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Generalist Genes and Learning Disabilities

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The authors reviewed recent quantitative genetic research on learning disabilities that led to the conclusion that genetic diagnoses differ from traditional diagnoses in that the effects of relevant genes are largely general rather than specific. This research suggests that most genes associated with common learning disabilities—language impairment, reading disability, and mathematics disability—are generalists in 3 ways. First, genes that affect common learning disabilities are largely the same genes responsible for normal variation in learning abilities. Second, genes that affect any aspect of a learning disability affect other aspects of the disability. Third, genes that affect one learning disability are also likely to affect other learning disabilities. These quantitative genetic findings have far-reaching implications for molecular genetics and neuroscience as well as psychology.

Keywords: genetics, learning disabilities, reading, language, mathematics

Quantitative genetic research in psychology has moved beyond merely demonstrating the widespread importance of genetic influence to ask more interesting questions, including questions about genetic overlap between traits. Although learning disabilities—such as language, reading, and mathematics disabilities—are relative newcomers to quantitative genetic research, this research has already begun to yield interesting results concerning genetic links within and between learning disabilities. Three types of research are relevant: genetic links between learning disabilities and learning abilities, genetic links within learning disabilities (genetic homogeneity), and genetic links between learning disabilities (genetic comorbidity). The purpose of this article is to review research on these three issues, which have not previously been reviewed, and to consider their implications. We use the term *genetic links* to refer to genetic effects that are in common between disabilities or dimensions, including specific quantitative genetic statistics such as genetic correlation, bivariate heritability, and group heritability—statistics explained later.

A few preliminary points should be made. First, our focus on genetic links within and between learning disabilities is not meant to imply that genes are only generalists. Indeed, as we emphasize in several places, this same research provides some of the best available evidence for the importance of genes specific to disabilities. Second, our focus on genetic research is not meant to denigrate the important contribution of environmental factors or the interplay between nature and nurture in the development of learning disabilities. We highlight genetic results because recent research suggests some surprising findings concerning genetic links within and between learning disabilities. Third, our review focuses on common disorders whose origins involve multiple genes and multiple environmental influences—not rare single-gene disorders such as phenylketonuria or chromosomal disorders such as Down's syndrome. In order to focus on these genetic findings, our review assumes some background in quantitative genetics, such as familiarity with the twin method; more background information is available elsewhere (Plomin, DeFries, McClearn, & McGuffin, 2001).

Finally, we acknowledge that strong views are held on the use of appropriate labels for children's low performance, with the pros and cons debated for such labels as challenge, delay, difficulty, disorder, and impairment. We use the word *disability* with its semantic link to the word *ability* because research reviewed in the following section suggests that common learning disabilities are the low end of the normal distribution of learning abilities.

Genetic Links Between Learning Disabilities and Abilities

A crucial issue for understanding learning disabilities is the extent to which the genes that affect learning disabilities also affect normal variation in learning abilities. To the extent that the same genes affect learning disabilities and abilities, this implies that learning disabilities are the quantitative extreme of the same genetic influences that contribute to the normal range of variation in learning abilities. Stated more provocatively, if this were the case, there are no etiologically distinct disabilities; what we call disability is just the low end of the normal distribution of ability.

A method called DeFries–Fulker (DF) extremes analysis (DeFries & Fulker, 1988) can be used to assess genetic links between learning disabilities and abilities. It is necessary to describe this method in some detail because the conclusion that there are genetic links between learning disabilities and abilities depends on it, especially because we extend the usual interpretation of DF extremes analysis. Traditionally, twin data on disabilities are presented as twin concordances in which the phenotype is treated as an affected-versus-unaffected dichotomy. If concordances for identical twins (monozygotic; MZ) are greater than concordances for fraternal twins (dizygotic; DZ), genetic influence is implicated in relation to the diagnostic dichotomy. In contrast, twin data on

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normal variation in abilities are presented as twin correlations, and greater MZ than DZ correlations suggest genetic influence on individual differences in ability. Heritability, a genetic effect size indicator, can be derived from twin concordances for disability and from twin correlations for ability. As shown below, such heritability estimates are substantial both for learning disabilities and abilities (Plomin, 2001a, 2003a). Although it might seem that finding similar heritability estimates for disabilities (as assessed by twin concordances) and abilities (as assessed by twin correlations) indicates genetic links between disabilities and abilities, this is not necessarily the case because completely different genes could be responsible for the heritabilities of disabilities and abilities even if the heritabilities are the same.

DF extremes analysis assesses genetic links between disability and ability by bringing together dichotomous diagnoses of disability and quantitative traits of ability. (The three types of approaches are contrasted in Figure 1.) Rather than assessing twin similarity in terms of individual differences on a quantitative trait of ability (Figure 1a) or in terms of concordance for a diagnostic cutoff (Figure 1b), DF extremes analysis (Figure 1c) assesses twin similarity as the extent to which the mean standardized quantitative trait score of cotwins is as low as the mean standardized score of selected extreme or diagnosed probands. This measure of twin similarity is called a *group twin correlation* (or *transformed cotwin mean*) in DF extremes analysis because it focuses on the mean quantitative trait score of cotwins rather than the individual differences. Genetic influence is implied if group twin correlations are greater for MZ than for DZ twins. Doubling the difference between MZ and DZ group twin correlations estimates the genetic contribution to the average phenotypic difference between the probands and the population. The ratio between this genetic estimate and the phenotypic difference between the probands and the population is called *group heritability*. It should be noted that group heritability does not refer to individual differences among the probands—the question is not why one proband is slightly more disabled than another, but rather why the probands as a group are so much more disabled than the rest of the population.

Although DF extremes group heritability can be estimated by doubling the difference in MZ and DZ group twin correlations (Plomin, 1991), DF extremes analysis is more properly conducted using a regression model (DeFries & Fulker, 1988). The DF extremes model fits standardized scores for MZ and DZ twins to the regression equation, $C = B_1P + B_2R + A$, where C is the predicted score for the cotwin, P is the proband score, R is the coefficient of genetic relatedness (1.0 for MZ twins and .5 for DZ twins), and A is the regression constant. B_1 is the partial regression of the cotwin score on the proband, an index of average MZ and DZ twin resemblance independent of B_2. The focus of DF extremes analysis is on B_2. B_2 is the partial regression of the cotwin score on R independent of B_1. It is equivalent to twice the difference between the means for MZ and DZ cotwins adjusted for differences between MZ and DZ probands. In other words, B_2 is the genetic contribution to the phenotypic mean difference between the probands and the population. Group heritability is esti-

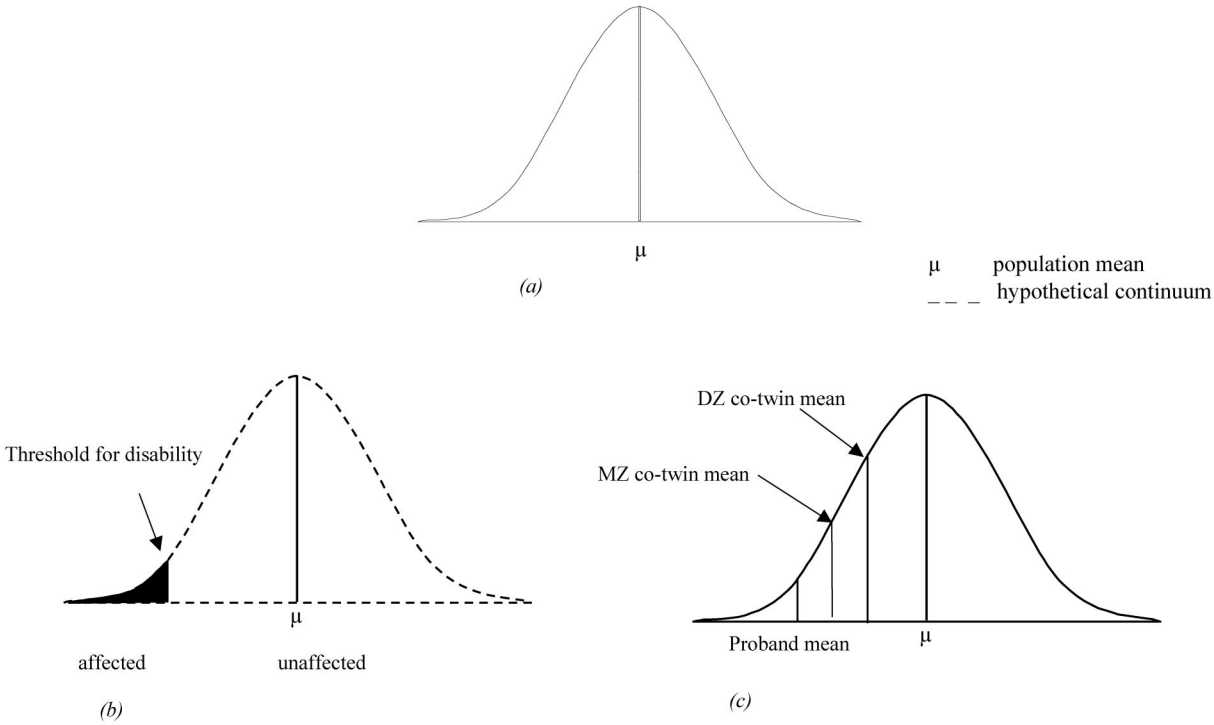

Figure 1. (a) Genetic approaches to disabilities and abilities. (b) Focusing on ability, twin correlations indicate twin similarity for individual differences in the normal range of variation. Focusing on disability, twin concordances (or polychoric correlations based on the liability-threshold model) describe twin similarity based on a dichotomy of affected versus not affected. (c) DF extremes analysis brings together disability and ability with the twin group correlation, an index of the similarity of the mean quantitative trait score of cotwins to the probands. DZ = dizygotic; MZ = monozygotic.

mated by dividing B_2 by the difference between the means for probands and the population.

Finding group heritability implies that disability and ability are both heritable and, most important in the present context, that there are genetic links between the disability and normal variation in the ability. That is, group heritability itself, not the comparison between group heritability and the other estimates of heritability, indicates genetic links between disability and ability. This is not the usual interpretation of group heritability estimated from DF extremes analysis. Group heritability is usually interpreted as the heritability of the extreme score, whereas we are suggesting that group heritability can be interpreted as a bivariate analysis of the relationship between an extreme score and a quantitative trait. If a measure of extremes (or a diagnosis) were not linked genetically to a quantitative trait, group heritability would be zero. For example, using height as an example, if we selected short people as probands and assessed their cotwins on a quantitative measure of height, we would expect that MZ cotwins would be much shorter on average than DZ cotwins, and thus we ought to find substantial group heritability. But suppose someone tricked us and put in an unrelated quantitative trait measure; group heritability would then be zero. In this sense, DF extremes analysis, even in the supposedly univariate case, is actually a bivariate analysis between one measure (an extreme score or diagnosis) and another measure (a quantitative trait score). Even when ostensibly the same measure is used to select extreme probands and to assess quantitative trait scores in cotwins (e.g., height), DF extremes analysis is best considered as a bivariate analysis because the genetic processes that operate at the extreme can differ from those that affect the rest of the distribution. If the genetic processes that operate at the extreme are completely different from those that operate for the rest of the distribution, group heritability will be zero. For example, it is possible that a severe form of learning disability is due to a single-gene disorder that contributes little to normal variation in learning ability. However, as discussed later, most researchers now believe that common disorders are caused by common genetic variants—the common disease/common variant hypothesis (Collins, Euyer, & Chakravarti, 1997)—rather than by a concatenation of rare single-gene disorders. To the extent that the same genes contribute to learning disability and normal variation in learning ability, group heritability can be observed but the magnitude of group heritability depends on the individual heritability for normal variation and the heritability of disability gleaned from concordances for disability.

One more digression is necessary in order to begin to address the strength of the genetic links between learning disabilities and abilities. We have just argued that if group heritability is substantial, disabilities and abilities must be linked genetically. But how strong are the genetic links? For example, group heritability cannot be substantial if the heritability of disability and ability are both low. Because DF extremes analysis brings together dichotomous diagnoses of disability and quantitative traits of ability, we suggest that if disability and ability are strongly linked genetically, group heritability (as estimated by DF extremes analysis) should be intermediate to the heritability of the disability diagnosis (as estimated from twin concordances) and the heritability of the ability dimension (as estimated from twin correlations). If the genetic link between a disability and ability is weak, DF extremes group heritability could be negligible even though the disability and the ability are highly heritable. It is possible to estimate more precisely the strength of the genetic link between disability and normal variation using multivariate genetic techniques as described in the next section. However, we will not describe these methods because they are under development and no data of this type have as yet been reported.

Thus, DF extremes analysis can be used to assess genetic links between disability and ability, although it is not usually viewed in this way. DF extremes analysis also appears similar to the liability-threshold model, which is often used to analyze dichotomous data such as twin concordances (Falconer, 1965; Plomin, 1991; Smith, 1974). However, there is a critical difference: The liability-threshold model assumes a continuous dimension even though it is based on dichotomous data (i.e., disabled or not). The liability-threshold analysis converts dichotomous diagnostic data to polychoric correlations (Smith, 1974) in order to analyze a hypothetical construct of a threshold with an underlying continuous liability. In contrast, DF extremes analysis assesses rather than assumes a continuum. If all of the assumptions of the liability-threshold model are correct for a particular disorder, it will yield results similar to DF extremes analysis to the extent that the quantitative dimension assessed is linked genetically to the qualitative disorder (Plomin, 1991). In the following review of genetic research on learning disabilities and abilities, we tested this assumption by comparing DF extremes group heritability with liability heritabilities calculated from twin concordance data.

Tables 1–3 summarize results from twin studies for language, reading, and mathematics disability and ability, respectively. Because interpretation of the strength of the genetic links between disability and ability requires comparisons between the three types of heritability, each table is divided into three panels: (a) DF extremes analysis, which combines analysis of a dichotomous diagnosis of disability and a continuous dimension of ability to yield group heritability estimates; (b) analysis of dichotomous diagnoses of disability, which yields liability heritability estimates based on polychoric twin correlations derived from twin concordances; and (c) analysis of continuous dimensions of ability, which yields individual differences heritability estimates based on twin correlations. We have reviewed 16 studies that provide enough information to extract all three estimates. Many other studies have been reported, although most involved small samples (e.g., studies of language disability and ability; see Stromswold, 2001). Each panel is divided into results from previous studies and results from our new study, called the Twins Early Development Study (TEDS; Plomin et al., 2001; Trouton, Spinath, & Plomin, 2002) that focuses on the issue of the links between the abnormal and normal. From previous studies, it is difficult to compare the three types of heritability estimates because different samples and different measures were used to investigate learning disabilities and learning abilities. The best way to compare heritabilities for disabilities and abilities is to study an unselected community sample that is large enough to make it possible to select children with disabilities within the same sample and with the same measures used to study abilities. TEDS is the first learning disabilities study of this type. The sampling frame for TEDS was about 7,500 pairs of twins born in the United Kingdom whose parents were contacted from birth records and who participated in a study of cognitive and language development when the twins were 2, 3, 4, and 7 years of age.

In the following review of twin studies of disability and ability, we have not discussed sex differences because neither quantitative

Table 1

Language Disability and Ability: Twin Resemblance and Heritability Estimates for DeFries–Fulker (DF) Extremes Analyses, Dichotomous Diagnoses of Disability, and Continuous Ability Measures

Reference	Age (years)	Measure	Cutoff (%)	Twin resemblance[a]				Heritability estimate[b] (95% CI)
				MZ	*N*/pairs	DZ	*N*/pairs	
DF extremes analysis								
Previous studies								
Bishop et al. (1999)[c]	7–13	Auditory repetition	16	.61	27	.56	21	0.11 (0.00, 0.73)
		Nonword repetition	16	.74	25	.15	22	1.17 (0.55, 1.79)
Tomblin & Buckwalter (1998)[d]	4–16	Composite of language tests	15	.98	43	.76	24	0.45 (0.24, 0.66)
TEDS								
Spinath et al. (2004)[e]	Aggregate (2, 3, 4)	MCDI composite	5	.96	44	.77	37	0.39 (0.15, 0.63)
Viding et al. (2004)[f]	4	Composite of 8 language tests	15	.86	160	.68	131	0.37 (0.15, 0.59)
Dichotomous disability analysis								
Previous studies								
Bishop et al. (1999)[c]	7–13	Auditory repetition	16	.50 (.78)	27	.44 (.72)	21	0.12
		Nonword repetition	16	.61 (.87)	25	.17 (.28)	22	1.18
Tomblin & Buckwalter (1998)[d]	4–16	Composite of language tests	15	.96 (1.00)	43	.69 (.87)	24	0.26
TEDS								
Spinath et al. (2004)[e]	Aggregate (2, 3, 4)	MCDI composite	5	.86 (.99)	44	.52 (.82)	37	0.34
Viding et al. (2004)[f]	4.5 years	Composite of 8 language tests	15	.75 (.92)	160	.54 (.73)	131	0.38
Continuous ability analysis								
Previous studies								
Bishop et al. (1999)[c]	7–13	Auditory repetition		.60	51	.49	49	0.22 (—)
		Nonword repetition	16	.74	25	.15	22	1.17 (0.55–1.79)
Tomblin & Buckwalter (1998)[d]	4–16	Composite of language tests		—	43	—	24	0.48 (0.06, 0.90)
TEDS								
Spinath et al. (2004)[e]	Aggregate (2, 3, 4)	MCDI composite		.96	656	.83	648	0.22 (0.19, 0.27)
Colledge et al. (2002)[g]	4.5 years	Composite of 9 language tests		.66	101	.58	97	0.16 (0.14, 0.64)

Note. MZ = monozygotic; DZ = dizygotic; CI = confidence interval; TEDS = Twins Early Development Study; MCDI = MacArthur Communicative Development Inventory.

