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Understanding the complex etiologies of developmental disorders: Behavioral and molecular genetic approaches

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Abstract

Objective—This paper has two primary goals. First, a brief tutorial on behavioral and molecular genetic methods is provided for readers without extensive training in these areas. To illustrate the application of these approaches to developmental disorders, etiologically-informative studies of reading disability (RD), math disability (MD), and attention-deficit/hyperactivity disorder (ADHD) are then reviewed. Implications of the results for these specific disorders and for developmental disabilities as a whole are discussed, and novel directions for future research are highlighted.

Method—Previous family and twin studies of RD, MD, and ADHD are reviewed systematically, and the extensive molecular genetic literatures on each disorder are summarized. To illustrate four novel extensions of these etiologically-informative approaches, new data are presented from the Colorado Learning Disabilities Research Center, an ongoing twin study of the etiology of RD, ADHD, MD, and related disorders.

Conclusions—RD, MD, and ADHD are familial and heritable, and co-occur more frequently than expected by chance. Molecular genetic studies suggest that all three disorders have complex etiologies, with multiple genetic and environmental risk factors each contributing to overall risk for each disorder. Neuropsychological analyses indicate that the three disorders are each associated with multiple neuropsychological weaknesses, and initial evidence suggests that comorbidity between the three disorders is due to common genetic risk factors that lead to slow processing speed

Keywords

Reading; math; ADHD; genetics; twins

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INTRODUCTION

Previous etiological models of complex disorders such as reading disability (RD), math disability (MD), and attention-deficit/hyperactivity disorder (ADHD) often implicated simple linear causal pathways in which a single genetic or environmental risk factor led to a single cognitive deficit that was necessary and sufficient to cause all of the symptoms of the disorder. These models worked well for single-gene disorders such as Huntington's Disease and phenylketonuria, but a growing literature consistently suggests that single-deficit models do not provide a satisfactory explanation for most developmental disorders[1]. In this paper we review several lines of etiological research that suggest that developmental disorders may be better conceptualized as heterogeneous conditions that arise from the additive and interactive effects of multiple genetic and environmental risk factors.

This paper is divided into five sections. The first section briefly describes the Colorado Learning Disabilities Research Center (CLDRC), an ongoing twin study funded by a Center grant from the National Institute for Child Health and Human Development[2;3]. Data from the CLDRC are used to illustrate many of the methodological approaches described in the paper. The second and third sections first describe each behavioral and molecular genetic method for readers without specific training in this area, then systematically review studies of RD, MD, or ADHD that used the approach. In the fourth section we present new data from the CLDRC to illustrate how novel extensions of these behavioral and molecular genetic methods may provide important new information regarding the complex etiologies of learning disorders and ADHD. The final section of the paper discusses the clinical implications of these results and describes several areas in which additional research is needed.

Colorado Learning Disabilities Research Center

Due to the paucity of well designed twin studies of reading disability, a twin study was initiated in 1982 as part of the Colorado Reading Project[4]. This project was incorporated into the CLDRC when it was initiated in 1991, and twins have been tested continuously since that time. The sample now includes over 1,280 twin pairs selected because at least one of the twins met screening criteria for RD or ADHD, 450 biological siblings of the selected twins, and 790 pairs of control twins in which neither twin met criteria for RD or ADHD. More stringent criteria based on psychometric testing are then applied to identify the final group of probands with RD or ADHD, as described in the subsequent section.

Participants—In collaboration with administrators in 22 Colorado school districts that have agreed to participate in the study, all twin pairs in each district are identified without regard to reading or ADHD status. After initial parental consent is obtained, independent screening procedures are conducted to identify twin pairs in which at least one twin meets criteria for ADHD, RD, or both disorders. If either member of a twin pair has a history of reading difficulties or meets screening criteria for ADHD, the pair and any biological siblings between 8 and 18 years of age are invited to participate in the full study. Each twin that participates in the full study completes an extensive test battery that includes a complete standardized IQ test, psychometric measures of reading, spelling, and mathematics achievement, measures of reading-related language processes, diagnostic measures of ADHD, and measures of key cognitive domains that may be related to one of the disorders[3].

A matched comparison group of control twins is selected from the overall sample of pairs who did not meet the screening criteria for RD or ADHD. Because the primary focus of the CLDRC is the etiology of RD and ADHD, pairs at risk for one or both disorders are oversampled to increase statistical power for analyses of these extreme groups.

Definitions of RD, MD, and ADHD—The definitions of RD and MD in the *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition*5 specify that an individual's reading or math achievement must be significantly discrepant from their overall intelligence. However, the utility of IQ scores as part of the diagnosis of learning disabilities is a long-standing area of controversy, and most experts argue against the use of an IQ-discrepancy criterion6;7. For the examples in this paper we defined RD by a cutoff score 1.25 SD below the estimated population mean on an age-adjusted composite measure of word reading derived from the Peabody Individual Achievement Test (PIAT) Reading Recognition subtest[8] and a time-limited word reading test9. Similarly, MD was defined by a score 1.25 SD below the population mean on a composite measure of math calculations derived from the Math subtests on the PIAT and the Wide Range Achievement Test10.

