goal of the moderator analyses was to determine whether differences already observed between INATT and HYP in the overall analyses persisted across gender, age, informant, and measurement method, we made use of one-tailed, $p < .05$ tests to determine statistical significance (note that this one-tailed significance level applies only to the moderator analyses).

When examining gender as a potential moderator, analyses were restricted to those studies (i.e., nine INATT studies and six HYP studies) in which correlations were presented separately by gender (e.g., male–male sibling pairs vs. female–female sibling pairs). Opposite-sex pairs were omitted (from the gender-moderator analyses only), which allowed estimates to be directly compared across males and females. When examining age as a moderator, studies that spanned multiple age categories were omitted (i.e., five INATT studies and two HYP studies), whereas studies that fell cleanly into a single age category (or where weighted averages could be computed within a single age category) were included. Finally, when examining informant effects, analyses focused upon mother and teacher informant reports, as father reports and child self-reports of symptoms were rare. Of note, maternal reports included both those reports specifically from mothers and those under the more ambiguous term of "parent," as close examination of methods sections revealed that informants for parent reports were generally mothers.

Results

Overall Analyses

The fit of the constrained and unconstrained ACE and ADE models were compared (see Table 3). The unconstrained ADE model provided the best fit to the data, as indicated by the smallest AIC and BIC values. Further, c^2 was estimated to be exactly zero in the ACE model, further suggesting that the ADE model provided a better fit to the data. These results indicated that additive genetic, dominant genetic, and nonshared environmental influences each contributed to the variance in INATT and HYP (as shown in Table 4). Additive genetic influences were large for both phenotypes but were significantly larger for HYP (71%) than for INATT (56%). In contrast, dominant genetic influences were significantly larger for INATT (15%) than for HYP (2%). Indeed, constraining the d^2 estimates to be equal for INATT and HYP resulted in a reduction in model fit (i.e., $\Delta\chi^2 = 6.26$ on 1df, $p < .05$, two tailed). Finally, nonshared environmental influences were significantly larger for INATT (29%) than for HYP (26%), although the difference in magnitude was small.

Table 3
Fit Indices

Model	χ^2	*df*	AIC	BIC
Unconstrained				
ACE	1,896.653	234	1,428.653	−522.91
ADE	**1,879.103**	**234**	**1,411.103**	**−540.46**
Constrained				
ACE	1,930.155	237	1,456.155	−520.43
ADE	1,916.898	237	1,444.898	−533.69

Note. AIC = Akaike information criterion; BIC = Bayesian information criterion. A = additive genetic influences; C = shared environmental influences; E = nonshared environmental influences; D = dominant genetic influences. In the unconstrained model, genetic and environmental parameter estimates were allowed to vary across inattention and hyperactivity. In the constrained model, they were constrained to be equal across both phenotypes. The model highlighted in bold provided the best fit to the data, as indicated by the lowest AIC and BIC values.

Supplemental Analyses

We next addressed the aforementioned issues of construct independence for INATT. Five studies of INATT used the Attention Problems subscale of the CBCL, which included two items tapping hyperactive behaviors (the remaining eight studies examined INATT using diagnostic interview or report on the Connors Rating Scales, which maps onto *DSM* operationalization for INATT and HYP). To evaluate the robustness of our results, we removed all INATT studies employing the Attention Problems subscale from the INATT group (leaving eight samples with 9,322 sibling pairs) and the INATT data were reanalyzed. Results were very similar to those reported above (a^2, d^2, and e^2 were estimated to be 63.6%, 10.1%, and 26.3% of the variance in INATT, respectively). Although the estimate of the contribution of additive genetic factors to INATT increased, additive genetic influences for INATT remained significantly smaller than those for HYP, whereas the dominant genetic influences remained significantly larger. The difference in nonshared environmental influences between INATT and HYP was no longer significant. These results indicate that the genetic distinctions between INATT and HYP persist, even when using an impure measure of INATT.

Influence of Moderators on Differences Between INATT and HYP

Sex. Genetic and environmental parameter estimates were then calculated separately for same-sex sibling pairs (e.g., male–male and female–female sibling pairs). As indicated in Table 5, the overall pattern of results (higher a^2 for HYP and higher d^2 for INATT) persisted for both boys and girls. Estimates of a^2 for INATT and HYP were 53% and 58%, respectively, for boys, and 48% versus 71% for girls. In contrast, estimates of d^2 were larger for INATT than HYP (18% vs. 16% in boys; 24% vs. 0% in girls). However, the differences in a^2 and d^2 between INATT and HYP failed to reach significance in boys. We next evaluated whether estimates varied across sex. Estimates of a^2 did not differ across sex for either INATT or HYP. Estimates of d^2 for INATT also did not differ across sex. However, estimates of d^2 for HYP were significantly larger in boys (16%) than in girls (0%), suggesting some sex-specific effects. In short, these results suggest that the observed differences in genetic and environmental influences on INATT versus HYP persist across gender, although there may be

Table 4
Parameter Estimates From Best-Fitting Unconstrained Model by Phenotype

Phenotype	%A	%D	%E
Inattention (13 samples, $N = 16{,}706$ pairs)	.558 (.483–.633)*	.152 (.08–.226)*	.290 (.281–.300)*
Hyperactivity (9 samples, $N = 14{,}241$ pairs)	.710 (.633–.750)*	.020 (0–.0941)*	.270 (.261–.280)*

Note. A, D, and E represent additive genetic, dominant genetic, and nonshared environmental influences, respectively.
* indicates that inattention and hyperactivity estimates were significantly different at $p < .05$.

important sex-specific differences in the influence of dominant genetic factors for hyperactivity.