[a] Twin resemblance refers to twin group correlations for DF extremes analysis, twin probandwise concordances (tetrachoric correlations in parentheses) for dichotomous disability analysis, and twin intraclass correlations for continuous ability analysis. The twin group correlation is the ratio of the mean cotwin score on the quantitative ability measure to the mean proband score. For example, expressed as standard scores, if the mean cotwin score is −1.0 (i.e., one standard deviation below the mean) and the mean proband score is −2.0, the twin group correlation is 0.5. For the dichotomous disability analysis, we report twin probandwise concordance (the number of probands in concordant pairs divided by the total number of probands), which is more appropriate than pairwise concordance (number of concordant pairs divided by the total number of pairs) when both members of the twin pair can be ascertained. For example, in a study in which 30 of 100 pairs of twins are concordant, pairwise concordance is 30% (30/100), whereas probandwise concordance is 46% (60 probands in concordant pairs divided by 130, the total number of probands). Twin probandwise concordance indicates the risk that a cotwin of a proband is affected. Tetrachoric correlations were calculated using a model-fitting program (Mx). Contingency tables representing concordant and discordant affected and unaffected pairs were derived from published twin probandwise concordances (or number of probands) and total numbers of pairs with at least one affected member. The numbers of pairs in the two discordant cells were obtained by equally dividing the total discordant number between them. The number of pairs in the unaffected concordant cell was estimated from the population prevalence of the disability as defined in each population-based study, usually a cutoff percentage. The threshold was obtained from the approximate population prevalence of the disability as reported in the literature. For the DF extremes analysis and the dichotomous disability analysis, *N*/pairs refers to the number of pairs with at least one proband. For continuous ability analysis, the twin intraclass correlation represents the ratio of the variance between pairs to the total variance (Shrout & Fleiss, 1979). The twin correlation is intraclass rather than the usual Pearson interclass correlation because members of a twin pair do not represent two separate classes (variables). The intraclass correlation is equivalent to the average interclass correlation for all possible pairings of twins. It can be estimated accurately by entering twins in a double-entry format in which Twin B follows Twin A for one class and Twin A follows Twin B for the other class, which guarantees equal means and variances for the two classes. Dashes indicate that relevant data are not available in the published report.

[b] The heritability estimate refers to group heritability for DF extremes analysis, liability heritability for dichotomous disability analysis, and individual differences heritability for continuous ability analysis. CIs for heritability estimates are presented in parentheses (dashes indicate that CIs are not available from the published data). Liability heritability estimates were obtained from tetrachoric correlations which were calculated using Mx. Because these were derived from published results, 95% CIs are not available for the liability heritability estimates. CIs for the tetrachoric correlations are presented in footnotes for each study.

[c] Probands were selected on the basis of low performance on at least one of four language measures. The following two tests were examined in relation to language ability and disability: Tallal's Auditory Repetition Test assesses detection, association, discrimination, sequencing, and serial memory; the Children's Nonword Repetition Test is a measure of phonological short-term memory. For the tetrachoric correlations, the threshold was estimated from the approximate population prevalence of specific language impairment (7%) reported in Leonard (1998). Tetrachoric correlations and 95% CIs were 0.78 (0.53, 0.91) for MZs and 0.72 (0.39, 0.90) for DZs for auditory repetition, and 0.87 (0.68, 0.96) for MZs and 0.28 (−0.19, 0.68) for DZs for nonword repetition.

[d] *N*/pairs refer to twinships rather than twin pairs as 3 sets of triplets were included in the analysis (resulting in five twin comparisons). For individual differences heritability, twin correlations were not reported; heritability was estimated using an augmented multiple regression model (DeFries & Fulker, 1988). Tetrachoric correlations and 95% CIs were 1.00 (0.99, 1.00) for MZs and 0.87 (0.66, 0.96) for DZs.

[e] Average *N*-weighted results for male and female pairs, excluding results for opposite-sex pairs are presented here. Verbal performance was assessed using age-appropriate vocabulary and grammar scales from the MCDI—U.K. Short Form, the abbreviated and anglicized adaptation of the MCDI. Combined vocabulary and grammar scores were used in the analyses. Only the results of the aggregate score based on scores across 2, 3, and 4 years of age are presented here; all scores had high age-to-age correlations. For the extremes analyses, only the results from the 5% cutoff are presented here. Similar results were obtained at the 10% cutoff. Tetrachoric correlations and 95% confidence intervals were 0.99 (0.97, 1.00) for MZs and 0.82 (0.66, 0.92) for DZs.

[f] The nine measures included in the composite assessed such diverse aspects of language as vocabulary, syntax, phonology, and articulation. Different cutoffs reported in the study showed similar results, although 5% and especially 1% cutoffs tended to yield even greater estimates of group heritability (h^2_g). Tetrachoric correlations and 95% confidence intervals were 0.92 (0.88, 0.95) for MZs and 0.73 (0.62, 0.82) for DZs.

[g] Results reported here for same-sex pairs only. The published model-fitting estimate of individual differences heritability is greater because opposite-sex twins were included in the model-fitting analysis. The nine measures assessed diverse aspects of language such as vocabulary, syntax, phonology, and articulation.

Table 2
Reading Disability and Ability: Twin Resemblance and Heritability Estimates for DeFries–Fuller (DF) Extremes Analysis, Dichotomous Diagnoses of Disability, and Continuous Ability Measures

Reference	Age (years)	Measure	Cutoff (%)	Twin resemblance[a]				Heritability estimate[b] (95% CI)
				MZ	*N*/pairs	DZ	*N*/pairs	
DF extremes analysis								
Previous studies								
Stevenson (1991)[c]	13	Schonell-graded word reading	10	.48	23	.46	42	0.03 (0.00, 0.76)
		Schonell-graded word spelling	10	.70	19	.47	43	0.47 (0.00, 1.12)
Light & DeFries (1995)[d]	8–20	PIAT composite	—[d]	.92	148	.66	111	0.52 (0.32, 0.72)
TEDS								
Harlaar, Dale, & Plomin (2005)	7	TOWRE	10	.90	308	.60	246	0.60 (0.32, 0.86)
Dichotomous disability analysis								
Previous studies								
Stevenson, Graham, Fredman, & McLoughlin (1987)[f]	13	Neale reading	—[f]	.33 (.59)	15	.29 (.29)	30	0.60
		Schonell-graded word reading		.35 (.62)	14	.31 (.36)	27	0.52
		Schonell-graded word spelling		.50 (.72)	18	.33 (.36)	30	0.72
Light & DeFries (1995)[d]	8–20	PIAT composite	—[d]	.68 (.91)	148	.40 (.68)	111	0.46
TEDS								
Harlaar et al. (in press)[e]	7	TOWRE	10	.72 (.92)	308	.45 (.67)	246	0.50

Table 2 (*continued*)

Reference	Age (years)	Measure	Cutoff (%)	Twin resemblance[a]				Heritability estimate[b] (95% CI)
				MZ	*N*/pairs	DZ	*N*/pairs	
			Continuous ability analysis					
Previous studies								
Stevenson et al. (1987)[f]	13	Neale accuracy reading		.62	97	.53	107	0.18
		Neale comprehension reading		.71	97	.49	107	0.44
		Schonell-graded word reading		.61	97	.51	107	0.19
		Schonell-graded word spelling		.76	97	.50	107	0.53
Light et al. (1998)[g]	8–20	Composite of PIAT reading and spelling subtests			132		91	0.42
TEDS								
Harlaar et al. (in press)[e]	7	TOWRE		.85	1,396	.50	1,298	0.70 (0.55, 0.79)

Note. MZ = monozygotic; DZ = dizygotic; CI = confidence interval; PIAT = Peabody Individual Achievement Test; TEDS = Twins Early Development Study; TOWRE = Test of Word Reading Efficiency.

[a] Twin resemblance refers to twin group correlations for DF extremes analysis, twin probandwise concordances (tetrachoric correlations in parentheses) for dichotomous disability analysis, and twin intraclass correlations for continuous ability analysis. The twin group correlation is the ratio of the mean cotwin score on the quantitative ability measure to the mean proband score. For example, expressed as standard scores, if the mean cotwin score is −1.0 (i.e., one standard deviation below the mean) and the mean proband score is −2.0, the twin group correlation is 0.5. For the dichotomous disability analysis, we report twin probandwise concordance (the number of probands in concordant pairs divided by the total number of probands), which is more appropriate than pairwise concordance (number of concordant pairs divided by the total number of pairs) when both members of the twin pair can be ascertained. For example, in a study in which 30 of 100 pairs of twins are concordant, pairwise concordance is 30% (30/100), whereas probandwise concordance is 46% (60 probands in concordant pairs divided by 130, the total number of probands). Twin probandwise concordance indicates the risk that a cotwin of a proband is affected. Tetrachoric correlations were calculated using a model-fitting program (Mx). Contingency tables representing concordant and discordant affected and unaffected pairs were derived from published twin probandwise concordances (or number of probands) and total numbers of pairs with at least one affected member. The numbers of pairs in the two discordant cells were obtained by equally dividing the total discordant number between them. The number of pairs in the unaffected concordant cell was estimated from the population prevalence of the disability as defined in each population-based study, usually a cutoff percentage. The threshold was obtained from the approximate population prevalence of the disability as reported in the literature. For the DF extremes analysis and the dichotomous disability analysis, *N*/pairs refers to the number of pairs with at least one proband. For continuous ability analysis, the twin intraclass correlation represents the ratio of the variance between pairs to the total variance (Shrout & Fleiss, 1979). The twin correlation is intraclass rather than the usual Pearson interclass correlation because members of a twin pair do not represent two separate classes (variables). The intraclass correlation is equivalent to the average interclass correlation for all possible pairings of twins. It can be estimated accurately by entering twins in a double-entry format in which Twin B follows Twin A for one class and Twin A follows Twin B for the other class, which guarantees equal means and variances for the two classes.

[b] The heritability estimate refers to group heritability for DF extremes analysis, liability heritability for dichotomous disability analysis, and individual differences heritability for continuous ability analysis. Liability heritability estimates were obtained from tetrachoric correlations which were calculated using Mx. See Table 1 for details.

[c] Only the results from the two measures that were also analyzed in the study of individual differences in the same sample (Stevenson et al., 1987) are presented here. Only results from a 10% cutoff without IQ controlled are presented here; changing the severity of the cutoff did not substantially change the results.

[d] School records were used initially to select twins in which at least one twin in each pair had a history of reading disability. This sample was then assessed on a battery of tests of reading and spelling abilities. Scores were transformed into a composite discriminant function reading score. Reading disability (proband status) was defined as follows: (a) a positive history of reading problems in school, (b) a negative discriminant reading score, (c) a Verbal or Performance IQ of at least 90, (d) no evidence of neurological or severe emotional problems, and (e) no uncorrected visual or auditory acuity deficits. The threshold was defined as 1.5 standard deviation of the control sample, which is consistent with the approximate population prevalence of reading disability of 6% (e.g., Mazzocco & Myers, 2003). Tetrachoric correlations and 95% CIs were 0.91 (0.87, 0.95) for MZs and 0.68 (0.54, 0.79) for DZs.

[e] Published results are presented separately for males and females. We report results for the total sample for same-sex twins only. Similar results were obtained at the 5% cutoff. The threshold was defined in the study as 10% of the sample (*SD* = 1.28). Tetrachoric correlations and 95% CIs were 0.92 (0.88, 0.95) for MZs and 0.67 (0.58, 0.76) for DZs.

[f] Two different measures of reading and spelling disability were used in the study: *backwardness* (the presence of reading/spelling age below chronological age) and *retardation* (marked underachievement in reading accuracy or comprehension/spelling in relation to that predicted from IQ and chronological age). The criterion for disability of 18 months below prediction was used in the study. The results from the two measures of disability were similar. Only the retardation results are presented here. Tetrachoric correlations and 95% CIs were 0.59 (0.10, 0.87) for MZs and 0.29 (−0.09, 0.61) for DZs for Neale reading; 0.72 (0.37, 0.91) for MZs and 0.36 (−0.01,0.67) for DZs for Schonell-graded word spelling.

[g] The study reports results from two different samples (control and reading disability); only the results from the control sample are presented here. The control sample consisted of pairs of twins in which neither twin had learning difficulties (school records) matched when possible with the reading disability sample. The study reports the results from fitting structural equation models, and only heritability estimates for the composite reading and math variable are presented here. Twin correlations were not reported in the study.

Table 3
Mathematics Disability and Ability: Twin Resemblance and Heritability Estimates for DeFries–Fulker (DF) Extremes Analysis, Dichotomous Diagnoses of Disability, and Continuous Ability Measures

Reference	Age (years)	Measure	Cutoff (%)	Twin resemblance[a] MZ	*N*/pairs	DZ	*N*/pairs	Heritability estimate[b] (95% CI)
DF extremes analysis								
Previous studies								
Alarcón et al. (1997)[c]	8–20	Composite of WRAT and PIAT	6.7	.96	40	.77	23	0.38 (0.03, 0.73)
TEDS								
Oliver et al. (2004)[d]	7	Composite of teacher assessments	15	.72	171	.40	198	0.65 (0.41, 0.89)
Dichotomous disability analysis								
Previous studies								
Alarcón et al. (1997)[c]	8–20	Composite of WRAT and PIAT	6.7	.73 (.94)	40	.56 (.83)	23	0.22
TEDS								
Oliver et al. (2004)[d]	7	Composite of teacher assessments	15	.67 (.86)	171	.44 (.59)	198	0.54
Continuous ability analysis								
Previous studies								
Knopik & DeFries (1999)	8–20	Composite of WRAT, WISC-R or WAIS-R, and PIAT		—	220	—	135	0.67 (—)
TEDS								
Oliver et al. (2004)[d]	7	Composite of teacher assessments		.74	1,044	.43	957	0.62 (0.56, 0.77)

Note. MZ = monozygotic; DZ = dizygotic; CI = confidence interval; WRAT = Wide Range Achievement Test; PIAT = Peabody Individual Achievement Test; TEDS = Twins Early Development Study; WISC-R = Wechsler Intelligence Scale for Children—Revised; WAIS-R = Wechsler Adult Intelligence Scale—Revised.

[a] Twin resemblance refers to twin group correlations for DF extremes analysis, twin probandwise concordances (tetrachoric correlations in parentheses) for dichotomous disability analysis, and twin intraclass correlations for continuous ability analysis. The twin group correlation is the ratio of the mean cotwin score on the quantitative ability measure to the mean proband score. For example, expressed as standard scores, if the mean cotwin score is −1.0 (i.e., one standard deviation below the mean) and the mean proband score is −2.0, the twin group correlation is 0.5. For the dichotomous disability analysis, we report twin probandwise concordance (the number of probands in concordant pairs divided by the total number of probands), which is more appropriate than pairwise concordance (number of concordant pairs divided by the total number of pairs) when both members of the twin pair can be ascertained. For example, in a study in which 30 of 100 pairs of twins are concordant, pairwise concordance is 30% (30/100), whereas probandwise concordance is 46% (60 probands in concordant pairs divided by 130, the total number of probands). Twin probandwise concordance indicates the risk that a cotwin of a proband is affected. Tetrachoric correlations were calculated using a model-fitting program (Mx). Contingency tables representing concordant and discordant affected and unaffected pairs were derived from published twin probandwise concordances (or number of probands) and total numbers of pairs with at least one affected member. The numbers of pairs in the two discordant cells were obtained by equally dividing the total discordant number between them. The number of pairs in the unaffected concordant cell was estimated from the population prevalence of the disability as defined in each population-based study, usually a cutoff percentage. The threshold was obtained from the approximate population prevalence of the disability as reported in the literature. For the DF extremes analysis and the dichotomous disability analysis, *N*/pairs refers to the number of pairs with at least one proband. For continuous ability analysis, the twin intraclass correlation represents the ratio of the variance between pairs to the total variance (Shrout & Fleiss, 1979). The twin correlation is intraclass rather than the usual Pearson interclass correlation because members of a twin pair do not represent two separate classes (variables). The intraclass correlation is equivalent to the average interclass correlation for all possible pairings of twins. It can be estimated accurately by entering twins in a double-entry format in which Twin B follows Twin A for one class and Twin A follows Twin B for the other class, which guarantees equal means and variances for the two classes. Dashes indicate that relevant data are not available in the published report.

[b] The heritability estimate refers to group heritability for DF extremes analysis, liability heritability for dichotomous disability analysis, and individual differences heritability for continuous ability analysis. Liability heritability estimates were obtained from tetrachoric correlations which were calculated using Mx. See Table 1 for details.

[c] The results reported here are for the combined sample, including math disability with and without reading disability; the paper also reports the results for the two subsamples separately. The threshold was defined as 1.5 standard deviation of the control sample, which is consistent with the approximate population prevalence of mathematic disability of 6% reported by Mazzocco and Myers (2003). Tetrachoric correlations and 95% CIs were 0.94 (0.86, 0.98) for MZs and 0.83 (0.61, 0.95) for DZs.

[d] Published results include three measures (using and applying; numbers; shapes, spaces, and measures) but we report results only for a composite of the three measures. The data in this study were teachers' assessments of academic achievement in three areas of mathematics based on U.K. National Curriculum criteria for Key Stage 1. The data were also analyzed separately for the members of a twin pair measured by the same or different teacher. Although twin concordances and correlations were lower when the children were assessed by different teachers, this applied to both MZ and DZ twins, so the heritability estimates obtained from these data were only slightly lower for the children assessed by the different teacher (the shared environment estimates were greater in the group assessed by the same teacher). Only the averages for the entire sample are presented here. The threshold was defined in the study as 15% of the sample (SD = 1.03). Tetrachoric correlations and 95% CIs were 0.86 (0.80, 0.90) for MZs and 0.59 (0.47, 0.69) for DZs.

nor qualitative sex differences have been found in previous research. That is, studies such as TEDS and the Colorado study of reading that are large enough to provide adequate power to detect differences in genetic influences for boys and girls find little evidence of sex differences in genetic or environmental parameter estimates (e.g., Wadsworth, Knopik, & DeFries, 2004). Also, studies such as TEDS and the Colorado study that include opposite sex twins to assess genetic correlations between boys and girls find

little evidence for such qualitative sex differences (e.g., Knopik, Alarcón, & DeFries, 1998; Viding et al., 2004).

