Twin Studies and Their Implications for Molecular Genetic Studies: Endophenotypes Integrate Quantitative and Molecular Genetics in ADHD Research

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**Objective:** To describe the utility of twin studies for attention-deficit/hyperactivity disorder (ADHD) research and demonstrate their potential for the identification of alternative phenotypes suitable for genomewide association, developmental risk assessment, treatment response, and intervention targets. **Method:** Brief descriptions of the classic twin study and genetic association study methods are provided, with illustrative findings from ADHD research. Biometrical genetics refers to the statistical modeling of data gathered from one or more group of known biological relation; it was apparently coined by Francis Galton in the 1860s and led to the “Biometrical School” at the University of London. Twin studies use genetic correlations between pairs of relatives, derived using this theoretical framework, to parse the individual differences in a trait into latent (unmeasured) genetic and environmental influences. This method enables the estimation of heritability, i.e., the percentage of variance due to genetic influences. It is usually implemented with a method called structural equation modeling, which is a statistical technique for fitting models to data, typically using maximum likelihood estimation. Genetic association studies aim to identify those genetic variants that account for the heritability estimated in twin studies. Measurements other than those used for the clinical diagnosis of the disorder are popular phenotype choices in current ADHD research. It is argued that twin studies have great potential to refine phenotypes relevant to ADHD. **Results:** Prior studies have consistently found that the majority of the variance in ADHD symptoms is due to genetic factors. To date, genomewide association studies of ADHD have not identified replicable associations that account for the heritable variation. Possibly, the application of genomewide association studies to these alternative phenotypic measurements will assist in identifying the pathways from genetic variants to ADHD. **Conclusion:** Power to detect associations should be improved by the study of highly heritable endophenotypes for ADHD and by reducing the number of phenotypes to be considered. Therefore, twin studies are an important research tool in the development of endophenotypes, defined as alternative, more highly heritable traits that act at earlier stages of the pathway from genes to behavior. Although genetic variation in liability to ADHD is likely polygenic, the proposed approach should help to identify improved alternative measurements for genetic association studies. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(9):874–883. **Key Words:** twin studies, ADHD, genomewide association, endophenotype, translational research

Biometrical genetic studies of attention-deficit/hyperactivity disorder (ADHD) in twins consistently support the hypothesis that there is genetic variation in liability to this disorder.¹⁻³ That the heritability of ADHD is so universally established and accepted might suggest that twin studies of ADHD have fulfilled their scientific utility and that research should focus on identifying the actual genetic variants underlying ADHD. However, after reviewing basic twin study methodology, we argue that the failure of molecular genetic research to live up to
its initial promise requires additional twin studies aimed at developing and validating more promising measurements for molecular genetic research.

BACKGROUND TO THE CLASSIC TWIN STUDY

Biometric genetic studies of human populations typically analyze data on monozygotic (MZ) and dizygotic (DZ) twin pairs reared together to partition the variation of a trait within a sample of individuals into constituent variance components (VCs). These VCs typically consist of additive genetic (A), nonadditive genetic (D), or shared environmental (C) and child-specific environmental (E) influences. This last component also subsumes measurement error. Four key assumptions are involved in this approach: MZ twins are genetically identical, whereas DZ twins share on average 50% of their segregating alleles; MZ and DZ twin pairs share external environmental influences to the same extent; there is no correlation between members of twin pairs for E influences; and the total variance is the same in all individuals. Assuming a purely additive genetic model (D = 0), these assumptions predict the following statistics: phenotypic variance, \( A + C + E \); MZ covariance, \( A + C \); and DZ covariance, \( 0.5A + C \). Estimates of these VCs may be obtained by using structural equation modeling (SEM) software, typically through maximum likelihood estimation.\(^4\)\(^5\) Differences in the relative impact of these VCs predict different patterns of the MZ and DZ correlations. Accordingly, examination of MZ and DZ twin correlations can be used to infer the relative magnitude of the VCs. Thus, MZ and DZ correlations of zero would imply no influence of A, C, or D. If the ratio of MZ to DZ twin correlations is between 1 and 2, A and C are implicated, and ratios greater than this suggest D. Variance due to sibling interaction, where the behavior of one twin affects the behavior or the rating of the other twin, is implicated if MZ and DZ variances for a trait differ.\(^6\)\(^7\)