The DSM-IV definition of ADHD includes three subtypes based on differential elevations of inattention and hyperactivity-impulsivity symptoms. The predominantly inattentive type is characterized by significant elevations of inattention but not hyperactivity-impulsivity, whereas the predominantly hyperactive-impulsive type exhibits significant hyperactivity-impulsivity but not inattention, and individuals with the combined type have clinically significant elevations on both symptom dimensions. Parent and teacher ratings[11] of ADHD symptoms and associated impairment were combined based on the algorithm from the DSM-IV field trials for the disruptive behavior disorders[12].

BEHAVIORAL GENETIC STUDIES OF RD, MD, AND ADHD

Family Studies

Family studies test whether the rate of a disorder is significantly higher in the biological family members of individuals with the disorder than in the family members of individuals without the diagnosis. If the disorder occurs more frequently in family members of individuals with the disorder, this suggests that familial factors increase susceptibility for the disorder.

Correlations between biological siblings are moderate to high on dimensional measures of reading (r = .40 – .70), math (r = .40 – .80), and ADHD symptoms (r = .20 – .50)[13–16]. In family studies of categorical diagnoses, the relative risk of RD is 4 – 8 times higher in first-degree relatives of probands with RD than in relatives of individuals without RD[17;18], and similar familiality is reported in studies of ADHD[19;20]. Fewer studies have tested the familiality of MD, but initial results suggest that the relative risk is 5 to 10 times higher in the biological relatives of probands with versus without MD[21;22].

Twin studies

Because members of intact biological families share both genetic influences and the home environment, other methods are needed to disentangle the relative contributions of genetic and environmental influences. By comparing the similarity of monozygotic (MZ) twins, who share all of their genes, to dizygotic (DZ) twins, who share half of their segregating genes on average, twin studies provide estimates of the extent to which a disorder is due to genetic or environmental influences[23].

Concordance rates—The most straightforward test for genetic influences on a clinical disorder compares the rate of concordance in pairs of MZ versus DZ twins. If a disorder is influenced by genes, the proportion of pairs that are concordant for the disorder will be higher in MZ pairs than DZ pairs. Consistent with this hypothesis, all previous studies of RD, ADHD, and MD (with one exception24) found that the probandwise concordance rate was higher in MZ twin pairs than DZ twin pairs, providing strong evidence that all three disorders are influenced by genes (Table 1).

Etiology of individual differences—Although the simplicity of a comparison of concordance rates is appealing, increasing evidence suggests that RD, MD, ADHD, and most other complex disorders are defined by a diagnostic threshold imposed upon a quantitative measure that is continuously distributed in the population[16;25]. Transformation of continuous measures such as reading or math performance or ADHD symptoms into a categorical diagnosis results in the loss of important information pertaining to both severity within the disorder and variability in subthreshold symptomatology. Therefore, several authors have developed more powerful variance components or multiple regression approaches for analyses of continuous data[26–28].

Basic twin models estimate three parameters. *Heritability* is the proportion of the total phenotypic variance in a trait that is attributable to genetic influences. The proportion of variance due to environmental factors is subdivided to distinguish two types of environmental influences. *Shared environmental influences* are environmental factors that increase the similarity of individuals within a family in comparison to unrelated individuals in the population. These effects may potentially include environmental influences within the home or any other shared experiences such as mutual friends or shared teachers. In contrast, *nonshared environmental influences* are environmental factors that that are independent or unique for members of twin pairs. These risk factors could include a head injury or other accident, a traumatic event, or exposure to physical or sexual abuse (if the other twin was not similarly exposed).

Figure 1 summarizes published twin studies of reading, math, and the two DSM-IV ADHD symptom dimensions[13;15;16;25;29–48]. Heritability estimates are moderate for individual differences in single-word reading and math, and are consistently high for inattention and hyperactivity-impulsivity. Shared environmental influences account for an additional 10 – 15% of the variance in reading and math, whereas shared environmental influences were not significant for the ADHD symptom dimensions. Nonshared environmental influences and measurement error account for the remaining 20 – 25% of the variance in each of the phenotypes.

Etiology of extreme scores—Although variance components analyses are optimal for analyses of individual differences in unselected or minimally selected samples, this approach is not designed for analyses of extreme groups. Therefore, DeFries and Fulker developed a multiple regression approach to test the etiology of extreme group membership[26;27]. DeFries-Fulker (DF) analysis is based on the differential regression of MZ and DZ co-twin scores toward the population mean when probands are selected due to an extreme score on a phenotype. Although scores of both MZ and DZ co-twins are expected to regress toward the population mean, scores of DZ co-twins should regress further than scores of MZ co-twins to the extent that the proband deficit is influenced by genes. After appropriate standardization and transformation of scores, the magnitude of differential regression by zygosity provides a direct estimate of the heritability of the extreme group deficit (h^2_g).

To illustrate the DF approach, univariate models were fitted to composite scores for reading, math, inattention, and hyperactivity-impulsivity in the CLDRC sample (Table 2). The selection criterion for the proband groups for this specific analysis yielded mean MZ and DZ proband scores approximately 2 SD below the population mean. MZ and DZ co-twin means regressed differentially on all four measures, and the multiple regression models revealed significant genetic influences on each group deficit, similar to results that have been reported in other samples for RD[32], MD[16], and ADHD[40;49].