Language Disability and Ability

Table 1 summarizes twin studies of language disability and ability. Only two previous studies have been reported totaling 70 MZ pairs and 46 DZ pairs (Bishop et al., 1999; Tomblin & Buckwalter, 1998). As a result of the small sample sizes, 95% confidence intervals (in parentheses) for the group heritability estimates are large and results are variable but suggest a moderate average estimate for DF extremes group heritability (see Table 1, top panel). For dichotomous diagnoses of language disability (see Table 1, middle panel), the average twin concordances of 76% for MZ twins and 50% for DZ twins also suggest moderate genetic influence for dichotomous diagnoses of language disability, which is confirmed by the average liability heritability estimate. For individual differences heritability (see Table 1, bottom panel), these two studies suggest an average estimate of .47 for language ability. Despite the small sample sizes and use of different measures, the results from these previous two twin studies of language disability suggest that DF extremes group heritability is similar to liability heritability of disability and individual differences heritability of ability, suggesting strong genetic links between language disability and ability.

In TEDS, twins were assessed for vocabulary and grammar at 2, 3, and 4 years using the MacArthur Communicative Development Inventory (MCDI), a parental rating instrument (Fenson et al., 2000). A composite language measure yielded a DF extremes group heritability estimate of .39 using a 5% cutoff (see Table 1, top panel), which suggests at least moderate links between disability and ability (Spinath, Price, Dale, & Plomin, 2004). Using the same measure and the same sampling frame, the DF extremes group heritability estimate is similar to the estimate of .34 for liability heritability (see Table 1, middle panel) based on concordances for dichotomous diagnoses (5% cutoff). These heritability estimates are also roughly similar to the estimate of individual differences heritability (.22, see Table 1, bottom panel) based on twin correlations for the entire sample. These findings suggest that to the extent that genetic influence affects language in early childhood, genetic overlap between disability and ability is substantial.

TEDS also conducted in-home tests of language at 4.5 years for low-language children and controls selected initially on the basis of their MCDI scores at 4 years. Eight hundred pairs of twins were assessed in their homes on eight language measures, which yielded a general factor that accounted for 41% of the total variance (Colledge et al., 2002). A composite measure representing this general language factor was used to select 579 children in 160 MZ twin pairs and 131 same-sex DZ twin pairs who were below the 15th percentile of a control group (Viding et al., 2004). DF extremes analysis for the composite language measure yielded a group heritability estimate of .37, which is similar to the liability heritability estimate of .38. The individual differences heritability estimate is .16 based on 101 MZ and 97 DZ control twin pairs. Although we report the results for a 15% cutoff in Table 1 in order to make the results more comparable with previous studies, we also examined results for more stringent cutoffs, such as 7%, 2%, and 0.1%. The results suggested increasing group heritability for more extreme cutoffs: .37, .42, .48, and .76, respectively, for 15%, 7%, 2%, and 0.1% cutoffs (Viding et al., 2004). However, caution is warranted because the sample sizes are small, as more extreme cutoffs are used to select probands so that a few extreme cases could determine the result. If this trend is true, it would suggest that genetic factors play a larger role for more severe language impairment or that environmental factors become overwhelmed as the genetic risk becomes stronger. In the present context, this result would suggest that genetic links between language disabilities and abilities are even stronger for more severe language disability, although it should be noted that TEDS is a community sample and is unlikely to include extremely severe language disorders.

In summary, in previous studies as well as in TEDS, group heritability is substantial, which suggests genetic links between language disability and ability. Moreover, group heritability is similar to liability heritability of language disability and is as great or greater than individual differences heritability of language ability. These results suggest strong genetic links between language disability and ability.

Reading Disability and Ability

Table 2 summarizes results for reading disability and ability for previous reports from two studies (Light & DeFries, 1995; Light, DeFries, & Olson, 1998; Stevenson, 1991; Stevenson, Graham, Fredman, & McLoughlin, 1987) that permit estimates of the three types of heritability, but not for other studies that estimate only one type of heritability (Bakwin, 1973; Matheny, Dolan, & Wilson, 1976). The major twin study is from Colorado (DeFries & Gillis, 1993; Willcutt et al., 2003). DF extremes analysis, which was devised initially for the specific purpose of analyzing data from this study (DeFries & Fulker, 1988), estimated group heritability as .52 (Light & DeFries, 1995), as shown in the top panel of Table 2. Twin concordances were 68% for MZ twins and 40% for DZ twins, which yields a liability heritability estimate of .46 (see Table 2, middle panel). The Colorado study also included a control group, which yielded an individual differences heritability of .42 (Light, DeFries, & Olson, 1998). A review of five twin studies of individual differences in various measures of reading ability in childhood yielded an average individual differences heritability estimate of .41 (Stromswold, 2001). An earlier twin study yielded an average heritability of .33, although the results are mixed across measures which is to be expected given the relatively small sample size (Stevenson, 1991; Stevenson, Graham, Fredman, & McLoughlin, 1987).

In TEDS, reading was assessed toward the end of the 2nd year of school, when the children were 7 years old, using the Test of Word Reading Efficiency (TOWRE; Torgesen, Wagner, & Rashotte, 1999), which was administered by telephone (Harlaar, Spinath, Dale, & Plomin, 2005). DF extremes group heritability is .60, which is in between the estimates of liability heritability (.50) and individual differences heritability (.70) from this same study. When the same children were assessed for reading by their teachers on the basis of criteria from the U.K. National Curriculum, the results were very similar.

In summary, results for reading are similar to those for language in showing substantial group heritability, which suggests genetic links between reading disability and ability. Also similar to the results for language, group heritability is similar to liability heritability and individual differences heritability, suggesting that the genetic links between disability and ability are strong.

Mathematics Disability and Ability

Only one twin study has been published regarding mathematics disability, which estimated DF extremes group heritability of .38 (Alarcón, DeFries, Light, & Pennington, 1997; see Table 3). Liability heritability estimated from the twin concordances is .22; individual differences heritability in a control sample was .67 (Knopik & DeFries, 1999). Thus, the DF group heritability estimate is in between those of liability heritability and individual differences heritability.

In TEDS, mathematics was assessed by teachers using criteria from the U.K. National Curriculum (Oliver et al., 2004). Group heritability is substantial (.65) and similar to liability heritability and individual differences heritability (.54 and .62, respectively; Oliver et al., 2004). Thus, the results from TEDS support the hypothesis that disability is linked genetically to ability.

Summary and Quantitative Trait Locus (QTL) Model

In summary, DF extremes analysis generally shows substantial group heritability for language, reading, and mathematics. These findings indicate genetic links between disability and ability. Moreover, group heritability of disability is intermediate to liability heritability of disability and individual differences heritability of ability, which suggests that genetic influences on disability largely overlap with genetic influences on ability. These findings suggest that common disabilities are merely the low end of the same genetic influences that affect abilities. That is, the abnormal is normal.

This quantitative genetic research has a clear implication for molecular genetic research: When a gene is found that is associated with a learning disability, the same gene can be expected to be associated with variation in the normal range of ability. This prediction is compatible with a major shift in molecular genetic research. Until the past decade, molecular genetic research focused on identifying genes responsible for single-gene disorders in which mutations in a single gene are necessary and sufficient to cause a disorder. For single-gene disorders, the abnormal is not normal—such disorders are etiologically distinct from normality. Although there are thousands of single-gene disorders, they are rare, with typical frequencies of .0001 or less (King, Motulsky, & Rotter, 2002). In contrast, learning disabilities are much more common, with frequencies greater than .01. It is now generally accepted that genetic influence on common disorders is caused by multiple genes of small effect size rather than a single gene of major effect size (Plomin, Owen, & McGuffin, 1994). These multiple-gene effects are known as quantitative trait loci (QTLs) because they produce a quantitative continuum of genetic effects even if the trait is assessed as a dichotomous diagnosis. In other words, the QTL model posits that the abnormal is normal in that the genes responsible for disorders are the same genes responsible for normal variation.

The research reviewed in this section thus supports the QTL model for common learning disabilities. The ultimate proof of the hypothesis that the abnormal is normal will come when QTLs identified for learning disabilities are found to be associated with the normal range of variation in abilities and vice versa. We return to this issue later in the section on DNA, which includes concrete examples of single-gene and QTL influences on learning disabilities.

Genetic Homogeneity Within Learning Disabilities and Abilities

The previous section described research using DF extremes analysis that indicates strong genetic links between learning disabilities and abilities. Two other types of research broach the issue of the generality of genetic effects on learning disabilities more directly by investigating the extent to which the same genes operate within a disability and between disabilities. That is, within a disability, to what extent do the same genes influence different components of the disability? Although this issue is usually referred to as *genetic heterogeneity,* which reflects the hope that genetically distinct components or subtypes will be found within a disability, it could just as well be called *genetic homogeneity* in the sense of assessing the extent to which the same genes influence different aspects of a disability. The other category of research addresses genetic links between disabilities and is called *genetic comorbidity*.

These issues of genetic homogeneity and comorbidity in research on learning disabilities and abilities can be addressed using multivariate genetic analysis. In contrast to univariate quantitative genetic analysis that decomposes the variance of a single trait into genetic and environmental sources of variance, multivariate genetic analysis decomposes the covariance between traits into genetic and environmental sources of covariance (Martin & Eaves, 1977). In other words, multivariate genetic analysis assesses genetic and environmental factors responsible for the phenotypic correlation between two traits. If the same genes affect different traits, a correlation will be observed between the traits. One of the genetic causes of correlation is that the same genes influence both traits, an effect called *pleiotropy*. The key concept in the present context is the genetic correlation, which indicates the extent to which genetic effects on trait *X* correlate with genetic effects on trait *Y* regardless of the heritabilities of *X* and *Y*. The genetic correlation, which is described in greater detail below, can be considered as the probability that a gene found to be associated with *X* will also be associated with *Y*. It should be noted that multivariate genetic analysis is completely different conceptually from the comparison between the heritabilities of two traits, which involve univariate genetic analyses of the variance of each trait considered separately. Highly heritable traits might show no genetic overlap, and modestly heritable traits might show complete genetic overlap. Genetic overlap can only be evaluated by means of multivariate genetic analysis.

Although multivariate genetic analysis can be used to analyze genetic overlap at the extremes of disability as discussed below, multivariate genetic research has primarily analyzed normal covariation in unselected samples using the standard multivariate extension of univariate quantitative genetic analysis (Martin & Eaves, 1977), shown in Figure 2. Such multivariate genetic analyses of normal variation in abilities are relevant to the investigation of disabilities if, as the previous section strongly suggests, disabilities are merely the quantitative extreme of the same genetic and environmental factors that operate throughout the continuum. For twin studies, multivariate genetic analysis is based on cross-trait twin correlations for two or more traits. That is, one twin's *X* is correlated with the cotwin's *Y*. The phenotypic covariance between two traits is attributed to their genetic overlap to the extent that the MZ cross-trait twin correlation exceeds the DZ cross-trait twin correlation. The proportion of the phenotypic co-

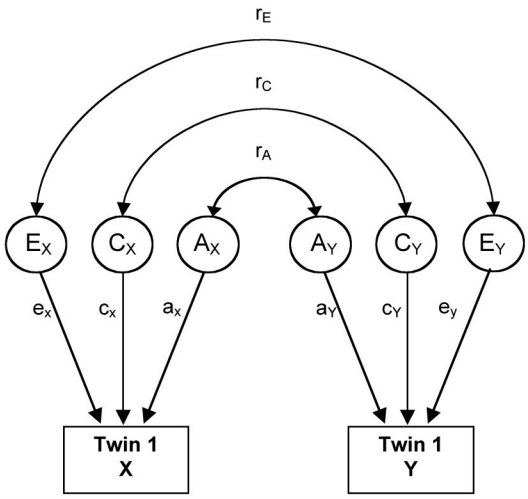

Figure 2. Correlated factors model for individual differences trait *X* and trait *Y* in one individual from a twin pair. Though not illustrated here, there are genetic and shared environmental correlations between the two members of a pair for both *X* and *Y* scores. Variance in each trait is divided into that due to latent additive genetic influences (*A*), shared environmental influences (*C*), and nonshared environmental influences (*E*) with the subscripts *x* and *y* to denote scores on traits *X* and *Y*, respectively. Paths, represented by lower case (*a*, *c*, and *e*), are the standardized regression coefficients and are squared to estimate the proportion of variance accounted for. Correlations between the latent genetic, shared environmental, and nonshared environmental influences are denoted by r_A, r_C, and r_E.

variance between *X* and *Y* attributed to genetic covariance between *X* and *Y* is called *bivariate heritability* (Plomin & DeFries, 1979).

As shown in Figure 2, the genetic contribution to the phenotypic covariance is the product of the square root of the heritability of *X* (a_x), the heritability of *Y* (a_y), and the *genetic correlation* (r_A) between *X* and *Y*. Because the heritabilities of *X* and *Y* are known, the genetic correlation can be extracted from this estimate of the genetic contribution to the phenotypic covariance (i.e., $a_x a_y r_A$). As mentioned earlier, the genetic correlation is the key concept in the present context because it indicates the extent to which genetic effects on *X* correlate with genetic effects on *Y* independent of the heritabilities of *X* and *Y*. A genetic correlation of 1.0 means that the same genes affect *X* and *Y* regardless of the heritabilities of *X* and *Y*, and a genetic correlation of 0.0 means that completely different genes affect *X* and *Y*. Roughly speaking, the genetic correlation can be viewed as a probability that when a gene is found to be associated with *X*, it will also be associated with *Y*. The genetic correlation thus provides evidence not only for generalist genes but also for genetic effects specific to a disability or ability. To the extent that the genetic correlation is less than 1.0, it suggests that there are genes that affect *X* but not *Y*.

Although few multivariate genetic analyses have as yet been reported for the extremes of learning disabilities, twin cross-concordance rates for MZ and DZ twins can be used to assess the etiology of homogeneity and comorbidity. A twin pair is cross-concordant if Twin 1 manifests disability *X* and Twin 2 manifests disability *Y*. As mentioned in the previous section on univariate analyses, twin concordance data can be converted to polychoric correlations using the liability-threshold model. Similarly, in multivariate analysis, cross-trait twin concordance data between symptom *X* and symptom *Y* within a disability (to test for genetic homogeneity) and between disability *X* and disability *Y* (to test for genetic comorbidity) can be converted to polychoric cross-trait twin correlations and analyzed with the same multivariate genetic model used to analyze normal variation in unselected samples.

DF extremes analysis has also been extended to bivariate analysis (Light & DeFries, 1995). Rather than selecting probands as extreme on *X* and comparing the quantitative scores of their MZ and DZ cotwins on *X*, as in univariate DF extremes analyses, bivariate DF extremes analysis selects probands on *X* and compares the quantitative scores of their cotwins on *Y*, a cross-trait twin group correlation. The genetic contribution to the phenotypic difference between the means of the probands on trait *X* and the population on *Y* is estimated by doubling the difference between the cross-trait twin group correlations for MZ and DZ twins. *Bivariate group heritability* is the ratio between this genetic estimate and the phenotypic difference between the probands on trait *X* and the population on *Y*. As in univariate DF extremes analysis, bivariate DF extremes analysis brings together disability and ability by analyzing the relationship between probands with extreme scores on *X* and normal variation in cotwins on *Y*. Unlike multivariate genetic analysis of normal variation or multivariate liability-threshold analysis of concordance, bivariate DF extremes analysis is directional in the sense that selecting probands on *X* and examining quantitative scores of cotwins on *Y* could yield different results compared with selecting probands on *Y* and examining quantitative scores of cotwins on *X*. A group genetic correlation can be derived from four group parameter estimates: bivariate group heritability estimated by selecting probands for *X* and assessing cotwins on *Y*, bivariate group heritability estimated by selecting probands for *Y* and assessing cotwins on *X*, and univariate group heritability estimates for *X* and for *Y* (see Knopik, Alarcón, & DeFries, 1997).

In this section and in the next, we report multivariate genetic analyses of these three types (multivariate genetic analyses of normal variation in ability, multivariate genetic analysis of dichotomous disabilities, and bivariate DF extremes analysis), although most research involves the first type of analysis. We highlighted estimates of genetic correlation because the genetic correlation directly assesses genetic overlap within and between disabilities and abilities. It should be emphasized that confidence intervals surrounding estimates of genetic correlation can be large; we report confidence intervals when available. Although several studies are not nearly large enough to provide adequate power to estimate genetic correlations, we have shown that the results are surprisingly consistent in pointing to substantial genetic correlations within and between disabilities and abilities. The present section focuses on multivariate genetic analyses of components within disabilities and abilities (genetic homogeneity), and the next section considers analyses across disabilities and abilities (genetic comorbidity). We reviewed all available multivariate genetic analyses, but our review is, of course, limited to the particular measures included in these published studies; much room is available for future studies using other measures that might be better motivated by cognitive theory.

Language Disability and Ability

Traditional linguistic accounts of language development have emphasized a discontinuity between grammar and lexicon (Pinker,

1994). However, subsequent empirical studies found substantial correlations between grammar and vocabulary (Fenson et al., 1994). Recent linguistic theories have assumed that there is a greater interdependence between grammar and lexicon (Bates & Goodman, 1997; Tomasello, 2003); phonological processes are now thought to be central to this interdependence (Chiat, 2001; Morgan & Demuth, 1996).