Age. Parameter estimates were next computed separately for sibling pairs in three different age ranges: 1–5 years, 6–10 years, and 11–18 years, respectively (see Table 6). During early childhood, the differences in genetic effects between INATT and HYP were striking. INATT was wholly influenced by dominant genetic factors (64% of the total variance and 100% of the genetic influences), whereas HYP was wholly influenced by additive genetic factors (66% of the total variance and 100% of the genetic influences). Moreover, these differences in a^2 and d^2 were statistically significant. The magnitude of unique environmental factors (e^2) did not differ between INATT and HYP in this age range. During middle childhood (ages 6–10 years), the pattern of results closely resembled that from the overall analyses. HYP was more influenced by additive genetic influences than was INATT (82% vs. 64%), whereas dominant genetic influences were stronger on INATT than on HYP (10% vs. 0%). Further, nonshared environmental influences were significantly greater for INATT than HYP during middle childhood. It is interesting, however, that there was less evidence of etiological differences across symptom dimensions during adolescence (ages 11–18). Only dominant genetic influences remained significantly stronger for INATT and HYP (11% vs. 0%). Indeed, dominant genetic influences for HYP were estimated at zero for all three age ranges and indicated a robust genetic difference with INATT regardless of age. Also of note, estimates of a^2 on HYP were largest during middle childhood and significantly decreased by adolescence. In turn, estimates of e^2 for HYP increased significantly from middle childhood to adolescence. By contrast, genetic and environmental influences on INATT remained largely constant across childhood and adolescence.

Informant. Estimates of genetic and environmental influence on INATT and HYP were also computed separately by informant (see Table 7). The pattern of results for mother report was again similar to the overall pattern of results, with greater additive genetic influences for HYP than INATT (64% vs. 46%) and greater dominant genetic influences for INATT compared to HYP (25% vs. 10%). For teacher report, however, a different pattern emerged, such that both INATT and HYP were largely influenced by additive genetic factors (both 77%), with smaller contributions from the nonshared environment (23%) and negligible contributions from dominant genetic factors (0%). Thus, the overall pattern of results appears to persist for mother reports but not teacher reports.

Measurement method. Genetic and environmental contributions to INATT and HYP were again computed separately by measurement method (i.e., diagnostic interview vs. questionnaire; see Table 8). Consistent with the overall results, estimates of additive genetic influences were again greater for HYP, whereas estimates of dominant genetic influences were greater for INATT for both diagnostic interview and questionnaire measurement methods. However, only the differences in dominant genetic influences for INATT were statistically significant. For diagnostic interviews, estimates yielded dominant genetic influences of 36% for INATT and 0% for HYP. Similarly, for questionnaire methods, differences in the estimates of d^2 were pronounced (INATT =

Table 5
Parameter Estimates for Inattention and Hyperactivity by Sex

Sex	%A	%D	%E
Male			
Inattention	.531 (.363–.600)	.181 (.037–.330)	.309 (.291–.323)
Hyperactivity	.588 (.430–.745)	.163 (.014–.318)	.249 (.235–.264)
Female			
Inattention	.481 (.334–.627)*	.235 (.093–.381)*	.284 (.270–.299)
Hyperactivity	.705 (.630–.741)*	.000 (.000–.070)*	.291 (.276–.308)

Note. A, D, and E represent additive genetic, dominant genetic, and nonshared environmental influences, respectively. Total N Inattention: males (9 samples, $N = 5{,}419$ pairs); females (9 samples, $N = 5{,}435$ pairs). Total N Hyperactivity: males (5 samples, $N = 4{,}327$ pairs); females (4 samples, $N = 4{,}278$ pairs).
* indicates that inattention and hyperactivity estimates were significantly different at $p < .05$.

Table 6
Parameter Estimates for Inattention and Hyperactivity by Age

Age	%A	%D	%E
0–5 years			
Inattention	.000 (.000–.018)*	.624 (.594–.653)*	.381 (.362–.402)
Hyperactivity	.660 (.508–.710)*	.000 (.000–.146)*	.341 (.312–.374)
6–11 years			
Inattention	.636 (.548–.724)*	.103 (.019–.189)*	.261 (.251–.272)*
Hyperactivity	.816 (.793–.841)*	.000 (.000–.011)*	.184 (.174–.208)*
12–18 years			
Inattention	.600 (.415–.744)	.112 (.009–.294)*	.289 (.270–.309)
Hyperactivity	.677 (.510–.724)	.000 (.000–.169)*	.322 (.301–.345)

Note. A, D, and E represent additive genetic, dominant genetic, and nonshared environmental influences, respectively. Total N Inattention: ages 0–5 (1 sample, $N = 1{,}307$ pairs); ages 6–11 (5 samples, $N = 11{,}050$ pairs); ages 11–18 (5 samples, $N = 3{,}278$ pairs). Total N Hyperactivity: ages 0–5 (1 sample, $N = 2{,}515$ pairs); ages 6–11 (4 samples, $N = 8{,}398$ pairs); ages 11–18 (4 samples, $N = 2{,}793$ pairs).
* indicates that inattention and hyperactivity estimates were significantly different at $p < .05$.