SUMMARY OF VC ESTIMATES ON ADHD SYMPTOMS MEASURED USING BEHAVIORAL RATINGS SCALE DATA

Meta-analyses of behavioral ratings of ADHD symptoms in the general population have concluded that variation is largely genetic (60% to 76%).\(^1\)\(^-\)\(^3\) Different methodologic approaches to meta-analysis may account for the differences across the three studies. In 2005 an influential review of behavioral ratings scale data concluded that 76% of the variance was due genetic influences, with the rest being attributable to E.\(^2\) However, this review used an average of “broad sense” heritability estimates across just 20 studies, unweighted for sample sizes. A more recent weighted meta-analysis using SEM methodology to combine the results of individual biometrical genetic studies drew a similar conclusion: 70% of the variance was due to \( A + D \), and the rest to E. This result was somewhat surprising because all other behaviors associated with childhood psychopathology indicated a significant influence of C.\(^1\) It is, however, possible that this finding was affected by methodologic limitations of metanalytic biometrical genetics, including a lack of power to detect sibling interaction, the confounding of C and D in genetic models using only MZ and DZ twins reared together, and the correction used for contrast effects (a form of rater bias, see below). Any one of these factors could lead to an overestimate of heritability. A more recent analysis, taking the unweighted average approach of Faraone et al.,\(^2\) which took further account of these limitations, concluded that 60% of the variance was due to genetic factors with the rest equally split between C and E.\(^3\)

MOLECULAR GENETIC STUDIES ON BEHAVIORAL RATINGS SCALE DATA

Consistent with the dimensional approach to studying ADHD, the quantitative trait locus model typically used in gene mapping studies assumes that the genetic variance (captured by the heritability estimates from twin studies) in ADHD symptoms is likely to be accounted for by multiple genetic variants, each conferring a relatively small risk for disease (or trait) susceptibility.\(^8\)\(^-\)\(^10\) A recent meta-analysis concluded that significant associations could be identified only for the dopamine transporter gene (DAT1), D4 and D5 receptor genes, the serotonin transporter and receptor genes, and the synaptosomal-associated protein 25 gene.\(^11\) Although findings across genetic association studies of ADHD (as with all psychiatric disorders) remain inconsistent, one clear conclusion does emerge: the estimated effect sizes of individual genetic variants are small, with odds ratios in the range of 1.12 to
Very large samples within powerful designs will be needed to detect odds ratios of this magnitude, given the observed minor allele frequencies for current ADHD-risk alleles. Genomewide association studies (GWAS), in which “a dense set of SNPs [single nucleotide polymorphisms] across the genome is genotyped to survey the most common genetic variation for a role in disease or to identify the heritable quantitative traits that are risk factors for disease,” offer promise due to their increased power to detect small effect sizes. However, currently no genomewide significance levels have been reached for ADHD traits (see Franke et al. for a review). Thus, to date, molecular genetic studies have accounted for less than 5% of the estimated heritability in ADHD symptoms, and although this is common to many neuropsychiatric and other phenotypes, it has lead some researchers to conclude that there is a disparity between molecular and quantitative approaches to understanding the genetic etiology of ADHD.

**PROBLEMS WITH PHENOTYPE DEFINITION IN ADHD**

Although ADHD is a dichotomous diagnostic category in the Diagnostic and Statistical Manual of Mental Disorders (the disorder is considered present or absent), twin studies have focused on the heritability of continuously distributed traits that contribute to the diagnosis (see Wood et al. for a summary of measurements used). This dimensional model approach assumes that a diagnosis of ADHD is given when individuals pass a clinically relevant threshold on these behaviors. Under this model, twin studies on such behaviors as “inattentiveness” and “overactivity” in the general population can be generalized to the clinical diagnosis of the disorder. This approach is supported by research studies that have found similar heritability estimates for dichotomous (reflecting the presence or absence of the disorder) and dimensional measurements of ADHD. In addition, using a regression-based method (extreme group), it is possible to compare heritability estimates in different parts of the distribution of the trait. ADHD behaviors yield similar heritability estimates regardless of where the threshold is placed to define the two groups.