As summarized in the top panel of Table 4, we are aware of only one multivariate genetic study of genetic homogeneity within language development other than studies involving TEDS twins. The first reported study was a small twin study suggesting very substantial genetic correlations between a phonological awareness factor and a general language factor (Hohnen & Stevenson, 1999). In TEDS, genetic links were investigated between parent-assessed vocabulary and grammar at 2 years for nearly 2,000 pairs of twins (Dale, Dionne, Eley, & Plomin, 2000). The genetic correlation was estimated as .61, suggesting that genetic effects on vocabulary and grammatical ability overlap substantially. Similar results were

Table 4
Genetic Homogeneity: Genetic Correlations Within Language, Reading, and Mathematics Learning Disabilities and Abilities

Reference	Age (years)	Measures	Unselected (U) or extremes (E)	*N*/pairs MZ	*N*/pairs DZ	Genetic correlations (95% CI)
		Language ability and disability				
Previous studies						
Hohnen & Stevenson (1999)	6 and 7	Phonological Awareness factor (phoneme blending, sound categorization and phoneme deletion) vs. General Language factor (grammar and vocabulary)	U	67	60	1.00[a] (6 years); .90[a] (7 years)
TEDS						
Dale et al. (2000)	2	MCDI vocabulary vs. MCDI grammar	U	1,008	959	0.61 (—)
Dionne et al. (2003)	3	MCDI vocabulary vs. MCDI grammar				
		1994 birth cohort	U	771	734	0.89 (0.74, 0.99)
		1995 birth cohort	U	502	547	0.63 (0.49, 0.77)
Hayiou-Thomas et al. (2004)	4.5	7 language (lexical and grammatical) measures (average)	U	281	275	0.61 (—)
		2 articulation measures	U	281	275	0.89 (0.69, 1.00)
		Latent factors of language vs. articulation	U	281	275	0.64 (0.32, 0.96)
		Reading ability and disability				
Previous studies						
Gayan & Olson (2003)	7–18	Word Recognition vs. Orthographic Coding	U[b]	257	183	0.92 (0.85, 0.99)
		Word Recognition vs. Phonological Decoding	U[b]	257	183	0.97 (0.93, 1.00)
		Orthographic Coding vs. Phonological Decoding	U[b]	257	183	0.82 (0.74, 0.94)
Gayan & Olson (2001)	7–18	Word Recognition vs. Orthographic Coding	E	30–215	14–159	0.81, 0.94 (—)
		Word Recognition vs. Phonological Decoding	E	30–215	14–159	0.97, 0.99 (—)
Davis et al. (2001)	8–20	Orthographic Coding vs. Rapid Naming (numbers and letters)	E	236	314	0.68 (—)
		Phonological Decoding vs. Rapid Naming (numbers and letters)	E	236	314	0.38 (—)
TEDS						
Previously unpublished TEDS data[c]	7	TOWRE sight word efficiency vs. TOWRE phonemic decoding efficiency	U	1,396	1,298	0.86 (0.84, 0.88)
Harlaar et al. (in press)	7	TOWRE total score vs. UK National Curriculum teacher assessment of reading				
		Same teacher	U	1,386	1,274	0.74 (0.66, 0.81)
		Different teacher	U	1,386	1,274	0.84 (0.80, 0.88)
		Mathematics ability and disability				
TEDS						
Previously unpublished TEDS data[d]	7	UK National Curriculum teacher assessments of 3 components of mathematics				
		Numbers vs. Shapes	U	1,146	1,032	0.88 (0.86, 0.91)
		Numbers vs. Applications	U	1,146	1,032	0.88 (0.85, 0.92)
		Shapes vs. Applications	U	1,146	1,032	0.85 (0.82, 0.89)

Notes Dashes indicate that relevant data are not available in the published report. MZ = monozygotic; DZ = dizygotic; CI = confidence interval; TEDS = Twins Early Development Study; MCDI = MacArthur Communicative Development Inventory; TOWRE = Test of Word Reading Efficiency. [a] Although genetic correlations were not reported in Hohnen and Stevenson (1999), we were able to calculate genetic correlations, but not CIs, from the published data. [b] Analysis based on combined samples of reading-disabled and control individuals. [c] Model-fit statistics for this previously unpublished analysis are $\chi^2(11) = 21.51$, $p = .03$, Akaike information criterion (AIC) = −.49, root-mean-square error of approximation (RMSEA) = .02. [d] Model-fit statistics for this previously unpublished analysis are: $\chi^2(24) = 30.46$, $p = .17$, AIC = −17.54, RMSEA = .02.

found at 3 years (Dionne, Dale, Boivin, & Plomin, 2003). Cross-lagged multivariate genetic analyses from 2 to 3 years suggest that, in equal measure, genetic influences on vocabulary at 2 years contribute to grammar at 3 years and genetic influences on grammar at 2 years contribute to vocabulary at 3 years (Dionne et al., 2003).

The use of parental assessment measures in TEDS might have led to increased genetic overlap if parents are unable to discriminate lexical and grammatical abilities of their children. However, substantial genetic overlap was also found in TEDS in a multivariate genetic analysis of a diverse battery of nine language tests administered by different testers to each twin in their home for 556 pairs of twins when the twins were 4.5 years old (Hayiou-Thomas, Kovas, et al., 2004). The nine language measures assessed lexical, grammatical, and phonological abilities (as described in detail in Viding et al., 2003). The average genetic correlation among the nine measures was .58. The seven phonological, lexical, and grammatical tests yielded an average genetic correlation of .61. The two articulation measures yielded lower genetic correlations with the other seven measures (average genetic correlation of .52). A two-factor model consisting of general language and articulation fit the data better than a single-factor model. Nonetheless, the genetic correlation between these two latent factors was .64. Thus, the results of this multivariate genetic study of language provide strong evidence for the hypothesis of substantial genetic overlap among diverse aspects of language.

This research analyzed normal covariation in unselected samples. No multivariate genetic analyses of homogeneity have been reported for language-impaired groups.

Reading Disability and Ability

It has been proposed that reading disabilities result from independent deficits such as phonological deficits and orthographic deficits (Castles & Coltheart, 1993) and deficits in rapid naming (Wolf & Bowers, 2000). It would follow from such theories that these processes are relatively independent genetically. Double-deficit models (e.g., Wolf & Bowers, 2000) and triple-deficit models (e.g., Badian, 1997) have also been proposed in which reading disability requires two or three deficits, but these deficits are also implicitly independent (Pennington, in press). To the contrary, although there are few multivariate genetic analyses of genetic homogeneity within reading, they support the hypothesis of substantial genetic homogeneity across components of reading, including phonological and orthographic processes.

As indicated in the middle panel of Table 4, the Colorado study has reported very high genetic correlations among multiple measures of reading such as word recognition, orthographic coding (e.g., distinguishing homophones), and phonological decoding (e.g., sounding out nonwords) in multivariate genetic analyses of a twin sample that combines reading-disabled and control samples combined (Gayán & Olson, 2003). In one of the only multivariate genetic analyses of reading disability, the Colorado group showed similarly high genetic group correlations (Gayán & Olson, 2001). The Colorado group also showed that poor performance on orthographic coding and phonological decoding is genetically linked with a rapid naming test involving numbers, colors, objects, and letters (Davis et al., 2001; see also, Tiu, Wadsworth, Olson, & DeFries, 2004).

In TEDS, a multivariate genetic analysis was conducted using the two subtests of the TOWRE thought to assess substantially different reading processes: Sight Word Efficiency (SWE), which assesses the ability to read aloud real words, and Phonemic Decoding Efficiency (PDE), which assesses the ability to read aloud pronounceable printed nonwords (e.g., "framble," "tegwop"), similar to the measure used in the Colorado study (Gayán & Olson, 2001). SWE and PDE were highly correlated phenotypically (r = .82), and both subtests were highly heritable (Harlaar, Spinath, et al., 2005). For the present review, we conducted a bivariate genetic analysis of the SWE and PDE subtests and found a genetic correlation of .86 between them.

Even more impressive evidence for genetic homogeneity comes from a bivariate genetic analysis based on the same sample that analyzed the covariance between the TOWRE total score, which specifically assesses reading accuracy, and year-long teacher assessments of reading based on U.K. national curriculum criteria, which assess diverse reading processes (Harlaar, Dale, & Plomin, in press). The genetic correlation between these two very different measures of reading was .74 for twins in the same classroom and .84 for twins in different classrooms. These findings from TEDS provide strong support for the hypothesis of genetic homogeneity, at least for early reading skills.

Mathematics Disability and Ability

We could find no published reports of multivariate genetic analyses within mathematics disability or ability. For this reason, we conducted a preliminary analysis of TEDS data for 2,178 7-year-old same-sex twin pairs whose mathematics performance was assessed by their teachers based on U.K. national curriculum criteria. Teachers rated the twins' performance on three aspects of mathematics: numbers, shapes, and application. As indicated in the bottom panel of Table 4, the genetic correlations between these three components of mathematics performance were between .85 and .88. Although the teachers rated these three components of mathematics performance using guidelines from the U.K. national curriculum, it is possible that these genetic correlations are inflated by teachers' inability to discriminate components of mathematics performance. Ongoing research in TEDS includes a mathematics project in which a battery of diverse tests of mathematics performance is being administered at 10 years via the Internet, which will provide a strong test of the hypothesis of genetic homogeneity for mathematics performance.

Summary

Multivariate genetic analyses of the normal range of variation consistently find substantial genetic homogeneity within the domains of language, reading, and mathematics. For language, genetic correlations are about .60 between vocabulary and grammar in 2- and 3-year-olds and between diverse language measures in 4.5-year-olds. For reading, genetic correlations are about .80 between word reading and nonword reading in 7-year-olds and about .80 between the TOWRE test of word identification and teacher assessments of general reading skills in 7-year-olds. For mathematics, a multivariate genetic analysis yielded genetic correlations in excess of .80 between three aspects of mathematics performance in 7-year-olds. Multivariate genetic analyses of genetic homogeneity within disabilities rather than analyses of individual differ-

ences in unselected samples have only been reported for reading disability. These analyses yielded group genetic correlations of about .90 between word recognition and component processes such as orthographic and phonological decoding. Although multivariate genetic analyses of genetic homogeneity within language and mathematics disabilities have not been reported, the results for language and mathematics ability and the findings presented in the previous section indicating strong genetic links between disability and ability suggest that substantial genetic homogeneity will also be found for components of language and mathematics disabilities.

Although the results showing substantial genetic homogeneity are remarkably consistent, genetic homogeneity is best viewed as a hypothesis to be tested in future research examining other components of language, reading, and mathematics rather than as a conclusion because of the limited number of studies that have addressed these issues, the limited types of measures that have been used, and the confidence intervals surrounding estimates of genetic correlations. As discussed later, the ultimate test of the hypothesis of genetic homogeneity will come when genes are found to be associated with any component of these disabilities and abilities: Will the same genes be associated with other components of these disabilities and abilities?

Genetic Comorbidity Between Learning Disabilities and Abilities

The previous section addressed multivariate genetic analyses of components within disabilities and abilities (genetic homogeneity). The present section considers multivariate genetic analyses across disabilities and abilities (genetic comorbidity). Comorbidity refers to the co-occurrence of different disorders in the same individual. The question addressed in this section is the extent to which learning disabilities overlap genetically rather than the processes by which the genetic overlap comes about (Neale & Kendler, 1995; Rhee et al., 2004). We review bivariate genetic research on comorbidity between language and reading, between language and mathematics, and between reading and mathematics. The results are summarized in Table 5. The section ends with a trivariate genetic analysis of language, reading, and mathematics.

Language Versus Reading

The question of whether oral language and reading impairments are fundamentally distinct or spring from common sources is as yet unresolved. Recent research has been concerned with elucidating the regions of overlap and specificity between them (Bishop & Snowling, 2004). As indicated in Table 5, although there are not many multivariate genetic studies of comorbidity between language and reading, they consistently yield estimates of substantial genetic correlations. The first study in this area yielded a genetic correlation of .98 (Thompson, Detterman, & Plomin, 1991); subsequent studies also estimated substantial genetic correlations in unselected samples (Bishop, 2001; Gayán & Olson, 1999; Hohnen & Stevenson, 1999) as well as for selected extreme groups (Bishop, 2001; Gayán & Olson, 2001). Although not included in Table 5, adoption data also point to substantial genetic overlap between language and reading. The etiology of covariation between language ability indexed by verbal subtests of the Wechsler Intelligence Scale for Children—Revised or the Wechsler Adult Intelligence Scale—Revised and reading performance assessed by the PIAT was investigated in a parent–offspring analysis of 198 adoptive and 220 nonadoptive families participating in the Colorado Adoption Project (Wadsworth, DeFries, Fulker, & Plomin, 1995a). The genetic correlation was .80 between language and reading composites. A sibling analysis of the same data at 7 years was reported for 100 pairs of nonadoptive siblings and 90 pairs of adoptive siblings (Wadsworth, DeFries, Fulker, & Plomin, 1995b). The genetic correlation between language and reading was also .80. It is noteworthy that the genetic correlation from the parent–offspring analysis was as great as the genetic correlation from the sibling analysis. Because the offspring were assessed in the summer following first grade (at the average age of 7.4 years) and the parents were of course adults, this finding indicates genetic overlap between language and reading that extends from middle childhood through adulthood.

In TEDS, multivariate genetic analyses have been conducted between language and articulation composites from nine measures administered in twins' homes at 4.5 years (see Viding et al., 2003, for details of measures) and a reading composite (TOWRE plus teacher assessments) at 7 years (see Harlaar, Dale, & Plomin, in press, for details of measures) for 1,074 twin pairs with data at both ages who were oversampled for language and cognitive problems (Hayiou-Thomas et al., 2004). Individual differences analyses of the entire sample yielded a genetic correlation of .59 between language at 4 years and reading at 7 years and a similar genetic correlation of .50 between articulation at 4 years and reading at 7 years. In one of the few multivariate genetic analyses of disability, the group genetic correlation between low language at 4 years and low reading at 7 years was .78; the group genetic correlation was similar (.68) between low articulation at 4 years and low reading at 7 years (Hayiou-Thomas, Harlaar, & Plomin, 2004). These results suggest strong genetic comorbidity between language and reading, even when language is assessed at 4 years and reading at 7 years.

Also in TEDS, multivariate genetic analyses have been reported between spoken language and reading abilities for 1,730 MZ and 1,566 same-sex DZ pairs of 7-year-old twins as assessed by teachers (Oliver, Dale, & Plomin, 2004). The genetic correlation between spoken language and reading was .71. Teacher-assessed writing skills were also included in this analysis and yielded genetic correlations of .70 (.64–.76) with spoken language and .84 (.80–.88) with reading.

Language Versus Mathematics

The middle panel of Table 5 summarizes the three twin studies that conducted multivariate genetic analyses of the relationship between language and mathematics. The first study was conducted before multivariate genetic analysis had been formally developed (e.g., Martin & Eaves, 1977). It was a twin study of 1,300 MZ and 864 DZ twin pairs in U.S. high schools who had been selected to compete on the National Merit Scholarship Qualifying Test (NMSQT; Loehlin & Nichols, 1976). Multivariate genetic analysis was later applied to these NMSQT data (Martin, Jardine, & Eaves, 1984) and modest genetic correlations were found between English Usage and Mathematics and between Vocabulary and Mathematics (.52 and .39, respectively; see Plomin & DeFries, 1979).

These genetic correlations from the NMSQT study are lower than those found between language and reading as reviewed in the previous section. Although language and mathematics could

be less genetically correlated than language and reading, it is also possible that the results of the NMSQT study are influenced by its use of a sample selected for high ability. This latter hypothesis is supported by the results of the Cleveland study, described in the previous section, which found a genetic correlation of .98 between language and mathematics for its community sample (Thompson et al., 1991). In previously unpublished analyses, TEDS finds a genetic correlation that lies in between the extremes of the NMSQT study and the Cleveland study: the genetic correlation was .59 between teacher-assessed spoken language and mathematics.

The Colorado Adoption Project, described in the previous section, also suggests moderate genetic overlap between language and mathematical ability. Genetic correlations were .48 in parent–offspring analyses (Wadsworth et al., 1995a) and .57 in sibling analyses (Wadsworth et al., 1995b).

These analyses involve individual differences in unselected samples. Analyses of genetic links at the extremes of language and mathematics disability have not been reported.

Reading Versus Mathematics

Finally, the bottom panel of Table 5 summarizes multivariate genetic studies of reading and mathematics. Again, the first multivariate genetic analysis of normal variation was the Cleveland study, which yielded a very high genetic correlation (.98; Thompson et al., 1991). Subsequent studies yielded more modest but nonetheless substantial genetic correlations: .47 and .61 in the Colorado study (Knopik & DeFries, 1999) and .74 in TEDS (Kovas, Harlaar, Petrill, & Plomin, in press). Data from the Colorado Adoption Project support the twin analyses and also suggest substantial genetic correlations between reading and mathematics. The genetic correlation between reading and mathematical performance was .80 in a parent–offspring analysis (Wadsworth et al., 1995a) and .83 in a sibling analysis (Wadsworth et al., 1995b).

The Colorado group also reported the first multivariate genetic analysis of reading disability and mathematics (Light & DeFries, 1995). Although the twins were selected for reading disability, they were unselected for mathematics disability; dichotomizing the mathematics variable yielded twin cross-concordances of 68% for MZ twins and 40% for DZ twins, suggesting substantial genetic influence. In a bivariate DF extremes analysis of reading disability using the mathematics variable as a continuous score, MZ and DZ cross-trait group correlations were .92 and .66, respectively. Bivariate heritability was .55, suggesting substantial genetic overlap between reading disability and mathematics ability.

A follow-up Colorado analysis selected twins both for reading disability (102 MZ and 77 same-sex DZ twin pairs) and for mathematics disability (42 MZ and 23 DZ pairs; Knopik et al., 1997). Bivariate DF extremes analysis for reading disability probands versus mathematics ability yielded results similar to those described above. Analysis of mathematics disability probands versus reading ability also yielded similar results. This was the first report in which a genetic correlation was calculated from bivariate DF extremes analysis. The genetic correlation between reading disability and mathematics disability was estimated as .53.

Language, Reading, and Mathematics

An analysis was conducted for this review that brings the foregoing series of bivariate comparisons together with the first trivariate genetic analysis of language, reading, and mathematics based on U.K. national curriculum teacher assessments in TEDS at 7 years for 1,538 MZ and 1,419 same-sex DZ pairs. The model is presented in Figure 3a as a Cholesky path model. The three measured variables (rectangles) are teacher-assessed language, reading, and mathematics and the latent variables (circles) represent *A* (additive genetic), *C* (common or shared environment), and *E* (nonshared environment) estimates. Focusing on the three genetic latent variables (Figure 3b), the three squared path estimates leading to mathematics are .22 for A_1, .12 for A_2, and .30 for A_3. These three genetic estimates sum to the heritability of mathematics (.64) and indicate that 34% (.22 out of .64) of the genetic variance of mathematics is in common with both language and reading, 19% (.12 out of .64) of the genetic variance of mathematics is in common with reading but independent of language, and 47% (.30 out of .64) of the genetic variance of mathematics is independent of both language and reading. Figure 3c shows univariate heritabilities and the genetic correlations derived from the Cholesky model. The correlations were .64 between language and reading, .59 between language and mathematics, and .71 between reading and mathematics. Thus, this trivariate analysis confirms the results of the previous series of bivariate analyses in showing substantial genetic correlations between language, reading, and mathematics.