Conclusions—Both individual differences and extreme scores on measures of math, reading and ADHD are significantly heritable. Although twin analyses cannot test definitively whether

the same genetic influences act on extreme scores and individual differences, the similarity of these results is consistent with this hypothesis. In the next section, we summarize results from studies that attempted to localize the specific genes that account for these high heritability estimates.

MOLECULAR GENETIC STUDIES OF RD, MD, AND ADHD

Molecular genetic studies have used three methods to identify genes that increase susceptibility to RD, MD, or ADHD. Space constraints permit only a short description of these methods, but more detailed overviews are provided elsewhere[23;50;51]. Briefly, the candidate gene approach examines specific genes that are targeted because they play a role in the pathophysiology of the disorder. For example, many candidate gene studies of ADHD have tested for associations with genes in the dopamine system due to the significant effect of stimulant medication on dopamine transmission[52]. In contrast to the theory-driven candidate gene approach, linkage and association analyses use a dense map of DNA markers to screen the entire genome or targeted chromosomal regions for polymorphisms (differences in the DNA sequence between individuals) that may increase susceptibility to the disorder.

ADHD

Over 200 studies have tested for associations between ADHD and over 100 different genes since the first candidate gene study was completed fifteen years ago[53]. Although many initial positive results failed to replicate in subsequent studies, a recent meta-analysis implicated seven genes as significant risk factors for ADHD[52]. The effect size of each of these genes is small (Odds Ratio = 1.1 – 1.3), however, and the combined effects of all seven loci explain only a small amount of the total genetic variance in ADHD. Because these results suggested that additional genes must play a role in ADHD, genome-wide linkage and association analyses were used to screen the entire genome for additional loci[54–56]. These studies found significant evidence of a susceptibility locus on chromosome 16q, and suggestive evidence for risk loci in nine additional regions of the genome. None of these regions overlapped with the locations of the candidate genes identified by the meta-analysis, and even with the combined effects of the candidate genes and the loci identified by the linkage and association studies the majority of the genetic variance in ADHD symptoms in the population remains unexplained.

RD

In contrast to the dopamine model of ADHD that was derived largely from response to medication, targets for candidate gene studies are not as obvious based on current knowledge about the pathophysiology of RD and MD. Therefore, molecular genetic studies of MD and RD first used linkage and association analyses to identify regions of the genome that may contain a risk locus for the disorder, then targeted fine-mapping procedures were used to test for candidate genes in these regions. Genome-wide and targeted linkage analyses have identified nine locations in the genome that are likely to include risk loci for RD[57], and subsequent analyses have identified potential candidate genes in six of these region[58–65]. Although some of these loci await independent replication, these results suggest that RD is also influenced by multiple genetic risk factors with relatively small effect sizes.

MD

Finally, initial results from the only molecular genetic study of MD are also similar to the results reported for RD and ADHD[66]. In a genome-wide association study of a population-based sample of 2,449 individuals, a total of 10 single nucleotide polymorphisms were significantly associated with math performance in two separate analyses. In combination, the 10 risk loci accounted for approximately 3% of the phenotypic variance in math performance.

Conclusions

The high heritability of RD, MD, and ADHD led to initial optimism that genes with major effects would be identified for each disorder. Contrary to this prediction, however, results of candidate gene, linkage, and association studies all suggest that the etiologies of RD, MD, and ADHD are complex and polygenic, with multiple genetic and environmental risk factors contributing to the total phenotypic variance in the population. Future molecular genetic studies could still uncover rare polymorphisms with major effects on ADHD, RD, or MD in a subset of the population[67], but the current literature argues against single-gene models of each disorder, and is similar to results reported for virtually all other developmental disorders and psychopathology, including pervasive developmental disorders[68], bipolar disorder[69], major depression[70], and schizophrenia[71;72]. In the next section we discuss four extensions of these basic behavioral and molecular genetic approaches that may help to begin to disentangle the complex etiologies of developmental disorders.

EXTENSIONS OF ETIOLOGICALLY-INFORMATIVE METHODS

Gene × Environment Interactions

Gene × environment (G × E) interactions occur if environmental circumstances modify the expression of an individual's genetic background, either strengthening or weakening genetic influences on a phenotype73. Significant G × E interactions have been reported for several psychopathologies, including conduct disorder74 and depression75. These are both examples of diathesis-stress interactions, which occur when genetic vulnerability (the diathesis) co-occurs with an environmental risk factor, resulting in more severe symptomatology than would be expected based on either risk factor alone or their additive combination.

These exciting initial findings have replicated inconsistently, however, leading others to encourage caution in the interpretation of G × E findings[76;77]. Among the key concerns that have been raised are statistical issues regarding data transformations and the failure to correct adequately for multiple testing, along with the fact that many putative environmental risk factors are partially heritable, such as parenting behavior, social support, and exposure to stressful life events[78]. In addition, many studies of humans have reported significant G × E interactions in the absence of a genetic main effect, a phenomenon that is extremely rare in well-controlled studies of nonhuman animals[79]. Each of these issues is an important caveat for the studies of ADHD and RD that are reviewed in this section, and these points of critique are discussed in detail elsewhere[80].