This use of the dimensional model in the study of ADHD has facilitated the collection of data from larger samples, because face-to-face interviews are not required. However, without recourse to a clinical category, defining the ADHD phenotype for genetic studies remains a contemporary and controversial issue. Interrater correlations for ADHD behaviors between parents are teachers are typically around 0.3. This low correlation has been attributed to many sources, and problems arise for genetic studies when differences in these assessments reflect sources of variance other than the ADHD trait of interest. These alternative sources of variance may include conflation with other correlated behaviors (such as oppositional behaviors, known as halo effects). Also possible are “contrast effects,” where the behavior of one child affects the perception and rating of the other child within a twin pair. Contributions from other sources of variance to ADHD behavioral assessments decrease the precision with which ADHD symptoms measure the underlying genetic liability for ADHD. In association and linkage studies, statistical power increases with the effect size of the quantitative trait locus. Thus a precise definition of ADHD, which measures as accurately as possible the trait of interest, remains a crucial issue in increasing the success of molecular genetic studies.

**ENDOPHENOTYPES IN ADHD RESEARCH**

One proposed approach to addressing the phenotype definition issues is to employ alternative measurements of ADHD symptoms instead of traditional behavioral rating scale data. This approach has been subject of much recent research and debate. Endophenotypes have been defined as stable, heritable measurements that are more proximal to the biological etiology of a disorder than the clinical diagnosis itself and thus partly a better measurement of the underlying genetic liability for a disorder. In ADHD research, this approach is seen as especially valuable because it eliminates rater effects. Further, whereas ADHD is a complex phenotype encompassing many different behaviors, endophenotypes measure simpler traits that may be influenced by a smaller number of genetic loci. In consequence, each genetic variant may account for a larger proportion of the variance and may be detected with smaller samples. There is controversy over what constitutes a measurement that is biologically closer to the underlying susceptibility, and some researchers differentiate “inter-
mediate” and “objective” phenotypes from endophenotypes. In this article we consider ADHD endophenotypes to be those measurements that are designed to assess a heritable, genetically simpler construct, which covaries with ADHD outcomes.

There is a lack of consensus regarding the necessary and sufficient steps for empirically validating a measurement as a suitable candidate for an ADHD endophenotype.\textsuperscript{32-37} However, there is almost unanimous agreement on the following four criteria. One, the measurement needs to have good metric properties; scores should be continuously distributed without obvious floor or ceiling effects, they should show high internal consistency (the components that make up the measurement should correlate highly with each other), and test-retest reliability should be high. Two, it must be correlated with the disorder or its behavioral symptoms. Three, the measurement must be heritable. Four, at least a portion of this heritable variance is shared with the genetic liability for ADHD. This fourth criterion is traditionally examined by “means comparisons analysis” on groups of ADHD probands, unaffected siblings of the probands, and controls. If familial factors contribute to the endophenotype, then the means should be ordered as follows: controls \textless \textless \textless unaffected siblings \textless \textless probands. This approach has been successful in other fields of neuropsychiatric research such as schizophrenia.\textsuperscript{38,39}

However, initial failures to substantiate measurements of sustained attention, cognitive flexibility, encoding, impulsivity,\textsuperscript{40} memory,\textsuperscript{40,41} visual information processing,\textsuperscript{42} and executive functions\textsuperscript{41} as potential ADHD endophenotypes may have contributed to a relative lag in the study of this disorder.\textsuperscript{43} Fortunately, recent research is more promising, with stronger evidence from means comparisons analysis for specific cognitive measurements such as reaction time (RT) data, response inhibition (typically indexed by commission errors), and sustained attention (usually indexed by omission errors\textsuperscript{44-48}), motor measurements,\textsuperscript{49} and activity level measurements.\textsuperscript{50} However, means comparison analyses have failed to consistently validate some measurements, such as delay aversion and motivation.\textsuperscript{51} Although several promising endophenotype candidates have not produced convincing results in molecular genetic studies, several significant associations have been reported: Actigraph data (a mechanical assessment of activity level) is associated with the 7-repeat allele of the DRD4 receptor gene\textsuperscript{52}, measurements of response inhibition with the 10/10 repeat genotype on DAT1\textsuperscript{53}, RT data and the absence of the ADHD-risk allele on the DRD4 gene\textsuperscript{54-56}, and homoyzgosity for the 10-repeat allele of DAT1 with left-sided inattention and enhanced methylphenidate response.\textsuperscript{57,58} A significant genomewide linkage signal was also reported for motor timing on 2q21.1 and digit span on 13q12.11.\textsuperscript{59} However, these studies need replication (e.g., Manor et al.\textsuperscript{60}).