Summary

The third way in which genes are generalists is that genes that affect one learning disability and ability also substantially affect other learning disabilities and abilities. Only a few studies have addressed the issue of genetic overlap across domains, but they consistently find evidence for substantial genetic overlap for the normal range of variability. For example, in five unselected twin samples, genetic correlations between language and reading range from .67 to 1.0. For language and mathematics, two twin studies using unselected twin samples found genetic correlations of .59 and .98. For reading and mathematics, three studies using unselected twin samples reported genetic correlations of .47, .76, and .98. In the only bivariate genetic analysis of disabilities rather than abilities, a correlation of .53 was found between reading disability and mathematics disability. Thus, it seems safe to hypothesize that genetic correlations between these learning disabilities and abilities are substantial.

This hypothesis might be difficult to accept because it goes against the common observation that there are specific disabilities. For example, some children with reading problems have no problem with mathematics and vice versa (Bishop, 1997; Van Orden, Pennington, & Stone, 2001). However, it should be noted that such so-called double dissociations occur even when disabilities are highly correlated. For example, in TEDS, the phenotypic correlation between reading and mathematics is .65, yet as shown in Figure 4, many children with scores one standard deviation below average for reading are above the mean in mathematics and vice versa. However, this apparent double dissociation is to be expected from the bivariate normal distribution. There are two issues: First, whether more cases of dissociation are observed than are expected from the bivariate normal distribution; second whether different causal processes are responsible for problems with reading and problems with mathematics. Moreover, genetic correlations within and between learning disabilities and abilities are greater than their

Table 5
Genetic Comorbidity: Genetic Correlations Between Language, Reading, and Mathematics Learning Disabilities and Abilities

Reference	Age (years)	Measures	Unselected (U) or extremes (E)?	*N*/pairs MZ	*N*/pairs DZ	Genetic correlations (95% CI)
		Language vs. reading				
Previous studies						
Thompson et al. (1991)	6–12	Metropolitan Achievement Test subtests of language and reading	U	146	132	1.00 (—)
Hohnen & Stevenson (1999)[a]	6 and 7	Phonological Awareness factor (phoneme blending, sound categorization and phoneme deletion) and Language factor (grammar and vocabulary) vs. Reading factor (single-word reading, spelling, irregular-word reading, prose reading, nonword reading, and pseudohomophones)				
		Phonological Awareness factor vs. Reading factor	U	66	60	0.67 (6 years) and 0.73 (7 years)
		Language factor vs. Reading factor	U	66	60	0.90 (6 years) and 0.69 (7 years)
Gayán & Olson (2003)[b]	7–18	Latent variable of phoneme awareness (phoneme transposition, phoneme deletion, and auditory conceptualization) and three latent variables of reading (word recognition, phonological decoding, and orthographic coding)				
		Phoneme Awareness vs. Word Recognition	U	257	183	0.75 (0.65, 0.86)
		Phoneme Awareness vs. Phonological Decoding	U	257	183	0.79 (0.70, 0.89)
		Phoneme Awareness vs. Orthographic Coding	U	257	183	0.55 (0.42, 0.70)
Gayán & Olson (2001)	7–18	Tests of Phoneme Awareness vs. Word Recognition	E	503	360	0.53, 0.70 (—)
Bishop (2001)	7–16	Factors of language impairment (1. Receptive Grammar, Comprehension, Recalling Sentences, Word Finding, Graded Naming; 2. Nonword Repetition) vs. reading (BAS Word Reading, Vernon Graded Word Spelling)				
		Language Impairment vs. Reading	E	64	23	0.64[c] (0.00, 1.29)
		Language Impairment vs. Spelling	E	64	23	0.49[c] (0.00, 1.09)
		Nonword Repetition vs. Reading	E	64	23	0.86[c] (0.45, 1.27)
		Nonword Repetition vs. Spelling	E	64	23	0.70[c] (0.30, 1.10)
TEDS						
Oliver et al. (in press)	7	UK National Curriculum teacher assessments of spoken language and reading	U	1730	1566	0.71 (0.65, 0.77)
Harlaar et al. (in press)	4 and 7	Language and articulation composites at 4 years vs. reading composite at 7 years				
		Language vs. Reading	U	386	688[d]	0.59 (0.39, 0.85)
		Articulation vs. Reading	U	386	688[d]	0.50 (0.24, 0.98)
Hayiou-Thomas et al. (2004)[e]	4 and 7	Language and articulation composites at 4 years vs. reading composite at 7 years				
		Language vs. Reading	E	114	158	0.78 (—)
		Articulation vs. Reading	E	102	161	0.68 (—)
		Language vs. mathematics				
Previous studies						
Loehlin & Nichols (1976)	17–18	U.S. National Merit Scholarship Qualifying Test		?		
		English Usage vs. Mathematics		1,300	864	0.52 (—)
		Vocabulary vs. Mathematics		1,300	864	0.39[f] (—)
Thompson et al. (1991)	6–12	Metropolitan Achievement Test subtests of language and mathematics	U	146	132	0.98 (—)
TEDS						
Previously unpublished TEDS data[g]	7	UK National Curriculum teacher assessments of spoken language and mathematics	U	1,538	1419	0.59 (0.53, 0.65)

Table 5 (*continued*)

Reference	Age (years)	Measures	Unselected (U) or extremes (E)?	*N*/pairs MZ	*N*/pairs DZ	Genetic correlations (95% CI)
		Reading vs. mathematics				
Previous studies						
Thompson et al. (1991)	6–12	Metropolitan Achievement Test subtests of reading and mathematics	U	146	132	0.98 (—)
Light & DeFries (1995)	8–20	Reading composite (PIAT reading comprehension, reading recognition, and spelling) vs. mathematics (PIAT mathematics and WISC-R arithmetic subtests)	E	148	111	0.55[h] (—)
Knopik et al. (1997)	8–20	Composites of reading (PIAT reading comprehension, reading recognition, and spelling) vs. mathematics (PIAT mathematics, WRAT arithmetic) disability	E	42–102	23–77	0.53 (—)
Knopik & DeFries (1999)	8–20	Composites of reading (as above) and mathematics (as above plus WISC-R or WAIS-R arithmetic) ability				
		Unselected sample	U	220	135	0.47 (0.20, 0.74)
		Reading-disabled sample	?[i]	290	236	0.61 (0.52, 0.68)
TEDS						
Kovas, Harlaar, Petrill, & Plomin (in press)		UK National Curriculum teacher assessments of mathematics and reading composite (TOWRE and UK National Curriculum teacher assessments of reading)	U	999	928	0.74 (0.68, 0.80)

Note. MZ = monozygotic; DZ = dizygotic; CI = confidence interval; BAS = British Ability Scales; TEDS = Twins Early Development Study; PIAT = Peabody Individual Achievement Test; WRAT = Wide Range Achievement Test; WISC-R = Wechsler Intelligence Scale for Children—Revised; WAIS-R = Wechsler Adult Intelligence Scale—Revised; TOWRE = Test of Word Reading Efficiency.

[a] Although genetic correlations were not reported in Hohnen and Stevenson (1999), we were able to calculate genetic correlations, but not CIs, from the published data.

[b] Analysis based on combined samples of reading-disabled and control individuals.

[c] Bivariate group heritability, not group genetic correlation. It is not possible to calculate bivariate group genetic correlations in this study because the sample was selected for language impairment, whereas bivariate group genetic correlations require bidirectional selection—that is, for probands low in reading as well as probands low in language.

[d] Analysis based on combined sample of same-sex and opposite-sex twins.

[e] The results reported here are from the sex-limitation analysis and on combined sample of same-sex and opposite-sex DZ twins. The best fitting model was the one that equated the parameters for the two sexes.

[f] Genetic correlations were not calculated in this publication but the data were used to calculate genetic correlations later (Martin, Jardine, & Eaves, 1984; Plomin & DeFries, 1979).

[g] Model-fit statistics for this previously unpublished analysis are $\chi^2(24) = 39.21$, $p = .03$, Akaike information criterion (AIC) = −8.79, root-mean-square error of approximation (RMSEA) = .02.

[h] Bivariate group heritability, not group genetic correlation. The genetic correlation between reading disability and mathematics disability cannot be calculated because the selected sample was reading disabled; the converse bivariate genetic analysis was not reported for low mathematics probands and a continuous measure of reading in the cotwins. However, assuming that an analysis of mathematics disability probands and reading ability in cotwins yielded the same result as in the reported analysis of reading disability probands and mathematics ability in cotwins, the group genetic correlation would be 0.71 between reading disability and mathematics disability.

[i] Although this analysis involved reading-disabled individuals, it was an analysis of individual differences rather than a bivariate DF extremes analysis.

phenotypic correlations and we do not see the genetic correlations to the same extent that we see phenotypic associations and dissociations. Finally, even in terms of genetics, genetic correlations are not 1.0, which means that there are specialist as well as generalist genes. However, what is interesting from this review of multivariate genetic research is the great extent to which genes are generalists.

How Do Generalist Genes Work?

Research reviewed in the previous sections suggests that, to a substantial extent, genes that affect learning disabilities and abilities are generalists in three ways: (a) genes that affect common learning disabilities are largely the same genes responsible for normal variation in learning abilities, (b) genes that affect one component of a learning disability or ability affect other components, and (c) genes that affect one learning disability or ability affect others as well. What are the mechanisms by which genes can have such general effects? This question can be addressed at several levels of analysis: DNA (molecular genetics), brain (neuroscience), and mind (cognitive psychology).

DNA

Molecular genetics will provide the most direct test of the three generalist genes hypotheses drawn from our review of quantitative genetic research. The obvious predictions are that (a) most genes found to be associated with a particular learning disability will also

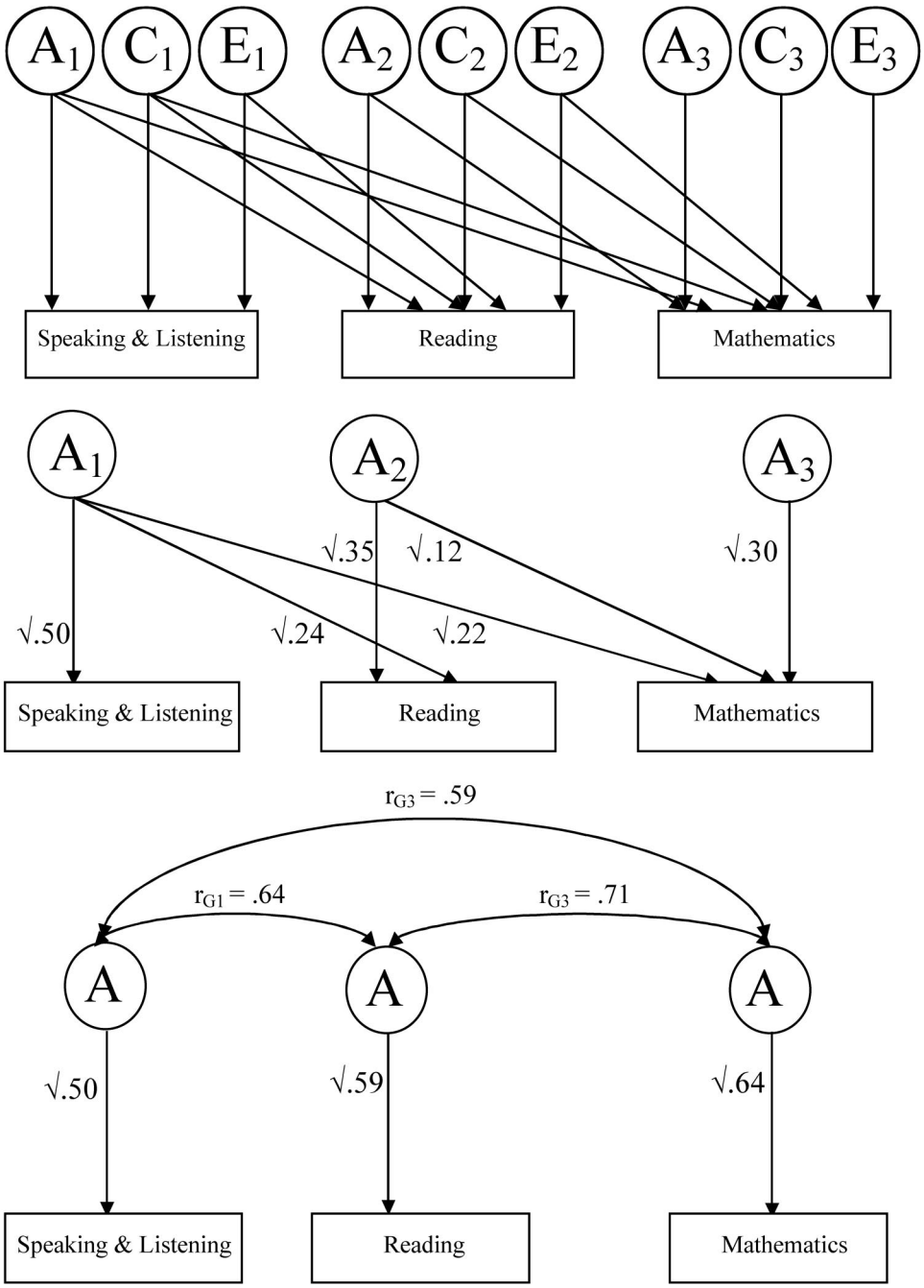

Figure 3. Trivariate analysis (Cholesky path model) of language, reading, and mathematics for teacher-assessed data at 7 years in the Twins Early Developmental Study. Top: Full model. The three measured variables (rectangles) are teacher-assessed language, reading, and mathematics, and the latent variables (circles) represent *A* (additive genetic), *C* (common or shared environment), and *E* (nonshared environment) estimates. Middle: Genetic results: The three genetic latent variables (circles) and the three path estimates leading to the three measured variables (rectangles). Bottom: Proportion of the total variance attributable to genetic influences for each trait is indicated by the paths leading from the latent genetic factors to the measured traits. Correlations between the latent genetic influences on each trait (transformed Cholesky parameters) are denoted by r_{Gx} and are represented by the double-headed arrows.

be associated with normal variation in the relevant learning ability, (b) most genes found to be associated with any component of a learning disability or ability will also be associated with all other components, and (c) most genes associated with a particular learning disability or ability will also be associated with other learning disabilities and abilities. However, these predictions cannot as yet be tested because no genes have been identified that are reliably associated with common learning disabilities or abilities. A major

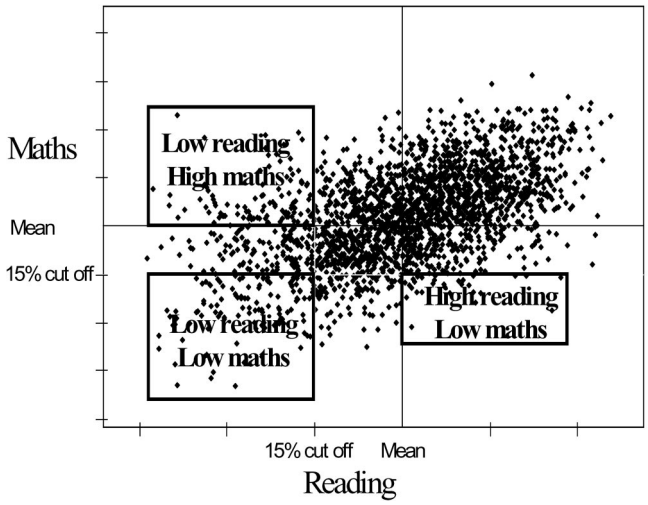

Figure 4. Scatterplot between reading and mathematics scores in the Twins Early Developmental Study for which the phenotypic correlation is .65.

reason why identification of genes has been slower than anticipated is that there are likely to be many more genes with much smaller effect sizes than had been anticipated, which means that larger studies with greater power to detect small effects are needed (Plomin, DeFries, Craig, & McGuffin, 2003; Zondervan & Cardon, 2004). Optimism is warranted with the advent of completely new approaches such as whole genome association studies involving thousands of DNA markers genotyped on microarrays (Carlson, Eberle, Kruglyak, & Nickerson, 2004), including microarray genotyping of DNA pooled across large samples of learning disabled individuals and controls (Butcher et al., 2004). The good news from the generalist genes theory is the prediction that the same set of genes is associated with most learning disabilities.

Reports are beginning to appear of genes associated with normal variation in cognitive abilities. Some of these associations involve general cognitive ability (Plomin, 2003b) and some are reported to be specific to executive functions of the prefrontal cortex (Diamond, Briand, Fossella, & Gehlbach, 2004). However, these results need to be replicated with larger samples. Although no genes have as yet been reliably identified as associated with learning disabilities, several linkages to chromosomal regions have been found for learning disabilities. The first QTL linkages for common learning disabilities were reported for reading disability, and replicated linkages have been found for Chromosomes 6 and 15 (Fisher & DeFries, 2002). Although there was considerable excitement during the past year about a gene (*EKN1*) that might be responsible for the Chromosome 15 linkage (Grigorenko et al., 2004; Taipale et al., 2003), several studies have failed to replicate the association (Grigorenko et al., 2004). The first genome screen for reading disability also found linkage to Chromosome 18 (Fisher et al., 2002). The first two QTL linkage studies of language disability suggested linkages on Chromosomes 16 (Inoue & Lupski, 2003; SLI Consortium, 2002) and Chromosome 13 (Bartlett et al., 2002). No linkage studies of mathematics disability have been reported.

These QTL linkage results provide some support for the theory of generalist genes. Because QTL linkage is based on the molecular genetic equivalent of DF extremes analysis, it supports the first hypothesis that genes associated with a particular learning disability will also be associated with normal variation in the relevant learning ability. In QTL linkage analysis, probands are selected on the basis of a diagnosis, and their cosiblings' regression to the mean on a quantitative trait is assessed as a function of how similar the siblings are for a particular DNA marker (Fisher & DeFries, 2002). That is, for a particular marker, siblings can be like adoptive siblings sharing neither of their two alleles at that locus, DZ twins sharing one of the two alleles, or MZ twins sharing both alleles. This allele-sharing index of 0, 1, or 2 for each sibling pair is substituted in the basic regression equation for the coefficient of genetic relatedness (R) in the DF extremes analysis shown earlier. Thus, analogous to the quantitative genetic version of DF extremes analysis, QTL linkage requires a genetic correlation between learning disability in the proband and normal variation in learning ability in the proband's sibling. Going against this first hypothesis of genetic links between the normal and abnormal is a recent QTL linkage report suggesting that linkages are stronger at the extreme (Francks et al., 2004).