ADHD—Table 3 summarizes results of studies of ADHD that tested for interactions between environmental risk factors and specific candidate genes[81–94]. Most studies tested for interactions between dopamine genes and prenatal risk factors, and all significant G × E interactions were diathesis-stress interactions. Interactions were significant between several dopamine genes and prenatal smoking, and several of these studies also found a significant interaction between the dopamine transporter gene and prenatal alcohol exposure. In both cases these results appear to be strongest for hyperactivity-impulsivity symptoms and the combined type. The primary postnatal environmental influences that were tested were socioeconomic status and environmental adversity. Although these constructs were measured a variety of different ways, all six studies reported a significant diathesis-stress interaction with a range of different candidate genes, and we recently found a similar diathesis-stress interaction with parental education in the CLDRC sample[80].

These initial studies of G × E interactions and ADHD are intriguing. However, these results must also be interpreted with caution because most studies did not control for socioeconomic

risk factors that may be correlated with prenatal smoking or alcohol use, and many did not test whether the results were explained by comorbid internalizing and externalizing disorders.

RD—Although no studies of RD or MD have tested for interactions between candidate genes and environmental risk factors, several studies have used twin data to test whether the heritability of RD or other cognitive phenotypes vary as a function of specific environmental variables. In contrast to studies of ADHD and other psychopathology, studies of cognitive abilities have typically found bioecological G × E interactions[33;95;96]. In a bioecological interaction, genetic influences are expressed most strongly in enriched environments due to the lesser impact of environmental risk factors, whereas genetic influences account for less phenotypic variance in high-risk environments due to increased environmental variance[97]. Recent analyses of the CLDRC and a sample of older adults indicate that the heritability of RD is significantly higher in families with high parental education than families with low parental education, and this result remained significant in the CLDRC even after controlling for potential genetic influences on parental education[98].

Conclusions—Few studies have tested G × E interactions for RD or MD, and many G × E interactions for ADHD await independent replication. Nonetheless, initial results for both RD and ADHD suggest that G × E interactions may play an important role in the etiology of developmental disorders. If the effect of genetic risk factors is moderated by environmental influences, this may help to explain the small effect sizes and inconsistent replication in candidate gene studies despite the high heritability estimates for each disorder.

Diagnostic heterogeneity

Etiologically-informative methods also provide a powerful tool for studies that attempt to dissect the marked heterogeneity that characterizes ADHD, learning disabilities, and many other developmental disorders. To illustrate this approach, we examined concordance rates for the DSM-IV ADHD subtypes in MZ and DZ twin pairs. Two key findings would support the validity of the three-subtype model described in DSM-IV. First, if the distinction between the subtypes is valid, the subtypes should “breed true”, such that co-twins tend to meet criteria for the same subtype as the proband. Second, the high heritability of the overall ADHD diagnosis suggests that each subtype should also be strongly influenced by genes. If one of the subtypes is primarily due to environmental influences, it may be better conceptualized as a separate disorder.

Figure 2 summarizes the ADHD status of co-twins of MZ and DZ probands with each DSM-IV subtype. Whether probands were selected for the combined type or inattentive type, the overall rate of ADHD was significantly higher in MZ co-twins than DZ co-twins. The inattentive and combined subtypes also breed true in twin pairs to some extent. In contrast, probands with the inattentive type also have significantly more co-twins with the combined type than expected by chance, and co-twins of probands with the combined type were equally likely to meet criteria for the combined type or the inattentive type. These results suggest that the subtypes are also influenced by shared genetic influences, a finding that is consistent with the similarity of the academic and neuropsychological profiles of the inattentive and combined types in the CLDRC[3;99;100], and with similar results reported for the subtypes in most candidate gene studies and nearly all treatment studies (reviewed by Willcutt, Nigg, et al., under review).

Results for the hyperactive-impulsive type are quite different. MZ and DZ concordance rates for the hyperactive-impulsive type are nearly identical, suggesting that this subtype is minimally familial and is not significantly heritable. Furthermore, although our results from the CLDRC should be interpreted with caution due to the small sample with the hyperactive-

impulsive type, a meta-analysis of 14 studies of the dopamine D5 receptor gene[101] and a genome scan of a large sample of affected sibling pairs with DSM-IV ADHD[102] both reported that evidence for association and linkage became stronger when probands with the hyperactive-impulsive type were excluded from analyses. Taken together, these results add to a growing literature that challenges the validity of the hyperactive-impulsive type after preschool[103].

Etiology of comorbidity

In addition to significant heterogeneity within each disorder, nearly all developmental disorders co-occur with other disorders more frequently than expected by chance. As one of the primary aims of the CLDRC we have used bivariate extensions of DF analysis38 to test the etiology of the significant comorbidity between RD and MD (28–64%)104–107, RD and ADHD (10–40%)44;108;109, and MD and ADHD (12–36%)21;110. Rather than comparing the relative similarity of MZ and DZ twins on the same trait, the bivariate model compares the relation between the proband's score on the selected trait and the co-twin's score on a second, unselected trait. If common genetic influences contribute to the association between the two traits, the MZ co-twin score on the unselected trait should regress less than the DZ co-twin score toward the population mean . This differential regression is used to estimate bivariate h^2_g, an index of the extent to which the proband deficit on the selected measure is due to genetic influences that also contribute to deficits on the unselected measure.