Table 7
Parameter Estimates for Inattention and Hyperactivity by Informant

Informant	%A	%D	%E
Mother			
Inattention	.463 (.375–.550)*	.245 (.160–.332)*	.292 (.282–.302)*
Hyperactivity	.639 (.539–.738)*	.104 (.009–.201)*	.257 (.248–.267)*
Teacher			
Inattention	.771 (.731–.848)	0 (0–.0533)	.229 (.199–.267)
Hyperactivity	.769 (.583–.842)	0 (0–.1765)	.225 (.200–.255)

Note. A, D, and E represent additive genetic, dominant genetic, and nonshared environmental influences, respectively. Total *N* Inattention: mother (9 samples, $N = 14{,}205$ pairs); teacher (3 samples, $N = 1{,}231$ pairs). Total *N* Hyperactivity: mother (7 samples, $N = 10{,}124$ pairs); teacher (3 samples, $N = 1{,}093$ pairs).
* indicates that inattention and hyperactivity estimates were significantly different at $p < .05$.

24%; HYP = 17%). Yet the overall pattern of results appeared to be robust across both measurement methods.

Discussion

The purpose of the meta-analysis was to examine potential similarities and differences in the magnitude of genetic and environmental influences across the ADHD symptom dimensions of INATT and HYP. Potential differences in types of genetic effects operating for INATT and HYP may have implications for future studies of the etiological processing underlying ADHD, particularly for molecular genetic investigations that are attempting to identify particular DNA variants that may increase the risk for the development of the disorder. The results of the current meta-analysis indicated that although broad heritability estimates were quite high for both INATT and HYP (71% and 73%, respectively), additive genetic influences on HYP were significantly larger than those on INATT. Conversely, dominant genetic influences were significantly larger for INATT compared with HYP, signaling that potentially different mechanisms and combinations of genetic risk factors may give rise to INATT and HYP. Nonshared environmental influences were also significantly larger for INATT than HYP, indicating that environmental factors that serve to distinguish siblings from one another contribute more to the variance in INATT than HYP. Thus, the overall pattern of results suggests important differences in the genetic and environmental etiology of the ADHD symptom domains.

The overall modeling results also revealed that shared environmental effects (c^2) were estimated to be zero in these data. These findings are in line with previous empirical studies and reviews suggesting that contributions from shared environmental factors are negligible for ADHD (Bergen, Gardner, & Kendler, 2007; Burt, 2009). However, prior reports have indicated that shared environmental variance may contribute to the covariation between INATT and HYP (McLoughlin et al., 2007) as well as to the comorbidity among ADHD and other externalizing disorders (Burt, Krueger, McGue, & Iacono, 2001). One possible explanation for these different results across studies relates to gene–environment interactions. As Purcell (2002) noted, the influence of Gene × Shared Environment interactions will be represented in the additive genetic variance component (a^2) in behavioral genetic models. Thus, although shared environmental factors do not account for any variance in the symptom domains of INATT and HYP (or ADHD, as defined more generally), shared environmental factors may exert their effects on the disorder through gene–environment interactions, which would be represented in the additive genetic variance term (a^2). Examination of gene–environment interplay for ADHD will likely remain an active line of research in the years to come.

Our moderation analyses revealed that the overall pattern of results (i.e., higher a^2 for HYP and higher d^2 for INATT) persisted across sex, although differences were significant only for girls. These analyses also revealed possible sex-specific dominant genetic influences on HYP in boys. Consistent with this, Eaves et al. (2000) found evidence of potential sex differences in the genetic etiology of ADHD. Given the large sex disparity in ADHD prevalence (estimates of male:female ratios range from 3:1 to 9:1) as well as reports of greater mean levels and variability of symptoms in males versus females (Gaub & Carlson, 1997), research involving sex differences in the development of ADHD symptoms may need to consider potential differences in etiological mechanisms between the sexes. Along these lines, initial work examining the effects of gonadal hormones indicated that prenatal testosterone exposure may be important for the development of ADHD in boys but not in girls (Martel, Gobrogge, Breedlove, & Nigg, 2008).

Examinations by age revealed the same pattern of results as the overall analyses. However, the contrast between both dominant and additive genetic influences for INATT versus HYP was most striking in early childhood (ages 1–5). In fact, all genetic influences on INATT during early childhood were nonadditive. It thus seems likely that early onset INATT (i.e., before age 5) may solely reflect dominant genetic factors. The contrast between dominant and additive genetic influences for INATT versus HYP persisted, but were smaller in magnitude, through middle childhood (ages 6–10). By adolescence, however, only dominant genetic influences remained significantly different across INATT than HYP. Thus, although differences in additive genetic influences across INATT and HYP may be specific to childhood, differences in dominant genetic influences across the symptom dimensions appear to persist through adolescence as well. Also of interest, e^2

Table 8
Parameter Estimates for Inattention and Hyperactivity by Measurement Method

Method	%A	%D	%E
Interview			
Inattention	.238 (0–.486)	.363 (.115–.619)*	.399 (.371–.430)*
Hyperactivity	.390 (.169–.460)	.000 (.000–.212)*	.611 (.556–.673)*
Questionnaire			
Inattention	.500 (.401–.595)	.239 (.145–.334)*	.264 (.254–.273)
Hyperactivity	.583 (.483–.682)	.166 (.071–.263)*	.251 (.241–.261)

Note. A, D, and E represent additive genetic, dominant genetic, and nonshared environmental influences, respectively. Total *N* Inattention: interview (2 samples, $N = 1{,}534$ pairs); questionnaire (9 samples, $N = 11{,}863$ pairs). Total *N* Hyperactivity: interview (2 samples, $N = 1{,}413$ pairs); questionnaire (6 samples, $N = 9{,}776$ pairs).
* indicates that inattention and hyperactivity estimates were significantly different at $p < .05$.

increased significantly for HYP from childhood to adolescence, indicating that environmental factors may be more important for the expression of HYP behaviors during adolescence compared with childhood. However, it is also important to note that *DSM* criteria for ADHD have been criticized as developmentally inappropriate for adolescents and adults (Barkley, 2006). This is particularly true for HYP, which is considered developmentally atypical during adolescence (particularly compared with childhood) and tends to decline with age. The increase in e^2, particularly for HYP, may thus be partially due to an increase in measurement error. Even so, more complete understanding of the types of child-specific environmental factors that may be influencing ADHD in adolescence (or serving to maintain symptoms through this developmental period) can potentially offer insight into the development of novel treatment approaches.