QTL linkage results are also relevant to the second hypothesis of genetic homogeneity. That is, to what extent are linkages specific to certain aspects of learning disabilities? For reading disability, the only learning disability for which sufficient research is available to address this issue, the answer is clear: The linkages are general. That is, the same linkages appear across measures of diverse reading processes, including orthographic coding, phonological decoding, word recognition, and rapid naming (Davis et al., 2001; Fisher & DeFries, 2002; Knopik et al., 2002). A similar conclusion about the generality of linkage results has been reached in a multivariate linkage analysis, which is a promising tool for testing the hypothesis of generalist genes in linkage studies (Marlow et al., 2003). A multivariate QTL linkage analysis of word recognition and IQ provide suggestive linkage for both traits on the long arm of Chromosome 2 (Luciano et al., in press).

Concerning the third hypothesis of genetic comorbidity, we predict that linkages for one learning disability will be found for other learning disabilities. Although linkages reported in the first two linkage studies of language impairment are not the same linkages found for reading disability, these two studies themselves report different linkages for language impairment (Bartlett et al., 2002; SLI Consortium, 2002). Failure to replicate linkages is a widespread problem for complex traits (Altmüller, Palmer, Fischer, Scherb, & Wjst, 2001).

The rest of this section considers the mechanisms that lie between DNA and their general effects on learning disabilities and abilities.

Pleiotropy. When genes are identified, powerful tools are available to study the mechanisms by which genes have their general effects within and between learning disabilities. Genes themselves are not correlated unless their loci happen to be in close proximity on the same chromosome. What is correlated is the effects of the gene products transcribed from DNA. The central dogma of DNA has focused on the less than 2% of DNA, called *coding regions of genes*, that are transcribed into messenger RNA (mRNA) and then travel outside the nucleus of the cell to form templates from which amino acids are assembled in a process called *translation*. For nearly all genes, a complicated process called *splicing* occurs between transcription and translation. All of the DNA within a gene is transcribed into mRNA, but segments of

mRNA (called *introns*) are deleted and remain in the nucleus, whereas the other segments (called *exons*) are spliced back together and exit the nucleus, where they are translated into amino acid sequences. In the past, introns were thought to be genetic junk that has hitched a ride evolutionarily, but it is now known that in some cases introns regulate the transcription of other genes. Moreover, it is likely that some of the other 98% of DNA not in coding regions of genes can also have effects. Exons are conserved evolutionarily—most of our exons are highly similar to DNA sequences in primates, mammals, and even invertebrates. This implies that the sheer number of such genes is not responsible for the greater complexity of the human species. More subtle variations in DNA rather than the number of genes are responsible for differences between mice and men (Brett, Pospisil, Valcarcel, Reich, & Bork, 2002). If subtle DNA differences are responsible for the differences between mice and men, even more subtle differences are likely to be responsible for individual differences within the human species. For example, noncoding DNA sequences outside of gene regions can act as genes by producing RNA molecules that regulate gene expression directly rather than being translated into amino acid sequences (Eddy, 2001). Although many rare and severe disorders caused by a single gene involve mutations in exons, DNA variations in introns and other noncoding regions might be sources of more subtle generalist effects on complex traits such as learning disabilities and abilities.

In genetics, manifold effects of such gene products are called pleiotropy. Tracing the pleiotropic pathways between genes and cognition through the brain is the key to understanding how generalist genes have their diffuse effects within and between learning disabilities and abilities. For example, genetic effects on basic physical properties (e.g., dendritic density) or physiological properties (e.g., synaptic plasticity) of the brain are likely to have diffuse effects downstream. These pathways will be complex (Fisher, in press; Inoue & Lupski, 2003) and determining direct causation will be difficult (Page, George, Go, Page, & Allison, 2003) precisely because these genetic effects are so highly pleiotropic (Gray & Thompson, 2004).

Gene expression. A powerful tool for tracing the pleiotropic effects of genes through the brain is gene expression (Carter et al., 2001; Lockhart & Barlow, 2001). Gene expression can be indexed by the presence of mRNA. Unlike DNA, which is the same in every cell in the body, the amount of mRNA transcribed from a gene varies in space and time as a function of the activity level of the gene. Research on patterns of gene expression in different brain regions and in response to different cognitive tasks is the genetic equivalent of functional neuroimaging.

In the present context, a central question is the relative specificity or generality of gene expression across brain regions and across tasks. The generalist genes theory predicts that genes will have general rather than specific effects both across brain regions and across tasks. Gene expression can be studied using postmortem human brain tissue; for example, a recent study shows reduced expression after age 40 in the frontal cortex of many genes involved in synaptic plasticity, vesicular transport, and mitochondrial function (Lu et al., 2004). However, most gene expression research involves mice. Mouse research on gene expression is obviously not useful as a behavioral model of uniquely human behaviors such as language, reading, and mathematics. However, mouse model research will play an important role in charting the expression of genes in the brain even for learning disability because nearly every human gene can be found in only slightly altered form in mice (Crusio & Gerlai, 1999; Plomin, 2001b). A critical development is microarray analysis, which can detect the expression of tens of thousands of genes simultaneously (Bassett, Eisen, & Boguski, 1999; Leach, 2004). Such gene expression profiling was first used in cell lines to diagnose diseases based on the profile of genes that are expressed in response to the disease (Golub et al., 1999) and to study the response to drugs (Iyer et al., 1999). Research on mice is underway that aims to create an atlas of patterns of gene expression throughout the brain during learning and memory tasks (Grant, 2003).

Proteomics. The next step beyond gene expression is to investigate the function of proteins that result from translation of RNA. This field is called *protein genomics*, which led to the neologism *proteomics.* Proteomics is much more difficult than genomics because, unlike the triplet code of DNA that governs the genome, there is no simple code for understanding the proteome. There are also several complications. First, perhaps as many as half of all human genes are alternatively spliced into exons and introns and thus translated into different proteins (Banks et al., 2000; International Human Genome Sequencing Consortium, 2001). Second, proteins are modified after translation. Although the amino acid sequence of a protein can be predicted with certainty from the expressed DNA sequence, the functioning of a protein depends on the way it folds, a process that is poorly understood. Third, proteins attach themselves to other proteins; understanding protein function depends on understanding the interactions between proteins in these protein complexes. Again, this complexity is a reflection of the highly pleiotropic nature of genetic effects.

FOXP2. Identifying just one of the many genes responsible for the heritability of learning disabilities can provide a small window through which we can view mechanisms by which genes have their pleiotropic effects. An instructive recent example is a mutation in the *FOXP2* gene that is responsible for a disorder of speech and language that appeared in one three-generation family called the KE family with 15 affected individuals (Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001). Although this single-gene disorder was originally thought to be specific to grammar (Gopnik, 1990), it is now known to involve wide-ranging language and cognitive impairments as well as motoric problems related to mouth movements (Vargha-Khadem et al., 1998). The mutation responsible for the disorder in the KE family is rare, perhaps unique to the KE family, and does not contribute to genetic variation in common language disabilities (Meaburn, Dale, Craig, & Plomin, 2002; Newbury et al., 2002). Nonetheless, identification of the *FOXP2* gene led to an intense research effort to explore mechanisms by which the gene has its effect on speech and language in the KE family.

Research on mice has been valuable in mapping the brain expression of the *FOXP2* gene. The central question is whether the gene is expressed in a specific region of the brain involved perhaps in communication such as the murine ancestor of Broca's area. The human gene is highly similar in mice: The mouse version of the protein differs from the human version in only 3 of more than 700 amino acids (Enard et al., 2002). In mice, *FOXP2* codes for a particular type of regulatory protein called a *transcription factor*, which regulates the transcription of other genes during embryonic development (Carlsson & Mahlapuu, 2002). Because this is such a basic function, *FOXP2* would be expected to have general effects,

and this is the case: *FOXP2* is expressed throughout the nervous system, as well as in embryonic lung, heart, and gut (Shu, Yang, Zhang, Lu, & Morrisey, 2001). In the brain, *FOXP2* is expressed throughout development in many regions including cortex, thalamus, hypothalamus, striatum, cerebellum, and medulla (Lai, Gerrelli, Monaco, Fisher, & Copp, 2003). We predict that most genes associated with common forms of learning disabilities will have similarly far-reaching pleiotropic effects, leading to genetic correlations within and between learning disabilities and abilities.

Brain

Understanding how generalist genes work in the brain is not limited to molecular methods such as gene expression and proteomics; standard tools such as neuroanatomical, pharmacological, electrophysiological, and imaging measures are also relevant. Figure 5 illustrates three basic models of how generalist genes could work in the brain. In Model 1, a single brain mechanism, influenced by multiple genes, is responsible for the genetic overlap between learning disabilities. For example, it has been argued that individual differences in a single fundamental brain mechanism such as neural plasticity could create overlap between independent brain processes in their downstream effects on behavior (e.g., Garlick, 2002). Other single mechanisms have been proposed such as dendritic complexity, myelinization, and speed of nerve conduction (Deary, 2000).

Model 2 suggests that several genetically independent brain processes affect multiple learning disabilities, thus creating phenotypic and genetic correlations at the level of learning disabilities, even though the brain processes are themselves uncorrelated genetically. In Model 3, brain processes that affect learning disabilities are themselves genetically correlated. That is, although some genes (e.g., Genes 1 and 6 in Figure 5) have effects specific to a particular brain mechanism, most genes (e.g., Genes 2, 3, 4, and 5) have pleiotropic effects on several brain mechanisms. Although all three models could account for genetic correlations between learning disabilities, we favor Model 3 because we predict that the theory of generalist genes applies just as much to the brain as to behavior. That is, we predict that brain processes related to learning disabilities are themselves genetically correlated. This prediction is contrary to the modularity view that dominates neuroscience, which is represented by Model 2. Although the original concept of modules as innate and invariant information-processing units (Fodor, 1983) has been watered down to the notion of domain specificity, it remains a pervasive view in neuroscience—from older lesion studies to newer neuroimaging research—that brain processes are discrete and independent (Elman et al., 1996;

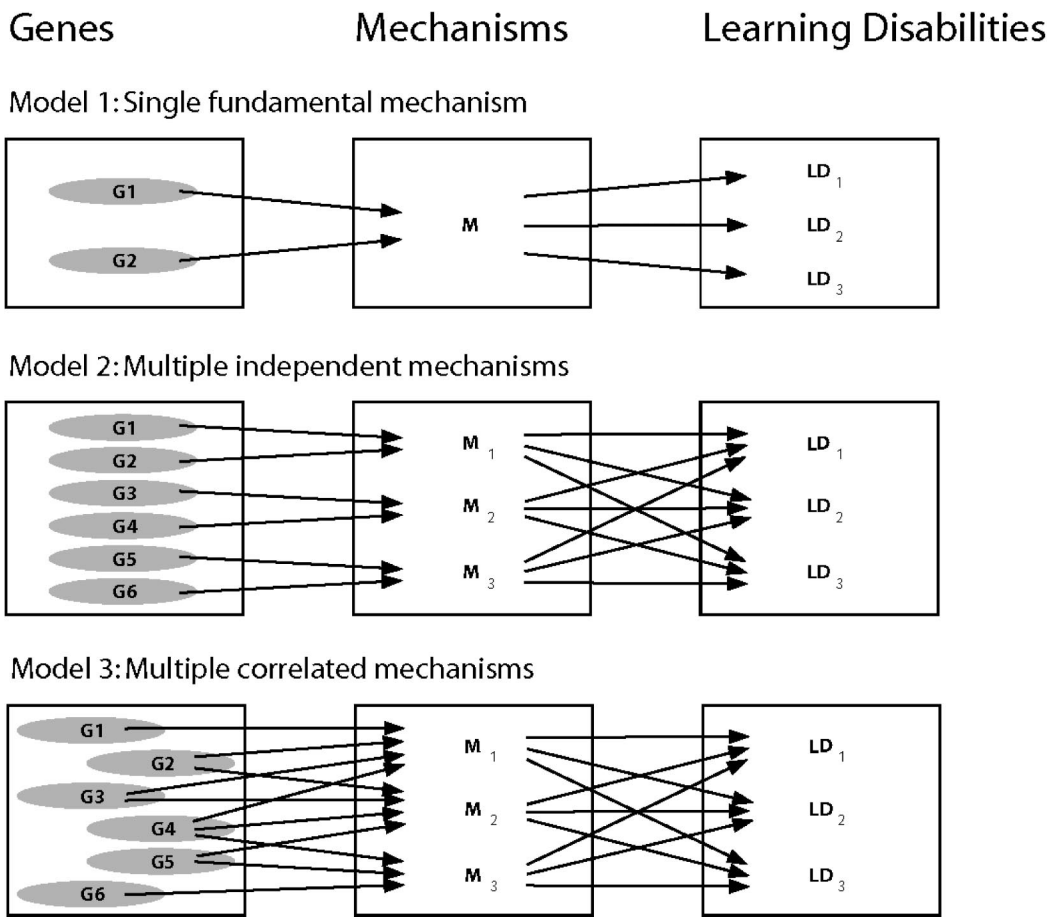

Figure 5. Models of the relationship between genes (*G*), mechanisms (*M*), and learning disabilities (*LD*). Although only two genes are shown influencing each mechanism, it is assumed that many genes are involved.

Karmiloff-Smith, 1992; Pinker, 1994). Modularity is usually discussed at a species-typical level of analysis, but when applied to learning disabilities, it motivates attempts to localize brain dysfunction, to assume heterogeneity rather than homogeneity within and between learning disabilities, and to consider learning disabilities as a "broken brain" rather than as a continuum of the same processes responsible for normal variation.

Although much research using structural and functional neuroimaging techniques has been reported for learning disabilities, hardly any of this research has used genetically sensitive designs that directly test the theory of generalist genes. One exception involves structural imaging research on individual differences in brain region volumes, which finds high heritability and shows correlations of about .40 with general cognitive ability (Deary, 2000; Vernon, Wickett, Banzana, & Stelmack, 2000), an association that is substantially mediated genetically (Pennington et al., 2000; Posthuma et al., 2002). In support of the theory of generalist genes, the association with cognitive ability is not specific to any single brain region (Plomin & Kosslyn, 2001). For example, a recent study shows that cognitive ability is associated with gray matter volumes in the frontal, temporal, parietal, and occipital lobes (Haier, Jung, Yeo, Head, & Alkire, 2004), although other research suggests that cognitive ability correlates primarily with prefrontal cortical volumes (Gray & Thompson, 2004; Thompson et al., 2001). Further support for a theory of generalist genes comes from research showing that brain volumes across regions are substantially correlated phenotypically (Pennington et al., 2000) and genetically (Posthuma, de Geus, & Boomsma, 2003).

Phenotypic research on brain function is also relevant. That is, if generalist genes contribute substantially to learning disabilities, it follows that brain mechanisms involved in learning disabilities can be expected to correlate phenotypically. A review of neuroscience research on learning disabilities is beyond the scope of this article, but it is interesting that neuroimaging research to date does not provide much support for modularity. For example, a review of functional imaging studies of reading disability concludes that "there is no convergence on a single mechanism or region of abnormal activation" (Grigorenko, 2001), although there is more recent evidence in support of left occipitotemporal systems (Shaywitz et al., 2004). Other functional brain measures using psychophysiological techniques have also been shown to be highly heritable but have not yet been shown to be related to cognitive disabilities or abilities (Deary, 2000), such as peripheral nerve conduction velocity (Rijsdijk & Boomsma, 1997), electroencephalograph alpha peak frequency (Posthuma, de Geus, & Boomsma, 2001), and electroencephalograph coherence, which is a measure of brain interconnectivity (van Baal, Boomsma, & de Geus, in press; Van Beijsterveldt, Molenaar, de Geus, & Boomsma, 1998). In summary, although much more research is needed to assess the generality of brain mechanisms involved in learning disabilities, extant data provide more support for the generalist genes theory than for modularity.

Mind

Cognitive models of how generalist genes work can also be considered in relation to Figure 5. That is, genetic correlations among learning disabilities could come about by a single fundamental process such as working memory (Blair, in press; Conway, Kane, & Engle, 2003) that affects all learning disabilities (see Figure 5, Model 1). This simple model is central to cognitive neuropsychology (Shallice, 1988). A recent evolutionary theory involving a single cognitive mechanism proposed that general intelligence evolved as a domain-specific adaptation to novelty but has general effects because we now live in an evolutionarily novel world (Kanazawa, 2004). A second possibility is that multiple genetically independent cognitive processes are involved such as central executive, phonological store, and articulatory loop processing speed (Baddeley, 1986) that affect all learning disabilities (see Figure 5, Model 2). Double-deficit models have been proposed for language and reading but these tend to be like two single-deficit models put together; single-deficit, double-deficit, and what might be called *multiple-deficit* models of learning disabilities have been recently discussed (Pennington, in press). The third possibility is that the multiple cognitive processes are themselves genetically correlated (see Figure 5, Model 3). Again, we favor Model 3, predicting that the theory of generalist genes also applies to the cognitive level of explanation.

Model 3 is supported by multivariate genetic research reviewed earlier suggesting genetic homogeneity within learning disabilities. That is, when component cognitive processes are analyzed, they are substantially correlated genetically. For example, large genetic correlations have been found, for language, between lexical, grammatical, and phonological processes; for reading, between word recognition, orthographic coding, and phonological decoding; and for mathematics, between numbers, shapes, and application. It should be noted that this multivariate genetic research assumes a model of correlated liabilities in which genes are viewed as causal risk factors within as well as between learning disabilities. Other models—for example, in which one disability causes the other or when disabilities reflect different degrees of severity—can also be addressed in multivariate genetic research (Rhee et al., 2004), although greater clarity will be achieved when specific genes and their mechanisms can be used.