Previous bivariate DF analyses have consistently shown that common genetic influences account for comorbidity between RD and ADHD, with stronger shared genetic influences for inattention symptoms than hyperactivity-impulsivity symptoms[15;38;44;111–113]. Because few previous studies have examined comorbidity between RD and MD and no studies have tested the etiology of comorbidity between ADHD and MD, we fitted bivariate DF models to test the etiology of these comorbidities (Table 4). These results suggest that comorbidity between RD and MD and between ADHD and MD is also primarily explained by common genetic influences. Similar to our previous results for reading and ADHD, shared genetic influences between ADHD and MD are strongest for inattention symptoms.

Incorporating neuropsychological measures

The inclusion of neuropsychological measures in etiologically-informative analyses provides another useful tool to dissect the complex etiology and neuropsychology of developmental disorders. We recently compared groups with RD, MD, and ADHD in the CLDRC on composite measures of verbal reasoning, naming speed, processing speed, response inhibition, working memory, and phoneme awareness. Consistent with the results of our recent meta-analysis of neuropsychological studies of nine childhood disorders[114], groups with RD, MD, and ADHD exhibited significant weaknesses on all six cognitive composites[3;99;115;116]. These results suggest that rather than unique neuropsychological deficits that are specific to each disorder, RD, MD, and ADHD may be distinguished by more subtle differences in the specific profile or severity of neuropsychological weaknesses across domains that are impaired to some extent in all three disorders.

Phenotypic structural equation models were then used to test which of these neuropsychological weaknesses were independently associated with each disorder when the other cognitive measures were also included in the model (McGrath et al., under review and 116), and multivariate twin analyses were used to test the etiology of any significant associations115;117. Results indicated that RD was independently associated with weaknesses in phonological decoding, verbal reasoning, working memory, naming speed, and processing speed, and MD is independently associated with each of these weaknesses with the exception of naming speed. In contrast, the only neuropsychological measures that independently predicted ADHD were weak response inhibition and slow processing speed. Individual

differences on each of the neuropsychological composite scores were significantly heritable, and multivariate twin analyses suggested that comorbidity between ADHD, RD, and MD is due primarily to common genetic influences that lead to slow processing speed[13;29;31;38;115–118].

In summary, the neuropsychological correlates of RD, MD, and ADHD are complex and multifactorial, consistent with the findings from molecular genetic studies. The heritability of the neuropsychological measures and their strong relationship with the three disorders suggests that these and other measures of brain functioning may be useful for future studies of the etiology of RD, MD, ADHD, and their comorbidity.

CONCLUSIONS AND FUTURE DIRECTIONS

Family and twin studies clearly show that RD, MD, and ADHD are familial and heritable. Although much more research is needed on the molecular genetic etiology of the three disorders, initial results suggest that each disorder is caused by the additive or interactive effects of multiple genetic and environmental risk factors, each of which may have a relative small effect in isolation. In the remainder of this section we summarize the clinical implications of these results and highlight the need for increased interdisciplinary research in the next generation of studies of the etiology of these disorders.

Clinical implications

There is currently no valid genetic test for RD, MD, or ADHD, and it is unlikely that a definitive diagnostic test will be developed in the near future. Because most developmental disorders have polygenic, multifactorial etiologies in which each risk factor confers only a small increase in susceptibility, it is unlikely that any specific risk factor will have sufficient predictive power to be useful as a diagnostic measure.

Even if behavioral and molecular genetic studies do not identify a definitive genetic test for each disorder, these methods may still have important clinical benefits in the future. It may eventually be possible to develop probabilistic risk profiles based on an individual's genetic background, family history, environmental circumstances, and other factors. These profiles could be used to identify individuals who are at higher risk for a specific disorder, facilitating primary prevention or early intervention. For example, if a perinatal screening revealed significant susceptibility to RD, early interventions could be provided to reduce the probability that child will develop RD. Similarly, by providing a better understanding of the underlying pathophysiology of ADHD, molecular genetic techniques may inform the development of tertiary pharmacological or psychosocial treatments that directly target the compromised physiological and psychological mechanisms.

Expansion of collaborative research

Multisite molecular genetic networks—One of the most important implications of initial molecular genetic studies of RD, MD, ADHD, and most other complex disorders is that current studies are severely underpowered[119]. Due to small effect sizes and etiological heterogeneity, procedures for gene localization are likely to require extremely large samples (5,000 – 10,000 individuals or more) that are simply not feasible for a single laboratory to collect in isolation. Fortunately, procedures for DNA collection and genetic analysis continue to become more automated and efficient, and it is now relatively inexpensive for studies without a primary focus on genetics to collect and store DNA for use in future collaborative genetic analyses. A network for collaborative molecular genetic studies already exists for ADHD[120], and the initiation of similar networks for RD and MD would provide a useful way to accelerate the progress of the field.

Interdisciplinary research—In conclusion, it is increasingly clear that future progress in understanding the complex etiologies of developmental disorders such as RD, MD, and ADHD is likely to require interdisciplinary research that integrates behavioral and molecular genetic techniques with state-of-the-art clinical, developmental, and cognitive methods. The infrastructure provided by the NICHD Center grant that supports the CLDRC has provided a unique opportunity for innovative interdisciplinary research that would have been difficult or impossible for any of our laboratories to initiate alone. Furthermore, the collaborative synergy within the CLDRC has facilitated the development of important collaborations with a number of groups outside the CLDRC, including molecular genetic studies of RD[63;121] and ADHD[122], studies of neuropsychological heterogeneity and neurocognitive phenotypes that may be useful for molecular genetic studies of ADHD[123;124], and the largest study of the etiology of high intelligence that has been conducted to date[125]. We hope that these examples and the others described in this paper may stimulate the development of additional innovative collaborations among a larger network of investigators in the field.