Despite these seemingly positive findings, some studies have found associations in the opposite direction to that predicted, i.e., the risk allele for ADHD seems to confer a protective effect on the endophenotype.\textsuperscript{55-57} These conflicting results and failures to replicate (see Kebir et al.\textsuperscript{60} for a comprehensive review and meta-analysis) have led to “a failure to establish a consistent pattern of findings on the modes of action of known risk genes [in] the current literature.”\textsuperscript{63} This situation strongly emphasizes the need to consider and refine the methodologic approach to selecting endophenotypes for molecular genetic research. Although means comparison analyses can be easily employed by nonstatisticians and have certain intuitive appeal, they are subject to several limitations: neither the familial variance underlying the measurement nor the covariance with ADHD can be parsed into separable genetic and environmental components;\textsuperscript{64} the amount of familial sharing is not explicitly quantified; and it is difficult to compare between measurements. SEM of twin data addresses all three of these problems. To the authors’ knowledge, only one study has directly compared the results of SEM and means comparison approaches in the selection of candidate endophenotypes.\textsuperscript{50} This study compared different measurements of “overactivity” and found that the two methodologic approaches yielded similar results because they validated the same measurements as candidate endophenotypes. However, the SEM approach quantified the amount of familial sharing of each measurement with ADHD, allowing future research to explicitly choose those measurements sharing the most familial variance with ADHD. Therefore, twin studies appear to be a valuable strategy for endophenotype research.

**TWIN RESEARCH AND ENDOPHENOTYPE DEVELOPMENT**

Several research groups have started to employ twin studies to identify endophenotypes for ADHD. Initially, samples were too small to draw
robust conclusions from parameter estimates gained from biometric genetic analyses, but recent analyses on larger-scale twin studies have been promising. For example, the heritability of RT data was estimated at 50% to 80%, with lower estimates increasing to around 70% when corrected for measured test-retest unreliability. This estimate is close to the average heritability of ADHD (~60% to 70%). Other measurements such as commission errors show somewhat lower estimates in the range of 18% to 48%, although these increase to 68% when also corrected for test-retest unreliability. Nevertheless, it is important to realize that biometrical genetic studies, including SEM analyses of twin data, transcend simple estimation of heritability. Such studies can address additional issues in the search for endophenotypes, in particular the identification and selection of appropriate endophenotypes from the many potential candidates.