Support for Model 3 also comes from multivariate genetic research on psychometric tests of cognitive abilities that consistently finds genetic correlations greater than .50 across diverse cognitive abilities (Petrill, 2002; Plomin & Spinath, 2002). Similar results suggesting substantial genetic overlap have been found for more basic information processing measures that typically involve reaction time or psychophysical measures of basic cognitive processing (Deary, 2001). For example, in a German study of 169 MZ and 131 DZ adult twin pairs, twins were assessed on two widely used tasks, Sternberg's memory scanning task and Posner's letter-matching task, which were designed to assess speed of accessing short-term and long-term memory, respectively (Neubauer, Spinath, Riemann, Borkenau, & Angleitner, 2000). A bivariate genetic analysis of the two tasks yielded a genetic correlation of .84 (Plomin & Spinath, 2002), indicating substantial genetic overlap between these tasks. Similar results were found in a study of choice reaction time that included two, four, and eight choices—which assess increasing cognitive load reflected in decision time—in 184 MZ and 206 DZ pairs of young adult twins (Luciano et al., 2003). Multivariate genetic analysis of the three choice reaction time conditions yielded genetic correlations ranging from .74 to .90.

These results support the hypothesis that generalist genes are also important at the cognitive level of explanation. Such strong genetic correlations among diverse cognitive measures suggest the possibility that generalist genes that affect learning disabilities and

abilities have even more general effects that extend to most cognitive abilities and elementary cognitive processes and perhaps even to perceptual processes. One of the oldest areas of psychological research involves a general factor that refers to the ubiquitous positive correlations among diverse tests of cognitive processes. This factor was discovered a century ago by Spearman who called it *g* in order to avoid the many connotations of the word intelligence (Spearman, 1904). A meta-analysis of 322 multivariate studies indicates that the average correlation among diverse cognitive tests is .29 (Carroll, 1993); the *g* factor accounts for about 40% of the variance (Jensen, 1998). The *g* factor is also indexed reasonably well by a total score as in IQ tests. The *g* factor has been a focal point for quantitative genetic research with meta-analyses yielding heritability estimates of about .50 (Plomin & Spinath, 2004). Genetic correlations among such tests generally exceed .50.

To what extent do the generalist genes that affect learning disabilities and abilities also affect the *g* factor? Several of the studies reviewed above explored this issue for language, reading, and mathematics and generally find evidence for moderate genetic overlap with the *g* factor. For example, in a report from the Colorado group, a multivariate genetic analysis of phoneme awareness, word recognition, phonological decoding, and orthographic coding yielded genetic correlations with IQ of .56 (.38–.72) for phoneme awareness, .53 (.37–.68) for word recognition, .49 (.30–.67) for phonological decoding, and .44 (.29–.61) for orthographic coding (Gayán & Olson, 2003). These genetic correlations with IQ are lower than the genetic correlations among the language and reading measures themselves (.76 on average), as reviewed earlier, suggesting that not all generalist genes for learning disabilities involve *g*. Other Colorado reports have yielded similar findings (Alarcón, Knopik, & DeFries, 2000; Brooks, Fulker, & DeFries, 1990; Light, DeFries, & Olson, 1998), although some comparisons yielded higher genetic correlations (Alarcón et al., 2000). In the Cleveland study, genetic correlations were also somewhat higher (.57–.85) between language, reading, and mathematics versus specific cognitive abilities of verbal, spatial, perceptual speed, and memory (Thompson et al., 1991). In TEDS, teacher assessments of reading and mathematics at 7 years for about 2,000 same-sex pairs of twins yielded genetic correlations of .58 (.46–.72) between reading and IQ and .67 (.53–.83) between mathematics and IQ, with IQ assessed by two verbal and two nonverbal tests administered by telephone (Kovas et al., in press). Similar results have been reported in other twin studies (Bartels, Rietveld, van Baal, & Boomsma, 2002; Hohnen & Stevenson, 1999; Luo, Thompson, & Detterman, 2003a, 2003b; Viding et al., 2003) and adoption studies (Wadsworth & DeFries, 2003; Wadsworth et al., 1995a, 1995b).

In summary, some generalist genes that affect learning disabilities and abilities appear to be even more general in that they also affect other sorts of cognitive abilities included in the *g* factor. Although these findings are relevant to the current debates about the role of intelligence in the diagnosis of learning disabilities (Lyon, Shaywitz, & Shaywitz, 2003), they do not take us much farther in terms of understanding mechanisms because we do not know what the *g* factor is any more than we know what causes the general factor that pervades learning disabilities and abilities.

It will be difficult to resolve these issues of the nature of the *g* factor and its relationship to learning disabilities and abilities at the behavioral or cognitive levels of analysis. As Spearman noted in 1927, ultimate understanding of the *g* factor "must needs come from the most profound and detailed direct study of the human brain in its purely physical and chemical aspects" (Spearman, 1927, p. 403). However, even the neural level of analysis cannot definitively disentangle causation from correlation, because behavior can affect the brain as well as the brain affecting behavior. DNA is not subject to this direction of effects confusion; neural, cognitive, and behavioral functioning does not change the structure of DNA. For this reason, we suggest that finding generalist genes associated with learning disabilities and abilities will be particularly useful in clarifying the nature of the *g* factor and its relationship to learning disabilities and abilities. As discussed earlier in this section, identifying these generalist genes will make it possible to investigate the gene expression, proteomic, and neural mechanisms by which these genes ultimately have their pleiotropic effects on learning disabilities and abilities as well as on the *g* factor.

Conclusions

Our review of quantitative genetic research indicates that the genes responsible for the high heritabilities of learning disabilities and abilities are largely general in their effects within and between learning disabilities and abilities. This research also indicates that not all genetic effects are general. Genetic effects that are specific within or between learning disabilities and abilities are just as important. However, because it is widely assumed that genetic effects are specific, we have highlighted the surprising extent to which genetic effects are general. We also reiterate that our focus on genetic research is not meant to disparage the important contribution of environmental factors; another review could be written based on these same multivariate genetic studies about the shared and nonshared environmental links between learning disabilities and abilities.

Definitive proof of the importance of generalist genes will come from molecular genetic research that identifies DNA associated with learning disabilities and abilities. The large genetic correlations within and between learning disabilities and abilities suggest that genes with general effects are important targets for molecular genetic research. When these generalist genes are identified, they will greatly accelerate research on general mechanisms at all levels from gene expression and proteomics to brain and mind to behavior.

The implications of generalist genes for clinicians are also far-reaching. For example, the research reviewed in this article suggests that genetic diagnoses differ from traditional diagnoses in that the relevant genes are largely generalists rather than specialists. That is, from a genetic perspective, language, reading, and mathematics disabilities are not distinct diagnostic entities. Although causes are not necessarily related to cures, it seems likely that more general treatments will be required to address such general problems. The full impact of generalist genes on clinical work will come when these genes and their mechanisms are identified. Generalist genes will serve as early warning systems that will foster attempts to prevent learning disabilities rather than waiting for learning disabilities to develop and cast their long shadows over children's lives before attempts are made to treat them.

References

Alarcón, M., DeFries, J. C., Light, J. G., & Pennington, B. F. (1997). A twin study of mathematics disability. *Journal of Learning Disabilities, 30,* 617–623.

Alarcón, M., Knopik, V. S., & DeFries, J. C. (2000). Covariation of mathematics achievement and general cognitive ability in twins. *Journal of School Psychology, 38,* 63–77.

Altmüller, J., Palmer, L. L., Fischer, G., Scherb, H., & Wjst, M. (2001). Genomewide scans of complex human diseases: True linkage is hard to find. *American Journal of Human Genetics, 69,* 936–950.

Baddeley, A. D. (1986). *Working memory.* Oxford, UK: Clarendon Press.

Badian, N. A. (1997). Dyslexia and the double deficit hypothesis. *Annals of Dyslexia, 47,* 69–87.

Bakwin, H. (1973). Reading disability in twins. *Developmental Medicine and Child Neurology, 15,* 184–187.

Banks, R. E., Dunn, M. J., Hochstrasser, D. F., Sanchez, J. C., Blackstock, W., Pappin, D. J., & Selby, P. J. (2000, November 18). Proteomics: New perspectives, new biomedical opportunities. *Lancet, 356,* 1749–1756.

Bartels, M., Rietveld, M. J., van Baal, G. C., & Boomsma, D. I. (2002). Heritability of educational achievement in 12-year-olds and the overlap with cognitive ability. *Twin Research, 5,* 544–553.

Bartlett, C. W., Flax, J. F., Logue, M. W., Vieland, V. J., Bassett, A. S., Tallal, P., & Brzustowicz, L. M. (2002). A major susceptibility locus for specific language impairment is located on 13q21. *American Journal of Human Genetics, 71,* 45–55.

Bassett, D. E., Jr., Eisen, M. B., & Boguski, M. S. (1999). Gene expression informatics—it's all in your mine. *Nature Genetics, 21,* 51–55.

Bates, E., & Goodman, J. C. (1997). On the inseparability of grammar and the lexicon: Evidence from acquisition. *Language and Cognitive Processes, 12,* 507–584.

Bishop, D. V. (1997). Cognitive neuropsychology and developmental disorders: Uncomfortable bedfellows. *Quarterly Journal of Experimental Psychology, 50,* 899–923.

Bishop, D. V. (2001). Genetic influences on language impairment and literacy problems in children: Same or different? *Journal of Child Psychology and Psychiatry, 42,* 189–198.

Bishop, D. V., Bishop, S. J., Bright, P., James, C., Delaney, T., & Tallal, P. (1999). Different origin of auditory and phonological processing problems in children with language impairment: Evidence from a twin study. *Journal of Speech, Language, and Hearing Research, 42,* 155–168.

Bishop, D. V., & Snowling, M. J. (2004). Developmental dyslexia and specific language impairment: Same or different? *Psychological Bulletin, 130,* 858–886.

Blair, C. (in press). Is EF, GF?: A developmental neuroscience examination of component process and psychometric approaches to the study of human cognitive abilities. *Psychological Review*.

Brett, D., Pospisil, H., Valcarcel, J., Reich, J., & Bork, P. (2002). Alternative splicing and genome complexity. *Nature Genetics, 30,* 29–30.

Brooks, A., Fulker, D. W., & DeFries, J. C. (1990). Reading performance and general cognitive ability: A multivariate genetic analysis of twin data. *Personality and Individual Differences, 11,* 141–146.

Butcher, L. M., Meaburn, E., Liu, L., Hill, L., Al-Chalabi, A., Plomin, R., et al. (2004). Genotyping pooled DNA on microarrays: A systematic genome screen of thousands of SNPs in large samples to detect QTLs for complex traits. *Behavior Genetics, 34,* 549–555.

Carlson, C. S., Eberle, M. A., Kruglyak, L., & Nickerson, D. A. (2004). Mapping complex disease loci in whole-genome association studies. *Nature, 429,* 446–452.

Carlsson, P., & Mahlapuu, M. (2002). Forkhead transcription factors: Key players in development and metabolism. *Developmental Biology, 250,* 1–23.

Carroll, J. B. (1993). *Human cognitive abilities.* New York: Cambridge University Press.

Carter, T. A., Del Rio, J. A., Greenhall, J. A., Latronica, M. L., Lockhart, D. J., & Barlow, C. (2001). Chipping away at complex behavior: Transcriptome/phenotype correlations in the mouse brain. *Physiological Behavior, 73,* 849–857.

Castles, A., & Coltheart, M. (1993). Varieties of developmental dyslexia. *Cognition, 47,* 149–180.

Chiat, S. (2001). Mapping theories of developmental language impairment: Premises, predictions and evidence. *Language and Cognitive Processes, 16,* 113–142.

Colledge, E., Bishop, D. V. M., Dale, P., Koeppen-Schomerus, G., Price, T. S., Happé, F., et al. (2002). The structure of language abilities at 4 years: A twin study. *Developmental Psychology, 38,* 749–757.

Collins, F. S., Euyer, M. S., & Chakravarti, A. (1997, November 28). Variations on a theme: Cataloguing human DNA sequence variation. *Science, 278,* 1580–1581.

Conway, A. R., Kane, M. J., & Engle, R. W. (2003). Working memory capacity and its relation to general intelligence. *Trends in Cognitive Science, 7,* 547–552.

Crusio, W. E., & Gerlai, R. T. (1999). *Handbook of molecular-genetic techniques for brain and behavior research.* New York: Elsevier.

Dale, P. S., Dionne, G., Eley, T. C., & Plomin, R. (2000). Lexical and grammatical development: A behavioral genetic perspective. *Journal of Child Language, 27,* 619–642.

Davis, C. J., Gayán, J., Knopik, V. S., Smith, S. D., Cardon, L. R., Pennington, B. F., et al. (2001). Etiology of reading difficulties and rapid naming: The Colorado twin study of reading disability. *Behavior Genetics, 31,* 625–635.

Deary, I. (2000). *Looking down on human intelligence: From psychometrics to the brain.* Oxford, United Kingdom: Oxford University Press.

Deary, I. J. (2001). Human intelligence differences: Towards a combined experimental-differential approach. *Trends in Cognitive Science, 5,* 164–170.

DeFries, J. C., & Fulker, D. W. (1988). Multiple regression analysis of twin data: Etiology of deviant scores versus individual differences. *Acta Geneticae Medicae et Gemellologicae, 37,* 205–216.

DeFries, J. C., & Gillis, J. J. (1993). Genetics and reading disability. In R. Plomin & G. E. McClearn (Eds.), *Nature, nurture, and psychology* (pp. 121–145). Washington, DC: American Psychological Association.

Diamond, A., Briand, L., Fossella, J., & Gehlbach, L. (2004). Genetic and neurochemical modulation of prefrontal cognitive functions in children. *American Journal of Psychiatry, 161,* 125–132.

Dionne, G., Dale, P. S., Boivin, M., & Plomin, R. (2003). Genetic evidence for bidirectional effects of early lexical and grammatical development. *Child Development, 74,* 394–412.

Eddy, S. R. (2001). Non-coding RNA genes and the modern RNA world. *Nature Reviews Genetics, 2,* 919–929.

Elman, J. L., Bates, E. A., Johnson, M. H., Karmiloff-Smith, A., Parisi, D., & Plunkett, K. (1996). *Rethinking innateness: A connectionist perspective on development.* Cambridge, MA: MIT Press.

Enard, W., Przeworski, M., Fisher, S. E., Lai, C. S., Wiebe, V., Kitano, T., et al. (2002, August 22). Molecular evolution of FOXP2, a gene involved in speech and language. *Nature, 418,* 869–872.

Falconer, D. S. (1965). The inheritance of liability to certain diseases estimated from the incidence among relatives. *Annals of Human Genetics, 29,* 51–76.

Fenson, L., Dale, P. S., Reznick, J. S., Bates, E., Thal, D., & Pethick, S. J. (1994). Variability in early communicative development. *Monographs of the Society for Research in Child Development, 59,* 1–173.

Fenson, L., Pethick, S., Renda, C., Cox, J. L., Dale, P. S., & Reznick, J. S. (2000). Short-form version of the MacArthur Communicative Development Inventories. *Applied Psycholinguistics, 21,* 95–116.

Fisher, S. E. (in press). Tangled webs: Tracing the connections between genes and cognition. *Cognition.*

Fisher, S. E., & DeFries, J. C. (2002). Developmental dyslexia: Genetic dissection of a complex cognitive trait. *Nature Reviews Neuroscience, 3,* 767–780.

Fisher, S. E., Francks, C., Marlow, A. J., MacPhie, I. L., Newbury, D. F., Cardon, L. R., et al. (2002). Independent genome-wide scans identify a chromosome 18 quantitative-trait locus influencing dyslexia. *Nature Genetics, 30,* 86–91.

Fodor, J. A. (1983). *The modularity of mind.* Cambridge, MA: MIT Press.

Francks, C., Paracchini, S., Smith, S. D., Richardson, A. J., Scerri, T. S., Cardon, L. R., et al. (2004). A 77-kilobase region of chromosome 6p22.2 is associated with dyslexia in families from the United Kingdom and from the United States. *American Journal of Human Genetics, 75,* 1046–1058.

Garlick, D. (2002). Understanding the nature of the general factor of intelligence: The role of individual differences in neural plasticity as an explanatory mechanism. *Psychological Review, 109,* 116–136.

Gayán, J., & Olson, R. K. (1999). Reading disability: Evidence for a genetic etiology. *European Child and Adolescent Psychiatry, 8,* 52–55.

Gayán, J., & Olson, R. K. (2001). Genetic and environmental influences on orthographic and phonological skills in children with reading disabilities. *Developmental Neuropsychology, 20,* 483–507.

Gayán, J., & Olson, R. K. (2003). Genetic and environmental influences on individual differences in printed word recognition. *Journal of Experimental Child Psychology, 84,* 97–123.

Golub, T. R., Slonim, D. K., Tamayo, P., Huard, C., Gaasenbeek, M., Mesirov, J. P., et al.(1999, October 15). Molecular classification of cancer: Class discovery and class prediction by gene expression monitoring. *Science, 286,* 531–537.

Gopnik, M. (1990, April 19). Feature-blind grammar and dysphagia. *Nature, 19,* 715.

Grant, S. G. N. (2003). An integrative neuroscience program linking genes to cognition and disease. In R. Plomin, J. C. DeFries, I. W. Craig, & P. McGuffin (Eds.), *Behavioral genetics in the postgenomic era* (pp. 123–138). Washington, DC: American Psychological Association.

Gray, J. R., & Thompson, P. M. (2004). Neurobiology of intelligence: Science and ethics. *Nature Reviews Neuroscience, 5,* 471–482.

Grigorenko, E. L. (2001). Developmental dyslexia: An update on genes, brains, and environments. *Journal of Child Psychology and Psychiatry, 42,* 91–125.

Grigorenko, E. L., Ngorosho, D., Romano, C., Naples, A., Turechek, L., Kochetkova, A., & Chang, J. (2004, June). Molecular-genetic studies of reading disability in candidate genes. Paper presented at the 34th annual meeting of the Behavior Genetics Association, Aix-en-Provence, France.

Haier, R. J., Jung, R. E., Yeo, R. A., Head, K., & Alkire, M. T. (2004). Structural brain variation and general intelligence. *NeuroImage, 23,* 425–433.