Informant proved to be an important moderator of our effects as well. For mothers, the overall pattern of results held, whereas for teachers, the variance in both INATT and HYP was largely due to additive genetic factors (77% for both INATT and HYP). Informant effects on the etiology of ADHD symptoms have been well documented, perhaps in part because the average correlation among reporters for ADHD behaviors remains low to moderate. These differences may reflect substantive discrepancies in observed behaviors, particularly for clinical samples, as children are more likely to be medicated at school than at home. Accordingly, teachers are exposed to different child behaviors, which could indeed evidence a different pattern of "heritability" (i.e., DZ twins may be more similar when one or both are medicated, thereby dampening the large MZ–DZ difference that underlies dominance in this design). Furthermore, teachers may have a wider comparison base and may thus be less likely to rate DZ twins as dissimilar, depressing genetic effect estimates (additive and nonadditive). Alternately, mothers may be prone to rater contrast effects, in which she rates her DZ twins as more different than they actually are (presumably because she is exposed to fewer children than are teachers and thus may focus more on differences between her twins). In any case, etiological differences across informant reports remain a fundamental issue to consider for research and clinical practice, particularly because *DSM–IV* specifies cross-situational symptom presence and impairment.

Finally, dominant genetic influences were significantly stronger for INATT than HYP using both diagnostic interview and questionnaire methods. Further, a^2 continued to be larger for HYP than INATT using both methods, although differences were not statistically significant. One potential confound in these results is that mothers primarily complete diagnostic interviews, whereas teachers do not, presumably because of research time and budget constraints. Given this, although the results of these analyses indicated that the overall pattern of results persists across measurement method, differences in these measurement methods must continue to be examined.

Although the moderator analyses generally revealed a similar pattern to the overall results (e.g., higher additive genetic influences for HYP and higher dominant genetic influences for INATT), examination of these specific moderator variables required us to parse the sample in several different ways. For example, for the informant analyses, only studies which included data from teachers were included in the analyses. Accordingly, the number of twin/sibling pairs available for analysis, and the resultant power for detecting significantly different estimates, was reduced. That said, as seen in the notes for Tables 5–8, the smallest sample size in any given "cell" in our moderator analyses was more than 1,000 twin/sibling pairs. As a consequence, all analyses presented herein were sufficiently powered to detect even small estimates of genetic and environmental influences (Martin, Eaves, Kearsey, & Davies, 1978). Moreover, we had more than 80% power in any given analysis to detect variance differences as small as 5% between HYP and INATT.

Implications

Overall, results indicate the presence of stronger dominant genetic influences on INATT compared with HYP and larger additive genetic influences on HYP than on INATT, effects that were generally robust across gender, age, informant, and measurement method. Such results suggest important differences in the genetic etiology of INATT and HYP. They also confirm much of the previous work validating differences between the ADHD subtypes as well as research into causal mechanisms involving neural systems. Phenomenologically, several studies have demonstrated differences in the behavioral correlates of ADHD–Combined (ADHD–C) and ADHD–Inattentive (ADHD–PI). First, numerous studies have shown that children with ADHD–C are more likely to be aggressive and to develop other externalizing behavior disorders (such as oppositional defiant disorder and conduct disorder) than are children with ADHD–PI (Eiraldi, Power, & Nezu, 1997). Further, studies of social functioning have shown that children with ADHD–C are more likely to experience peer rejection than are those with ADHD–PI (Maedgen & Carlson, 200). Children with ADHD–C are also more likely to be male than are those with ADHD–PI (Gaub & Carlson, 1997). In turn, children with ADHD–PI are more likely than those with ADHD–C to have mathematics disorders, to have internalizing disorders, and to have been less responsive to stimulant medication (Milich et al., 2001). These key differences in external correlates suggest that there may be some etiological differences between those children with ADHD–C and ADHD–PI. The current meta-analysis provides additional evidence for this conclusion of different etiological mechanisms for INATT versus HYP, the symptom dimensions underlying the *DSM* subtype classifications.

Second, some neuropsychological studies have shown that children with and without hyperactivity demonstrate different patterns of deficits on a variety of tasks (Fischer, Barkley, Edelbrock, & Smallish, 1990; Schmitz et al., 2002), although others have not (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). Even so, recent theories regarding the development of neuropsychological impairments and ADHD symptoms have suggested different etiologies for INATT and HYP. The dual pathway theory (Sonuga-Barke, 2003, 2005) posited that inattention is related to deficits in executive functions and underlying impairments in prefrontal-striatal circuitry, whereas hyperactivity may arise from dysfunctions in reward response and motivation problems, underpinned by frontal-limbic circuitry. Further, recent work by Rapport et al. (2009) has demonstrated that, although certainly problematic in some areas of life, the increased activity level characteristic of children with HYP may be adaptive when completing short-term memory tasks. This notion makes good intuitive and theoretical sense, as arousal level has been hypothesized to be a key problem

for children with ADHD. In short, activity level may serve to maintain arousal and therefore improve performance. In any case, such findings again suggest that pattern of neuropsychological deficits (or advantages) may differ across the two symptom dimensions. In sum, the different patterns of genetic and environmental contributions to INATT and HYP observed in the current study map onto theories suggesting differing patterns of neural system involvement and neuropsychological performance for the two symptom domains.