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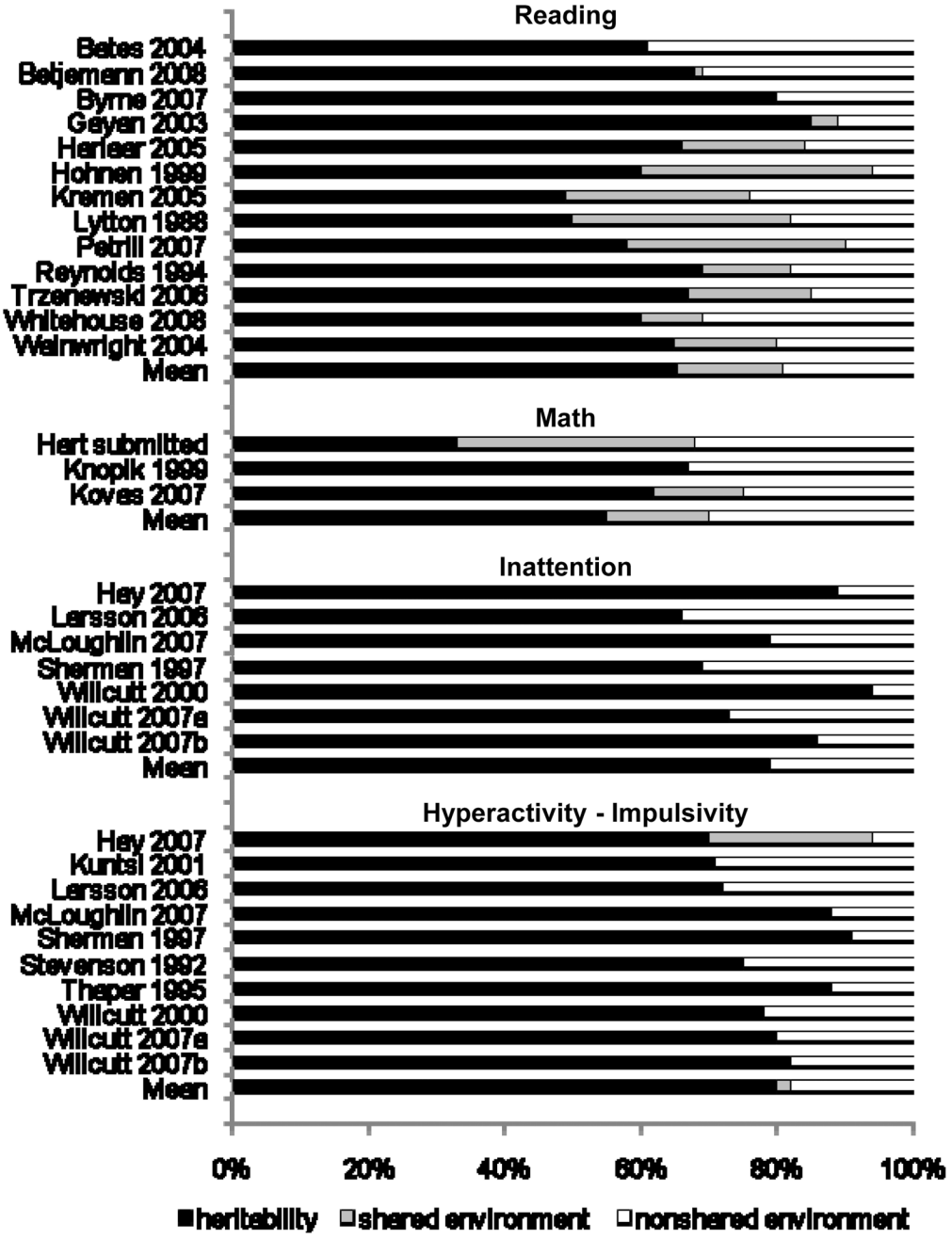