ADVANTAGES OF ANALYSIS OF DATA COLLECTED FROM RELATIVES

It is not widely recognized that factor analysis of data from relatives confers several advantages over factor analysis from unrelated individuals. One benefit is that it is possible to analyze data from structured interviews, in which certain questions are asked if and only if a previous item has been responded to affirmatively. For example, in substance-use research it is possible to factor analyze jointly the initiation of substance use and subsequent symptoms of abuse or dependence. In the context of developing ADHD endophenotypes, it is possible to analyze commission errors for contributing characteristics and to ascertain how much they reflect biological characteristics specific to ADHD and how much they may reflect more generalized cognitive deficits. Second, when data have been collected from relatives and the factors correlate between relatives, it becomes possible to identify a greater number of factors than is the case with data from unrelated individuals. The data to identify a larger number of factors come from the cross-relative, cross-phenotype correlations. Third, given a genetically informative design, it is possible to partition variation in the latent factors into genetic and environmental components. For example, Figure 1 shows a path diagram of a model with three latent factors and seven observed variables, comprising three endophenotype measurements (End1 to End3, e.g., Actigraph data) and four behavioral measurements (Beh1 to Beh4). Application of this model to such a dataset might yield a general factor (F1) with substantial loadings on all measures, a factor F2 with large loadings on the endophenotypes but little effect on the behavioral measurements, and a third factor F3, which has the opposite pattern to F2. Under these circumstances, interest might center on F1 because both domains of measurement are influenced by it. Factor scores for all persons in the sample could be derived by maximum likelihood, and this could be used in, e.g., GWAS to identify genetic factors that contribute to the endophenotype and the behavioral components of ADHD. Without data from twins or other genetically informative studies of relatives, it is not possible to know in advance whether there is any evidence for genetic factors influencing the common factor F1. The addition of twin data
enables examination of the impact of genes on variation in each of the common factors, as shown in Figure 2. Here, variation in factors F1, F2, and F3 has been partitioned into genetic and environmental components, and the same separation is applied to the residual VCs specific to each measure. The parameters of this model can be freely estimated with data from a study of MZ and DZ twins. Possibly, the common factor F1 would have substantial genetic variation (a1 is large but c1 and e1 are small). If estimates for a particular factor appear to be largely genetic (e.g., a1 is large but c1 and e1 are small), it would be a good candidate for genomewide association studies. Beh = behavioral measurement; End = endophenotypes.

FIGURE 2  Factor model for genetically informative data from relatives assessed on seven measures (M1 to M7). Variation in the latent factors (F1 to F3) and residual components is partitioned into additive genetic (A1 to A3 and ARM1 to ARM7), shared or common environment (C1 to C3 and CRM1 to CRM7), and specific environment (E1 to E3 and ERM1 to ERM7) components. The regressions on each of these sources are estimated as free parameters (l1 to l7, a1 to a3, c1 to c3, e1 to e3, arm1 to arm7, crm1 to crm7, erm1 to erm7). If estimates for a particular factor appear to be largely genetic (e.g., a1 is large but c1 and e1 are small), it would be a good candidate for genomewide association studies. Beh = behavioral measurement; End = endophenotypes.

It is not uncommon to find that a model in which some factors are designated as purely additive genetic (and therefore correlate 1.0 between MZ twins and 0.5 between DZ twins), whereas others are purely environmental, fits the data well. In this situation, estimating latent genetic factor scores can be particularly valuable, although there is no barrier to estimating latent factor scores even when a factor is highly, but not completely, heritable. This latent factor score method was successful in a study of anxiety disorders, in which Diagnostic and Statistical Manual of Mental Disorders diagnoses and neuroticism trait scores were analyzed jointly in a multivariate twin model to derive a genetic latent trait factor score. The same approach could be applied to joint analyses of objective measurements of ADHD-related phenotypes such as RT or Actigraph measurements and more subjective but widely accepted ratings of attention and hyperactivity.

Of particular note is the potential of twin studies to distinguish between different models for the covariation between an endophenotype and an outcome variable. Models for comorbidity such as those described by Klein and Riso and implemented statistically for twin data by Neale and Kendler (see also Rhee et al.) are potentially very valuable in this context. Interest in an endophenotype is usually diminished if it is a consequence of the ADHD phenotype as opposed to a cause of it. A more promising possibility is that the endophenotype and the outcome variable share certain liability risk factors. Bivariate analyses of data from twins permit some resolution between these alternative hypotheses.

TWIN STUDIES CAN MAXIMIZE POWER IN FUTURE MOLECULAR GENETIC STUDIES

Maximizing power remains a key issue for molecular genetic studies, even with the endophenotype approach. Twin studies can increase power in endophenotype association studies (or GWAS) by decreasing the number of phenotypes to be tested for molecular genetic associations.

This decrease may be achieved in three main ways. First, they may help determine which measurements may be dropped; second, they may determine which measurements may be combined; and third, they can help determine
which measurements are most likely to have the power to result in successful gene-hunting.