These results also have broader implications for future etiological investigations of ADHD, with particular relevance to molecular genetic studies. Genes of the dopamine neurotransmission system have shown replicated associations with ADHD (see Faraone et al., 2005), yet numerous nonreplications of these and other genetic markers have also been reported. Several investigators have suggested the use of more homogenous phenotypes for molecular genetic investigations, including the use of empirically derived latent subclasses (see Todd et al., 2001). The results of the current meta-analysis suggest that separate examination of association with ADHD symptom domains of INATT and HYP is warranted. Moreover, the finding of greater additive genetic influences for HYP suggests that studies examining additive associations of multiple markers across alleles (i.e., summing the effects of individual loci) are more likely to show association with HYP rather than INATT, which showed significant contribution of dominant genetic effects. This is particularly true for family-based association tests that rely on additive transmission of alleles from parents to offspring across multiple markers (only additive genetic effects show significant similarities across parents and offspring, whereas nonadditive genetic effects typically do not). These results thus clearly suggest that association tests within parent–child designs would reveal different patterns of results for INATT versus HYP and may be more beneficial for identifying association effects with HYP. That said, nonadditivity can yield similarities across full siblings (as full siblings could conceivably inherit the same set of genes from their parents). Accordingly, designs involving examining genetic transmission and associations with sibling data might prove to be particularly beneficial for studies of INATT. Further, more recent developments in statistical genetics have allowed for testing additive and dominant models of transmission when using family-based analyses. Testing both models of transmission (as seen in Brookes et al., 2006) may prove also to be particularly beneficial for INATT. In sum, future molecular genetic investigations of main effects and gene–environment interplay will be well served by examining the symptom dimensions of INATT and HYP separately in addition to the combined ADHD phenotype.

Limitations

There are limitations of the current study that are important to note. The current analysis was restricted to those studies that provided data for INATT and/or HYP separately. Thus, all studies examining ADHD as a unidimensional construct were omitted. Because of this, the pattern of results observed here will likely not map directly onto previous reviews and meta-analyses examining ADHD as a single phenotype (see Bergen et al., 2007; Burt, 2009). That said, there are several similarities in our results. Shared environmental contributions to the ADHD phenotype, regardless of definition, were minuscule across a variety of moderators. In addition, recent work by Burt (2009), which included several of the studies examined here, demonstrated large dominant and moderate additive genetic influences for ADHD as a single construct, indicating that when examined together (as would be the case for ADHD–Combined subtype), genetic effects for ADHD may be more likely to be multiplicative than additive. However, both sets of results are important to consider for future etiological work examining ADHD as a construct and the symptom dimensions separately. Also of note, although the current meta-analysis did not examine the categorical subtypes of ADHD (including the Combined subtype), we did not exclude samples of individuals with ADHD diagnoses (including Combined subtype diagnoses), provided that the study differentiated between INATT and HYP. Next, the informant analysis was restricted to mother and teacher reports only. Reports from fathers and the children themselves have been included in a small number of studies within the larger behavioral genetic literature for ADHD. However, too few of these reports included data that separated INATT and HYP to warrant inclusion in the meta-analysis. Despite this, future investigation of informant effects is clearly warranted, as the differences between mother and teacher report for INATT and HYP were pronounced.

Furthermore, although behavioral genetic studies yield important conclusions regarding the magnitude of genetic and environmental contributions to a given phenotype, they may also be limited by particular assumptions involved in the methodology. For example, the equal environments assumption supposes that the environmental factors that are etiologically relevant to the phenotype in question are no more likely to be shared among MZ twin pairs than among DZ twin pairs. The equal environments assumption has been repeatedly tested and found to be valid for numerous phenotypes, including many mental disorders (see Plomin et al., 2008), but it remains an assumption for any particular phenotype, including ADHD, until subjected to empirical testing.

Finally, the current meta-analysis aimed to examine the etiological influences on INATT and HYP and found that although the types of genetic influences differed, both symptom dimensions were largely influenced by genetic factors. It is important to note, however, that the presence of genetic influences (even strong genetic influences) on a given disorder bears little to no relation to its treatability. Indeed, pharmacological and behavioral interventions for ADHD have been developed and tested with very promising results. For example, the Multi-Modal Treatment of ADHD (MTA) studies have demonstrated significant improvements in ADHD (and even in related disruptive behaviors) with the combined use of medications and behavioral interventions (Jensen et al., 2001), demonstrating that the degree to which a disorder is genetically influenced does not correspond with its treatability.

Conclusion

Overall, the current meta-analysis provides strong evidence of meaningful etiological differences between INATT and HYP. Future studies of causal mechanisms, particularly those focusing on genetic factors (the strongest contributor to ADHD), will likely benefit from examining the symptom dimensions separately and together to elucidate the complex set of genetic and environmental factors that give rise to ADHD.