Figure 1.
Twin studies of reading, math, and DSM-IV ADHD symptom dimension

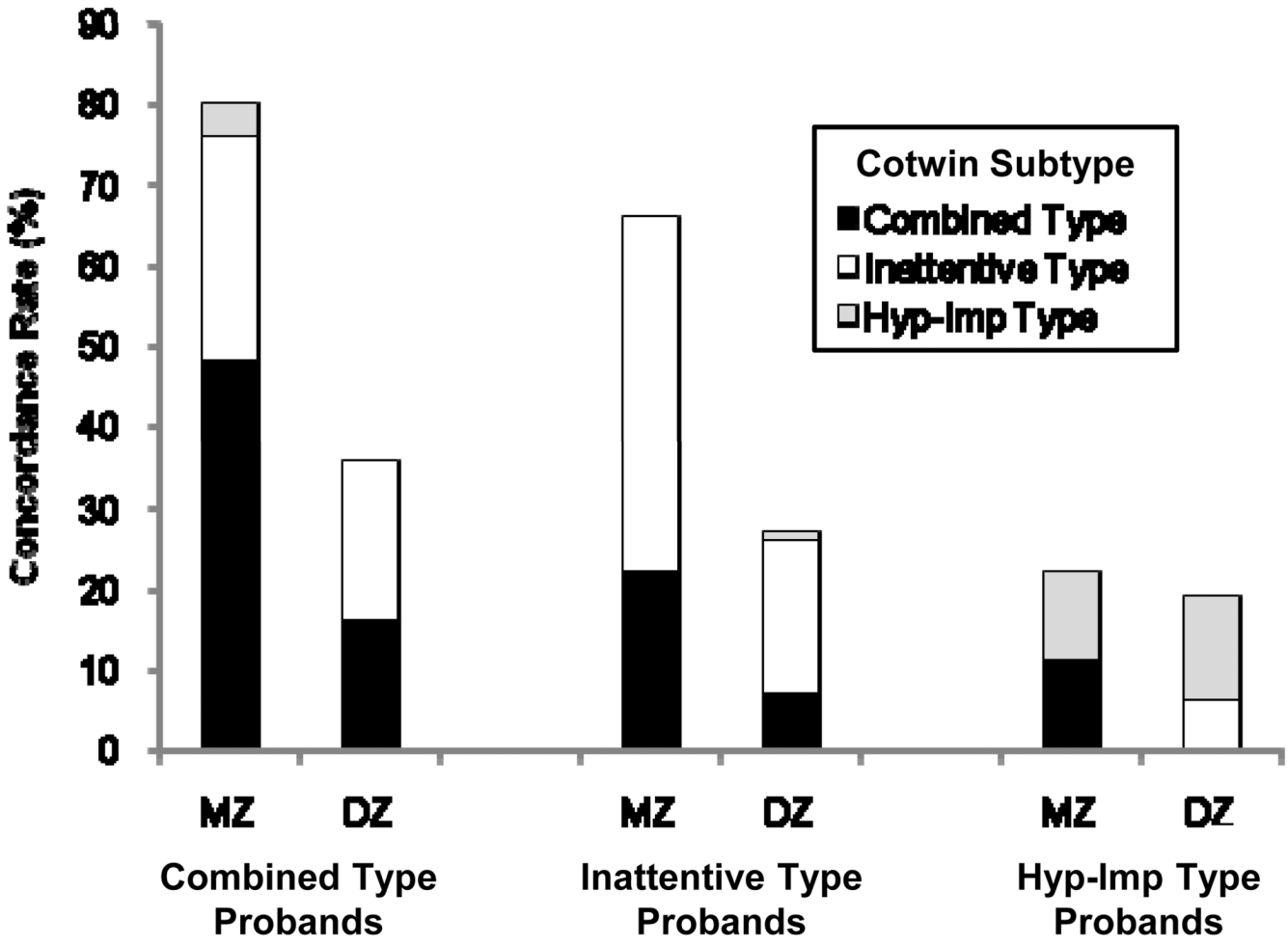

Figure 2.
Rates of DSM-IV ADHD subtypes in the co-twins of MZ and DZ probands who meet criteria for the inattentive type, combined type, or hyperactive-impulsive type.

Table 1

Concordance rates for RD and ADHD in pairs of MZ and DZ twins

	Number of pairs		Probandwise Concordance	
	MZ	**DZ**	**MZ**	**DZ**
Reading Disorder				
Bakwin (1973)[126]	31	31	91%	45%
Harlaar et al. (2005)[32]	308	246	72%	45%
Hawke et al. (2006)[127]	306	247	66%	35%
Stevenson et al. (1987)[24]	14 – 18[a]	27 – 38[a]	33 – 50%[a]	29 – 54%[a]
Zerbin-Rudin (1967)[128]	17	34	100%	52%
Weighted average			70%	41%
ADHD				
Goodman & Stevenson (1989)[129]	39	54	51%	33%
Levy et al. (1997)[49]	57	46	82%	38%
Levy et al. (2001)[130]	138	109	67%	42%
Sherman et al. (1997)[131]	69	32	58%	31%
Thapar et al. (2001)[132]	175[b]	410[b]	79%	54%
Todd et al. (2001)[133]	72	135	68%	22%
Willcutt et al. (2000)[25]	88	82	78%	38%
Willcutt et al. (2007)[38]	83	78	68%	24%
Weighted average			71%	41%
Math Disorder				
Alarcón et al. (1997)[134]	63	32	76%	56%
Kovas et al. (2007)[16]	93	83	40%	24%
Weighted average			55%	33%

[a] concordance rates were provided for several different definitions of RD. The average MZ and DZ concordance was use for the weighted average.

[b] specific Ns were not provided, so Ns are estimated based on the total sample and the 80th percentile threshold used to define the extreme ADHD probands.