Twin studies have helped to decrease the number of phenotypes by showing that, although closely related to the behavioral disorder, not all phenotypes are familial. For example, when collected in a laboratory setting, only mechanical motion sensor data from the waist, and not the leg, show significant familial overlap with ADHD, although both body loci show a significant within-person correlation. Studies of twins and families also provide an empirical basis for combining data across measurements, which decreases the number of phenotypes to be analyzed. This decrease mitigates the loss of power incurred when correcting for multiple testing. Recent analyses have highlighted that, although phenotypic correlations across RT data collected across different tasks may be low, genetic correlations can approach unity. Findings for activity-level data are similar: mechanical assessments of activity level across situations show modest phenotypic correlations, in the region of 0.5 to 0.6, but the genetic factors underlying laboratory-based tests and those from a “free play” session are very highly correlated, indicating that the two situations measure the same underlying genetic liability. Twin and factor analysis further indicate that mean RT and RT variability measure the same underlying construct or liability in the general population, indicating that only one cognitive construct need be analyzed in gene-finding studies. Thus twin studies can identify which measurements can be dropped, or preferably combined, because, despite modest phenotypic correlations, the genetic factors underlying the measurements may be largely identical.

After data reduction, further phenotype selection may be necessary. If data cannot be aggregated, selecting those measurements with the highest heritabilities may increase the power of genetic association studies; this has been highlighted as a key avenue of research in recent studies (e.g., Doyle et al.). Selection may be at the individual measurement level (e.g., measurements of RT variability show higher heritabilities than do measurements of mean RT) or at the aggregation level, with twin analysis having indicated higher heritabilities (or higher familial variance) for latent factor scores over mean measurements.

Whether this approach will translate into a “real-world effect” remains an empirical question. Similarly, understanding the etiology of the covariance between endophenotype measurements and ADHD will help researchers to select measurements that covary with ADHD for reasons other than being due to a general underlying deficit. This is a newer line of research, but data from larger-scale twin studies, for example, have indicated that the covariance between RT data and ADHD scores in the general population is independent of the covariation between ADHD scores and lowered IQ. To date, a multivariate genetic approach with twin data has not been employed in the development of endophenotypes for ADHD, and replication remains a key outstanding issue. Nevertheless, the potential value of twin studies to endophenotype and phenotype definitions seems clear given these interesting and promising initial results.

**TRANSLATIONAL IMPLICATIONS**

Zerhouni identified translational studies as a key priority for the National Institute of Health, and the importance of twin studies of endophenotypes for clinicians and those outside the genetic field should not be overlooked. Translational research is normally taken to mean “from science to bedside.” However, with research that does not involve clinical trials or direct clinical interventions, such as quantitative genetic studies, it is important to take a broader view. The road from science to bedside may involve many steps, and it is necessary to understand the role of research findings to yield individual health benefits. Much endophenotype research is concerned with identifying objective measurements that can be used as measurements of ADHD. Such assessments and their biological markers may provide powerful phenotypes for future studies that will enhance the lives of those with ADHD. For example, molecular genetic and functional magnetic resonance imaging studies may improve the characterization of biological pathways between genes, brain, and behavior. This improvement may in turn help to identify more homogenous clinical subgroups that differ in their responses to treatment. In addition, although the research discussed in this review might be thought to be focused on identifying, and maximizing, heritable variance, it does, of course, follow that the nonheritable variance can be refined in a similar fashion. This, too, can help target future research, by portioning the environ-
mental variance into shared and nonshared environmental factors, indicating where epidemiologic studies should be directed. Better still, multivariate twin studies have the potential to clarify the role of putative environmental risk factors by assessing whether they affect ADHD behaviors directly or moderate the influence of genetic or other environmental sources of variation. Further, multivariate SEM of twin data reveals environmental causes of covariation, indicating where clinicians can direct target treatment in, for example, addressing comorbid oppositional and ADHD behaviors. This is particularly valuable where twin studies establish that the same behaviors in different settings (e.g., across tasks or situations) do not share the same environmental factors. The validation of increased ADHD correlates in unaffected relatives indicates where clinicians can direct target treatment in, for example, addressing comorbid oppositional and ADHD behaviors. This is particularly valuable where twin studies establish that the same behaviors in different settings (e.g., across tasks or situations) do not share the same environmental factors. The validation of environmental factors, indicating where epidemio-

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