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Appendix

Effect Sizes for Twin and Adoption Studies

Sample and study	Phenotype and sex	Informant	Age (years)	*N*	Relationship	Effect size (r)	Inclusion
Virginia Twin Study of Adolescent Behavioral Development							
Silberg et al. (1996)	HYP	mother	8–11	106	MZ_M	.58	Included-AVG
				162	MZ_F	.57	Included-AVG
				82	DZ_M	−.01	Included-AVG
				77	DZ_F	.21	Included-AVG
				130	DZ_OS	−.11	Included-AVG
	HYP	mother	12–16	159	MZ_M	.47	Included-AVG
				185	MZ_F	.47	Included-AVG
				81	DZ_M	−.11	Included-AVG
				83	DZ_F	.10	Included-AVG
				132	DZ_OS	−.06	Included-AVG
Eaves et al. (1997)	HYP	mother	8–16	275	MZ_M	.51	Excluded[a]
				364	MZ_F	.49	Excluded[a]
				169	DZ_M	.01	Excluded[a]
				168	DZ_F	.16	Excluded[a]
				268	DZ_OS	−.05	Excluded[a]
	HYP	teacher	8–16	258	MZ_M	.62	Excluded[a]
				330	MZ_F	.52	Excluded[a]
				151	DZ_M	.25	Excluded[a]
				152	DZ_F	.23	Excluded[a]
				243	DZ_OS	.28	Excluded[a]
Simonoff et al. (1998)	HYP	teacher	8–16	86	MZ_M	.78	Included
				111	MZ_F	.66	Included
				38	DZ_M	−.02	Included
				43	DZ_F	.50	Included
				67	DZ_OS	.37	Included
Nadder et al. (2001)	HYP	mother	8–16	289	MZ_M	.21	Included-AVG
				385	MZ-F	.25	Included-AVG
				174	DZ_M	−.16	Included-AVG
				177	DZ_F	−.03	Included-AVG
	HYP	mother	8–16	283	MZ_M	.50	Included-AVG
				378	MZ_F	.46	Included-AVG
				174	DZ_M	.03	Included-AVG
				181	DZ_F	.11	Included-AVG
	INATT	mother	8–16	289	MZ_M	.39	Included-AVG
				386	MZ_F	.31	Included-AVG
				177	DZ_M	−.02	Included-AVG
				179	DZ_F	.00	Included-AVG

Appendix (*continued*)

Sample and study	Phenotype and sex	Informant	Age (years)	*N*	Relationship	Effect size (r)	Inclusion
Nadder et al. (2002)	HYP	mother	8–16	229	MZ_M	.28	Included-AVG
				278	MZ_F	.19	Included-AVG
				126	DZ_M	−.09	Included-AVG
				124	DZ_F	.01	Included-AVG
	INATT	mother	8–16	232	MZ_M	.33	Included-AVG
				279	MZ_F	.21	Included-AVG
				130	DZ_M	−.10	Included-AVG
				123	DZ_F	−.03	Included-AVG
Manchester Twin Registry							
Thapar et al. (2000)	HYP	mother	5–17	731	MZ	.72	Included
				1,184	DZ	.24	Included
	INATT	mother	5–17	727	MZ	.66	Included
				1,177	DZ	.22	Included
	HYP	mother		729	MZ	.61	Included
				1,185	DZ	−.01	Included
Cardiff Twin Study							
Martin et al. (2002)	HYP	mother	5–16	264	MZ	.73	Included
				352	DZ	.25	Included
	HYP	mother		256	MZ	.55	Included
				347	DZ	−.04	Included
	HYP	teacher		163	MZ	.81	Included
				227	DZ	.38	Included
	HYP	teacher		156	MZ	.73	Included
				214	DZ	.29	Included
Netherlands Twin Registry							
van den Oord (1993)	HYP	mother	3	407	MZ	.65	Included-AVG
(From Goldsmith et al., 1997)				1,263	DZ	.27	Included-AVG
van den Oord et al. (1996)	HYP	mother	3	210	MZ_M	.40	Included-AVG
				236	MZ_F	.63	Included-AVG
				265	DZ_M	.10	Included-AVG
				238	DZ_F	.10	Included-AVG
				409	DZ_OS	.15	Included-AVG
van den Oord et al. (2000)	HYP	mother	5	446	MZ	.50	Included-AVG
			5	912	DZ	.07	Included-AVG
Rietveld et al. (2003)	HYP	mother	3	621	MZ_M	.63	Included-AVG
				708	MZ_F	.63	Included-AVG
				583	DZ_M	.08	Included-AVG
				536	DZ_F	.07	Included-AVG
				1,223	DZ_OS	.11	Included-AVG
	INATT	mother	7	590	MZ_M	.68	Included-AVG
				676	MZ_F	.70	Included-AVG
				530	DZ_M	.15	Included-AVG
				528	DZ_F	.23	Included-AVG
				1,049	DZ_OS	.26	Included-AVG
	INATT	mother	10	452	MZ_M	.70	Included-AVG
				526	MZ_F	.70	Included-AVG
				392	DZ_M	.20	Included-AVG
				380	DZ_F	.30	Included-AVG
				735	DZ_OS	.28	Included-AVG
	INATT	mother	12	246	MZ_M	.75	Included-AVG
				287	MZ_F	.70	Included-AVG
				201	DZ_M	.25	Included-AVG
				200	DZ_F	.31	Included-AVG
				371	DZ_OS	.25	Included-AVG

(*Appendix continues*)

Appendix (*continued*)