Table 2

Etiology of group deficits in reading, math, and ADHD symptoms

	MZ pairs[a]			DZ pairs[a]			
	N[b]	Proband M (SD)	Co-twin M (SD)	N[b]	Proband M (SD)	Co-twin M (SD)	h^2_g (SE)
Reading	106	−2.00 (0.68)	−1.73 (0.75)	89	−1.99 (0.72)	−1.07 (1.23)	0.65 (0.13)***
Math	91	−2.01 (0.56)	−1.38 (0.99)	84	−2.04 (0.55)	−0.81 (1.12)	0.58 (0.15)***
Inattention	98	−2.03 (0.58)	−1.46 (1.23)	83	−2.07 (0.59)	−0.59 (1.07)	0.87 (0.14)***
Hyperactivity - impulsivity	85	−2.17 (0.57)	−1.47 (0.58)	65	−2.09 (0.58)	−0.62 (1.16)	0.76 (0.15)***

Note.

*** P < .001.

[a] Scores are expressed as standard deviations from the estimated population mean. All scores are scaled so that lower scores indicate greater impairment on all measures.

[b] Total number of pairs in which at least one twin met the criteria for the proband group (score at least 1.25 SD below the population mean).

Table 3

Studies of candidate gene × environment interactions in ADHD

Environmental Risk / Study	Candidate Genes[a]	ADHD Phenotype	Genetic Main Effect	Sig. G × E Interaction
Prenatal Smoking				
Becker et al. (2008)[88]	DAT1	ADHD	No	Yes[b]
Brookes et al. (2006)[93]	DAT1	ADHD	Yes	No
Kahn et al. (2003)[89]	DAT1	Inattention symptoms	No	No
Kahn et al. (2003)[89]	DAT1	Hyp-Imp symptoms	No	Yes
Langley et al. (2008)[90]	DAT1, DRD4, 5HTT, DRD5	ADHD	No	No[c]
Neuman et al. (2007)[91]	DAT1, DRD4	Combined Type	No	Yes
Neuman et al. (2007)[91]	DAT1, DRD4	Inattentive Type	No	No
Todd et al. (2007)[92]	CHRNA4	Combined Type	No	Yes
Todd et al. (2007)[92]	CHRNA4	Inattentive Type	No	No
Prenatal Alcohol				
Brookes et al. (2006)[93]	DAT1	ADHD	Yes	Yes
Kahn et al. (2003)[89]	DAT1	Inattention symptoms	No	No
Kahn et al. (2003)[89]	DAT1	Hyp-Imp symptoms	No	Yes
Langley et al. (2008)[90]	DAT1, DRD4, 5HTT, DRD5	ADHD	No	No
Neuman et al. (2007)[91]	DAT1, DRD4	Combined Type	No	No
Neuman et al. (2007)[91]	DAT1, DRD4	Inattentive Type	No	No
Low Birth Weight				
Langley et al. (2008)[90]	5HTT, DRD4, DAT1, DRD5	ADHD	No	No[d]
Season of birth				
Seeger 2004[87]	DRD4	ADHD+CD	No	Yes
Brookes 2008[86]	DRD4	ADHD	No	No
Socioeconomic status / environmental adversity				
Lasky-Su et al. (2007)[81]	BDNF	Inattention symptoms	Yes	No[e]
Lasky-Su et al. (2007)[81]	BDNF	Hyp-Imp symptoms	Yes	Yes
Laucht et al. (2007)[82]	DAT1	ADHD	No	Yes
Nobile et al. (In press)[135]	COMT	ADHD	No	Yes
Nigg et al. (2007)[94]	DAT1, DRD4, ADRA2A[f]	ADHD	Yes	Yes
Retz et al. (2008)[84]	5HTT	ADHD	Yes	Yes
Waldman et al. (2007)[85]	DRD2	ADHD	No	Yes

[a] ADRA2A = , BDNF = brain-derived neurotrophic factor, CHRNA4 = Nicotinic acetylcholine receptor α-4 , COMT = catechol-O-methyltransferase, DAT1 = dopamine transporter, DRD2 = dopamine D2 receptor, DRD4 = dopamine D4 receptor, DRD5 = dopamine D5 receptor, 5HTT = serotonin transporter,

[b] significant in males only,

[c] the G × E interaction was significant for DRD5 and oppositional defiant disorder,

[d] the interaction was significant interaction for DAT1 and conduct disorder symptoms and for DRD5 and ODD,

[e] marginally significant,

[f] combined genetic risk.

Table 4

Bivariate heritability with math in twin pairs selected for reading or ADHD symptoms

	MZ pairs[a]			DZ pairs[a]			
		Proband	Co-twin Math		Proband	Co-twin Math	Bivariate
Selected variable	N[b]	M (SD)	M (SD)	N[b]	M (SD)	M (SD)	h^2_g (SE)
Reading	106	−2.00 (0.68)	−1.03 (1.01)	89	−1.99 (0.72)	−0.63 (0.99)	0.40 (0.15)**
Inattention	98	−2.03 (0.58)	−0.75 (1.13)	83	−2.07 (0.59)	−0.28 (1.11)	0.47 (0.15)**
Hyperactivity - impulsivity	85	−2.17 (0.57)	−0.47 (1.18)	65	−2.09 (0.58)	−0.18 (1.21)	0.26 (0.16)

Note.

** P < .01.

[a] Scores are expressed as standard deviations from the estimated population mean. All scores are scaled so that lower scores indicate greater impairment on all measures.

[b] Total number of pairs in which at least one twin met the criteria for the proband group (score at least 1.25 SD below the population mean).