Sample and study	Phenotype and sex	Informant	Age (years)	*N*	Relationship	Effect size (r)	Inclusion
Derks et al. (2004)	HYP	mother	3	1,519	MZ_M	.69	Included-AVG
				1,736	MZ_F	.69	Included-AVG
				1,594	DZ_M	.14	Included-AVG
				1,454	DZ_F	.15	Included-AVG
				3,142	DZ_OS	.205	Included-AVG
Groot et al. (2004)	INATT	teacher	5	44	MZ_M	.85	Included-AVG
				65	MZ_F	.81	Included-AVG
				30	DZ_M	.60	Included-AVG
				31	DZ_F	.27	Included-AVG
				39	DZ_OS	.29	Included-AVG
Rietveld et al. (2004)	HYP	mother	3	2,008	MZ	.66	Included-AVG
				3,690	DZ	.13	Included-AVG
	INATT	mother	7	1,891	MZ	.71	Included-AVG
				3,310	DZ	.28	Included-AVG
			10	1,151	MZ	.72	Included-AVG
				1,861	DZ	.28	Included-AVG
			12	608	MZ	.72	Included-AVG
				907	DZ	.26	Included-AVG
van Beijsterveldt et al. (2004)	INATT	mother	5	1,220	MZ_M	.59	Included-AVG
				1,445	MZ_F	.64	Included-AVG
				1,270	DZ_M	.03	Included-AVG
				1,188	DZ_F	.00	Included-AVG
				2,556	DZ_OS	.115	Included-AVG
Hudziak et al. (2005)	INATT	mother	7	905	MZ_M	.73	Included-AVG
				1,023	MZ_F	.72	Included-AVG
				879	DZ_M	.23	Included-AVG
				838	DZ_F	.28	Included-AVG
				1,753	DZ_OS	.295	Included-AVG
	INATT	mother	10	598	MZ_M	.72	Included-AVG
				726	MZ_F	.73	Included-AVG
				542	DZ_M	.22	Included-AVG
				538	DZ_F	.22	Included-AVG
				1,111	DZ_OS	.285	Included-AVG
	INATT	mother	12	360	MZ_M	.69	Included-AVG
				410	MZ_F	.71	Included-AVG
				308	DZ_M	.20	Included-AVG
				303	DZ_F	.29	Included-AVG
				590	DZ_OS	.225	Included-AVG
Polderman et al. (2006)	INATT	teacher	5	67	MZ	.81	Included-AVG
				59	DZ	.58	Included-AVG
Derks et al. (2007)	INATT	teacher	7	152	MZ_M	.90	Included-AVG
				175	MZ_F	.92	Included-AVG
				127	DZ_M	.64	Included-AVG
				131	DZ_F	.60	Included-AVG
				292	DZ_OS	.44	Included-AVG
	HYP	teacher	7	152	MZ_M	.81	Included-AVG
				175	MZ_F	.83	Included-AVG
				127	DZ_M	.42	Included-AVG
				131	DZ_F	.34	Included-AVG
				292	DZ_OS	.30	Included-AVG
Minnesota Twin and Family Study							
Sherman et al. (1997)	INATT	mother	11–12	194	MZ_M	.70	Included-AVG
				93	DZ_M	.30	Included-AVG
	HYP	mother	11–12	194	MZ_M	.92	Included-AVG
				93	DZ_M	.32	Included-AVG
	INATT	teacher	11–12	181	MZ_M	.78	Included-AVG
				93	DZ_M	.57	Included-AVG
	HYP	teacher	11–12	181	MZ_M	.69	Included-AVG
				93	DZ_M	.42	Included-AVG
Johnson et al. (2005)	INATT	mother	10–12	253	MZ_M	.65	Included-AVG
				259	MZ_F	.65	Included-AVG
				121	DZ_M	.32	Included-AVG
				165	DZ_F	.26	Included-AVG

Appendix (*continued*)

Sample and study	Phenotype and sex	Informant	Age (years)	*N*	Relationship	Effect size (r)	Inclusion
Australian Twin Registry							
Hay et al. (2004)	INATT	mother	4–12	698	MZ	.88	Included-AVG
				462	DZ	.47	Included-AVG
	HYP	mother	4–12	698	MZ	.93	Included-AVG
				462	DZ	.59	Included-AVG
	INATT	mother	7–15	698	MZ	.83	Included-AVG
				462	DZ	.44	Included-AVG
	HYP	mother	7–15	698	MZ	.87	Included-AVG
				462	DZ	.52	Included-AVG
Martin et al. (2006)	INATT	mother	5–16	907	MZ	.86	Included-AVG
				1,106	DZ	.45	Included-AVG
	HYP	mother	5–16	907	MZ	.86	Included-AVG
				1,106	DZ	.45	Included-AVG
Hay et al. (2007)	INATT	mother	6–9	275	MZ	.80	Included-AVG
				253	DZ	.32	Included-AVG
	HYP	mother	6–9	275	MZ	.85	Included-AVG
				253	DZ	.56	Included-AVG
	INATT	mother	6–9	275	MZ	.81	Included-AVG
				253	DZ	.50	Included-AVG
	HYP	mother	6–9	275	MZ	.91	Included-AVG
				253	DZ	.70	Included-AVG
	INATT	mother	12–20	293	MZ	.80	Included-AVG
				195	DZ	.38	Included-AVG
	HYP	mother	12–20	293	MZ	.84	Included-AVG
				195	DZ	.37	Included-AVG
	INATT	mother	12–20	293	MZ	.87	Included-AVG
				195	DZ	.50	Included-AVG
	HYP	mother	12–20	293	MZ	.94	Included-AVG
				195	DZ	.79	Included-AVG
Swedish Twin Registry							
Larsson et al. (2006)	INATT	mother	8–9	477	MZ_M	.57	Included-AVG
				473	MZ_F	.64	Included-AVG
				348	DZ_M	.26	Included-AVG
				350	DZ_F	.21	Included-AVG
	HYP	mother	8–9	477	MZ_M	.87	Included-AVG
				473	MZ_F	.75	Included-AVG
				348	DZ_M	.24	Included-AVG
				350	DZ_F	.47	Included-AVG
	INATT	mother	13–14	477	MZ_M	.61	Included-AVG
				473	MZ_F	.69	Included-AVG
				348	DZ_M	.23	Included-AVG
				350	DZ_F	.24	Included-AVG
	HYP	mother	13–14	477	MZ_M	.61	Included-AVG
				473	MZ_F	.70	Included-AVG
				348	DZ_M	.30	Included-AVG
				350	DZ_F	.31	Included-AVG
	INATT	mother	16–17	477	MZ_M	.61	Included-AVG
				473	MZ_F	.71	Included-AVG
				348	DZ_M	.20	Included-AVG
				350	DZ_F	.34	Included-AVG
	HYP	mother	16–17	477	MZ_M	.61	Included-AVG
				473	MZ_F	.61	Included-AVG
				348	DZ_M	.23	Included-AVG
				350	DZ_F	.32	Included-AVG
Norwegian Twin Study							
Gjone et al. (1996)	INATT	mother	5–9	109	MZ_M	.72	Included
				120	MZ_F	.76	Included
				81	DZ_M	.21	Included

(*Appendix continues*)

Appendix (*continued*)

Sample and study	Phenotype and sex	Informant	Age (years)	*N*	Relationship	Effect size (r)	Inclusion
				80	DZ_F	.23	Included
	INATT	mother	12–15	140	MZ_M	.78	Included
				158	MZ_F	.73	Included
				105	DZ_M	.45	Included
				123	DZ_F	.33	Included
Missouri Twin Study							
Hudziak et al. (2000)	INATT	mother	8–12	129	MZ_M	.69	Included
				91	MZ_F	.66	Included
				156	DZ_M	.26	Included
				115	DZ_F	.20	Included
Neuman et al. (2001)	INATT	mother	13–23	773	MZ_F	.62	Included
				579	DZ_F	.19	Included
	HYP	mother	13–23	773	MZ_F	.71	Included
				579	DZ_F	.33	Included
Finn Twin Study							
Pulkkinen et al. (1999)	INATT	mother	12	154	MZ	.68	Included-AVG
				132	DZ_SS	.38	Included-AVG
				137	DZ_OS	.22	Included-AVG
	HYP	mother	12	154	MZ	.77	Included-AVG
				132	DZ_SS	.11	Included-AVG
				137	DZ_OS	.21	Included-AVG
	INATT	teacher	12	154	MZ	.79	Included-AVG
				132	DZ_SS	.61	Included-AVG
				137	DZ_OS	.53	Included-AVG
	HYP	teacher	12	154	MZ	.87	Included-AVG
				132	DZ_SS	.54	Included-AVG
				137	DZ_OS	.43	Included-AVG
Dick et al. (2005)	INATT	teacher	14	167	MZ_M	.53	Included-AVG
				169	MZ_F	.72	Included-AVG
				160	DZ_M	.45	Included-AVG
				135	DZ_F	.31	Included-AVG
Western Reserve							
Edelbrock et al. (1995)	INATT	mother	7–15	99	MZ	.68	Included
				82	DZ	.29	Included
Willerman et al. (1973)	HYP	mother	1–13	54	MZ	.90	Included
				39	DZ	.57	Included
Dutch Adoption Study							
van den Oord et al. (1994)	INATT	mother	12	30	FS_M	.17	Included
				35	FS_F	.14	Included
				46	FS_OS	.47	Included
				44	URT_M	.09	Included
				48	URT_F	−.13	Included
				129	URT_OS	.09	Included
van der Valk et al. (1998)	INATT	mother	12	111	FS	.33	Excluded[a]
				221	URT	.08	Excluded[a]
	INATT	mother	15	76	FS	.33	Included
				155	URT	.10	Included
Taiwan Twin Study							
Kuo et al. (2004)	INATT	mother	12–16	85	MZ_M	.83	Included
				108	MZ_F	.71	Included
				23	DZ_M	.24	Included
				27	DZ_F	−.07	Included
UK Twins Early Development Study							
Kuntsi et al. (2000)	INATT	teacher	7–11	61	MZ	.79	Included-AVG
				64	DZ	.47	Included-AVG
	HYP	teacher	7–11	61	MZ	.57	Included-AVG
				64	DZ	.27	Included-AVG
McLoughlin et al. (2007)	INATT	mother	6–9	1,043	MZ_M	.78	Included-AVG
				1,183	MZ_F	.80	Included-AVG
				998	DZ_M	.39	Included-AVG
				1,027	DZ_F	.37	Included-AVG
				1,971	DZ_OS	.39	Included-AVG

Appendix (*continued*)

Sample and study	Phenotype and sex	Informant	Age (years)	*N*	Relationship	Effect size (r)	Inclusion
	HYP	mother	6–9	1,043	MZ_M	.88	Included-AVG
				1,183	MZ_F	.80	Included-AVG
				998	DZ_M	.50	Included-AVG
				1,027	DZ_F	.53	Included-AVG
				1,971	DZ_OS	.52	Included-AVG

Note. MZ_M = monozygotic male; MZ_F = monozygotic female; DZ_M = dizygotic male; DZ_F = dizygotic female; DZ_OS = dizygotic opposite sex; FS_M = full sibling male; FS_F = full sibling female; FS_OS = full sibling opposite sex; URT_M = adopted siblings male; URT_F = adopted siblings female; URT_OS = adopted siblings opposite sex; INATT = Inattention; HYP = Hyperactivity; AVG = average.

[a] Studies excluded had the exact data represented in a separate publication with more information on gender, age, or informant.

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