Harlaar, N., Dale, P. S., & Plomin, R. (in press). Correspondence between telephone testing and teacher assessments of reading skills in a sample of 7-year-old twins: II. Strong genetic overlap. *Reading and Writing: An Interdisciplinary Journal.*

Harlaar, N., Hayiou-Thomas, M. E., & Plomin, R. (in press). Reading and general cognitive ability: A multivariate analysis of 7-year-old twins. *Scientific Studies of Reading.*

Harlaar, N., Spinath, F. M., Dale, P. S., & Plomin, R. (2005). Genetic influences on early word recognition abilities and disabilities: A study of 7-year-old twins. *Journal of Child Psychology and Psychiatry, 46,* 373–384.

Hayiou-Thomas, M. E., Harlaar, N., & Plomin, R. (2004). *Pre-school language and 7-year-old reading: Aetiological links.* Manuscript submitted for publication.

Hayiou-Thomas, M. E., Kovas, Y., Harlaar, N., Bishop, D. V. M., Dale, P., & Plomin, R. (2004). *Common genetic aetiology for diverse language skills in 4½ year old twins.* Manuscript submitted for publication.

Hohnen, B., & Stevenson, J. (1999). The structure of genetic influences on general cognitive, language, phonological, and reading disabilities. *Developmental Psychology, 35,* 603.

Inoue, K., & Lupski, J. R. (2003). Genetics and genomics of behavioral and psychiatric disorders. *Current Opinion in Genetic Development, 13,* 303–309.

International Human Genome Sequencing Consortium. (2001, February 15). Initial sequencing and analysis of the human genome. *Nature, 409,* 860–921.

Iyer, V. R., Eisen, M. B., Ross, D. T., Schuler, G., Moore, T., Lee, J. C. F., et al. (1999, Jan 1). The transcriptional program in the response of human fibroblasts to serum. *Science, 283,* 83–87.

Jensen, A. R. (1998). *The g factor: The science of mental ability.* Westport, CT: Praeger.

Kanazawa, S. (2004). General intelligence as a domain-specific adaptation. *Psychological Review, 111,* 512–523.

Karmiloff-Smith, A. (1992). *Beyond modularity: A developmental perspective on cognitive science.* Cambridge, MA: MIT Press.

King, R. A., Motulsky, A. G., & Rotter, J. I. (2002). *The genetic basis of common diseases (Oxford Monographs on Medical Genetics*). Oxford, United Kingdom: Oxford University Press.

Knopik, V. S., Alarcón, M., & DeFries, J. C. (1997). Comorbidity of mathematics and reading deficits: Evidence for a genetic etiology. *Behavior Genetics, 27,* 447–453.

Knopik, V. S., Alarcón, M., & DeFries, J. C. (1998). Common and specific gender influences on individual differences in reading performance: A twin study. *Personality and Individual Differences, 25,* 269–277.

Knopik, V. S., & DeFries, J. C. (1999). Etiology of covariation between reading and mathematics performance: A twin study. *Twin Research, 2,* 226–234.

Knopik, V. S., Smith, S. D., Cardon, L., Pennington, B., Gayán, J., Olson, R. K., DeFries, J. C. (2002). Differential genetic etiology of reading component processes as a function of IQ. *Behavior Genetics, 32,* 181–198.

Kovas, Y., Harlaar, N., Petrill, S. A., & Plomin, R. (in press). Generalist genes and mathematics in 7-year-old twins. *Intelligence.*

Lai, C. S., Fisher, S. E., Hurst, J. A., Vargha-Khadem, F., & Monaco, A. P. (2001, October 4). A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature, 413,* 519–523.

Lai, C. S., Gerrelli, D., Monaco, A. P., Fisher, S. E., & Copp, A. J. (2003). FOXP2 expression during brain development coincides with adult sites of pathology in a severe speech and language disorder. *Brain, 126,* 2455–2462.

Leach, M. (2004). Gene expression informatics. *Methods in Molecular Biology, 258,* 153–166.

Leonard, L. B. (1998). *Children with specific language impairment.* Cambridge, MA: MIT Press.

Light, J. G., & DeFries, J. C. (1995). Comorbidity of reading and mathematics disabilities: Genetic and environmental etiologies. *Journal of Learning Disabilities, 28,* 96–106.

Light, J. G., DeFries, J. C., & Olson, R. K. (1998). Multivariate behavioral genetic analysis of achievement and cognitive measures in reading-disabled and control twin pairs. *Human Biology, 70,* 215–237.

Lockhart, D. J., & Barlow, C. (2001). Expressing what's on your mind: DNA arrays and the brain. *Nature Reviews Neuroscience, 2,* 63–68.

Loehlin, J. C., & Nichols, J. (1976). *Heredity, environment and personality.* Austin, TX: University of Texas Press.

Lu, T., Pan, Y., Kao, S. Y., Li, C., Kohane, I., Chan, J., & Yankner, B. A. (2004, June 24). Gene regulation and DNA damage in the aging human brain. *Nature, 429,* 883–891.

Luciano, M., Wainwright, M., Wright, M. J., Geffen, G. M., Duffy, D. L., & Martin, N. G. (in press). Using multivariate linkage methods to locate QTLs for word recognition and IQ [Abstract]. *Behavior Genetics.*

Luciano, M., Wright, M. J., Smith, G. A., Geffen, G. M., Geffen, L. B., & Martin, N. G. (2003). Genetic covariance between processing speed and IQ. In R. Plomin, J. C. DeFries, I. W. Craig, & P. McGuffin (Eds.), *Behavioral genetics in the postgenomic era* (pp. 163–181). Washington, DC: American Psychological Association.

Luo, D., Thompson, L. A., & Detterman, D. K. (2003a). The causal factor

underlying the correlation between psychometric g and scholastic performance. *Intelligence, 31,* 67–83.

Luo, D., Thompson, L. A., & Detterman, D. K. (2003b). Phenotypic and behavioral genetic covariation between elemental cognitive components and scholastic measures. *Behavior Genetics, 33,* 221–246.

Lyon, G. R., Shaywitz, S. E., & Shaywitz, B. A. (2003). Defining dyslexia, comorbidity, teachers' knowledge of language and reading: A definition of dyslexia. [Abstract]. *Annals of Dyslexia, 53,* 1.

Marlow, A. J., Fisher, S. E., Francks, C., MacPhie, I. L., Cherny, S. S., Richardson, A. J., et al. (2003). Use of multivariate linkage analysis for dissection of a complex cognitive trait. *American Journal of Human Genetics, 72,* 561–570.

Martin, N. G., & Eaves, L. J. (1977). The genetical analysis of covariance structure. *Heredity, 38,* 79–95.

Martin, N. G., Jardine, R., & Eaves, L. J. (1984). Is there only one set of genes for different abilities? A reanalysis of the National Merit Scholarship Qualifying Tests (NMSQT) data. *Behavior Genetics, 14,* 355–370.

Matheny, A. P., Jr., Dolan, A. B., & Wilson, R. S. (1976). Twins with academic learning problems: Antecedent characteristics. *American Journal of Orthopsychiatry, 46,* 464–469.

Mazzocco, M. M., & Myers, G. F. (2003). Complexities in identifying and defining mathematics learning disability in the primary school-age years. *Annals of Dyslexia, 53,* 218–253.

Meaburn, E., Dale, P. S., Craig, I. W., & Plomin, R. (2002). Language-impaired children: No sign of the FOXP2 mutation. *NeuroReport, 13,* 1075–1077.

Morgan, J. L., & Demuth, K. (1996). *Signal to Syntax: Bootstrapping from speech to grammar in early acquisition.* Mahwah, NJ: Erlbaum.

Neale, M. C., & Kendler, K. S. (1995). Models of comorbidity for multifactorial disorders. *American Journal of Human Genetics, 57,* 935–953.

Neubauer, A. C., Spinath, F. M., Riemann, R., Borkenau, P., & Angleitner, A. (2000). Genetic (and environmental) influence on two measures of speed of information processing and their relation to psychometric intelligence: Evidence from the German Observational Study of Adult Twins. *Intelligence, 28,* 267–289.

Newbury, D. F., Bonora, E., Lamb, J. A., Fisher, S. E., Lai, C. S. L., Baird, G. et al. (2002). FOXP2 is not a major susceptibility gene for autism or specific language impairment. *American Journal of Human Genetics, 70,* 1318–1327.

Oliver, B., Dale, P. S., & Plomin, R. (2004). *Writing and its relationship with reading and oral language as assessed by teachers in seven-year olds: A behavioural genetic approach.* Manuscript submitted for publication.

Oliver, B., Harlaar, N., Hayiou-Thomas, M. E., Kovas, Y., Walker, S. O., Petrill, S. A., et al. (2004). A twin study of teacher-reported mathematics performance and low performance in 7-year-olds. *Journal of Educational Psychology, 96,* 504–517.

Page, G. P., George, V., Go, R. C., Page, P. Z., & Allison, D. B. (2003). "Are we there yet?": Deciding when one has demonstrated specific genetic causation in complex diseases and quantitative traits. *American Journal of Human Genetics, 73,* 711–719.

Pennington, B. F. (in press). A multiple deficit model for understanding developmental disorders. *Cognition.*

Pennington, B. F., Filipek, P. A., Lefly, D., Chhabildas, N., Kennedy, D. N., Simon, J. H., et al. (2000). A twin MRI study of size variations in human brain. *Journal of Cognitive Neuroscience, 12,* 223–232.

Petrill, S. A. (2002). The case for general intelligence: A behavioral genetic perspective. In R. J. Sternberg & E. L. Grigorenko (Eds.), *The general factor of intelligence: How general is it?* (pp. 281–298). Mahwah, NJ: Erlbaum.

Pinker, S. (1994). *The language instinct.* New York: Morrow.

Plomin, R. (1991). Genetic risk and psychosocial disorders: Links between the normal and abnormal. In M. Rutter & P. Casaer (Eds.), *Biological risk factors for psychosocial disorders* (pp. 101–138). Cambridge, United Kingdom: Cambridge University Press.

Plomin, R. (2001a). Genetic factors contributing to learning and language delays and disabilities. *Child and Adolescent Psychiatric Clinics of North America, 10,* 259–277.

Plomin, R. (2001b). The genetics of g in human and mouse. *Nature Reviews Neuroscience, 2,* 136–141.

Plomin, R. (2003a). Genes and behaviour: Cognitive abilities and disabilities in normal populations. In M. A. Ron & T. Robbins (Eds.), *Disorders of Brain and Mind II* (2nd ed., pp. 3–29). Cambridge, United Kingdom: Cambridge University Press.

Plomin, R. (2003b). Genetics, genes, genomics and g. *Molecular Psychiatry, 8,* 1–5.

Plomin, R., & DeFries, J. C. (1979). Multivariate behavioral genetic analysis of twin data on scholastic abilities. *Behavior Genetics, 9,* 505–517.

Plomin, R., DeFries, J. C., Craig, I. W., & McGuffin, P. (2003). *Behavioral genetics in the postgenomic era.* Washington, DC: American Psychological Association.

Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2001). *Behavioral Genetics* (4th ed.). New York: Worth Publishers.

Plomin, R., & Kosslyn, S. (2001). Genes, brain and cognition. *Nature Neuroscience, 4,* 1153–1155.

Plomin, R., Owen, M. J., & McGuffin, P. (1994, June 17). The genetic basis of complex human behaviors. *Science, 264,* 1733–1739.

Plomin, R., & Spinath, F. M. (2002). Genetics and general cognitive ability (*g*). *Trends in Cognitive Science, 6,* 169–176.

Plomin, R., & Spinath, F. M. (2004). Intelligence: Genetics, genes, and genomics. *Journal of Personality and Social Psychology, 86,* 112–129.

Posthuma, D., de Geus, E. J., Baare, W. F., Pol, H. E. H., Kahn, R. S., & Boomsma, D. I. (2002). The association between brain volume and intelligence is of genetic origin. *Nature Neuroscience, 5,* 83–84.

Posthuma, D., de Geus, E. J. C., & Boomsma, D. I. (2001). Perceptual speed and IQ are associated through common genetic factors. *Behavior Genetics, 31,* 593–602.

Posthuma, D., de Geus, E. J. C., & Boomsma, D. I. (2003). Genetic contributions to anatomical, behavioral, and neurophysiological indices of cognition. In R. Plomin, J. C. DeFries, I. W. Craig, & P. McGuffin (Eds.), *Behavioral genetics in the postgenomic era* (pp. 141–161). Washington, DC: American Psychological Association.

Rhee, S. H., Hewitt, J. K., Lessem, J. M., Stallings, M. C., Corley, R. P., & Neale, M. C. (2004). The validity of the Neale and Kendler model-fitting approach in examining the etiology of comorbidity. *Behavior Genetics, 34,* 251–265.

Rijsdijk, F. V., & Boomsma, D. I. (1997). Genetic mediation of the correlation between peripheral nerve conduction velocity and IQ. *Behavior Genetics, 27,* 87–98.

Shallice, T. (1988). *From neuropsychology to mental structure.* New York: Cambridge University Press.

Shaywitz, B. A., Shaywitz, S. E., Blachman, B. A., Pugh, K. R., Fulbright, R. K., Skudlarski, P., et al. (2004). Development of left occipitotemporal systems for skilled reading in children after a phonologically-based intervention. *Biological Psychiatry, 55,* 926–933.

Shrout, P. E., & Fleiss, J. (1979). Intraclass correlations: Uses in assessing rater reliability. *Psychological Bulletin, 86,* 420–428.

Shu, W., Yang, H., Zhang, L., Lu, M. M., & Morrisey, E. E. (2001). Characterization of a new subfamily of winged-helix/forkhead (Fox) genes that are expressed in the lung and act as transcriptional repressors. *Journal of Biological Chemistry, 276,* 27488–27497.

SLI Consortium. (2002). A genome wide scan identifies two novel loci involved in specific language impairment. *American Journal of Human Genetics, 70,* 384–398.

Smith, C. (1974). Concordance in twins: Methods and interpretation. *American Journal of Human Genetics, 26,* 454–466.

Spearman, C. (1904). "General intelligence," objectively determined and measured. *American Journal of Psychology, 15,* 201–292.

Spearman, C. (1927). *The abilities of man: Their nature and measurement.* New York: Macmillan.

Spinath, F. M., Price, T. S., Dale, P. S., & Plomin, R. (2004). The genetic and environmental origins of language disability and ability. *Child Development, 75,* 445–454.

Stevenson, J. (1991). Which aspects of processing text mediate genetic effects? *Reading & Writing, 3,* 249–269.

Stevenson, J., Graham, P., Fredman, G., & McLoughlin, V. (1987). A twin study of genetic influences on reading and spelling ability and disability. *Journal of Child Psychology and Psychiatry, 28,* 229–247.

Stromswold, K. (2001). The heritability of language: A review and meta-analysis of twin, adoption, and linkage studies. *Language, 77,* 647–723.

Taipale, M., Kaminen, N., Nopola-Hemmi, J., Haltia, T., Myllyluoma, B., Lyytinen, H., et al. (2003). A candidate gene for developmental dyslexia encodes a nuclear tetratricopeptide repeat domain protein dynamically regulated in brain. *Proceedings of the National Academy of Sciences, USA, 100,* 11553–11558.

Thompson, L. A., Detterman, D. K., & Plomin, R. (1991). Associations between cognitive abilities and scholastic achievement: Genetic overlap but environmental differences. *Psychological Science, 2,* 158–165.

Thompson, P. M., Cannon, T. D., Narr, K. L., van Erp, T., Poutanen, V. P., Huttunen, M., et al. (2001). Genetic influences on brain structure. *Nature Neuroscience, 4,* 1253–1258.

Tiu, R. D., Jr., Wadsworth, S. J., Olson, R. K., & DeFries, J. C. (2004). Causal models of reading disability: A twin study. *Twin Research, 7,* 275–283.

Tomasello, M. (2003). *Constructing a language: A usage-based theory of language acquisition.* Boston: Harvard University Press.

Tomblin, J. B., & Buckwalter, P. R. (1998). Heritability of poor language achievement among twins. *Journal of Speech, Language, and Hearing Research, 41,* 188–199.

Torgesen, J. K., Wagner, R. K., & Rashotte, C. A. (1999). *Test of word reading efficiency.* Austin, TX: Pro-Ed.

Trouton, A., Spinath, F. M., & Plomin, R. (2002). Twins early development study (TEDS): A multivariate, longitudinal genetic investigation of language, cognition, and behavior problems in childhood. *Twin Research, 5,* 444–448.

van Baal, G. C. M., Boomsma, D. I., & De Geus, E. J. C. (in press). Genetics of EEG coherence and IQ in young twins. *Behavior Genetics.*

Van Beijsterveldt, C. E., Molenaar, P. C., de Geus, E. J., & Boomsma, D. I. (1998). Genetic and environmental influences on EEG coherence. *Behavior Genetics, 28,* 443–453.

Van Orden, G. C., Pennington, B. F., & Stone, G. O. (2001). What do double dissociations prove? *Cognitive Science, 25,* 111–172.

Vargha-Khadem, F., Watkins, K. E., Price, C. J., Ashburner, J., Alcock, K. J., Connelly, A., et al. (1998). Neural basis of an inherited speech and language disorder. *Proceedings of the National Academy of Sciences, USA, 95,* 12695–12700.

Vernon, P. A., Wickett, J. C., Banzana, P. G., & Stelmack, R. M. (2000). The neuropsychology and psychophysiology of human intelligence. In R. J. Sternberg (Ed.), *Handbook of Intelligence* (pp. 245–264). Cambridge, United Kingdom: Cambridge University Press.

Viding, E., Price, T. S., Spinath, F. M., Bishop, D. V., Dale, P. S., & Plomin, R. (2003). Genetic and environmental mediation of the relationship between language and nonverbal impairment in 4-year-old twins. *Journal of Speech, Language, and Hearing Research, 46,* 1271–1282.

Viding, E., Spinath, F. M., Price, T. S., Bishop, D. V. M., Dale, P. S., & Plomin, R. (2004). Genetic and environmental influences on language impairment in 4-year-old same-sex and opposite-sex twins. *Journal of Child Psychology and Psychiatry, 45,* 315–325.

Wadsworth, S. J., & DeFries, J. C. (2003). Etiology of the stability of reading performance from 7 to 12 years of age and its possible mediation by IQ. In S. A. Petrill, R. Plomin, J. C. DeFries, & J. K. Hewitt (Eds.), *Nature, nurture, and the transition to early adolescence.* New York: Oxford University Press.

Wadsworth, S. J., DeFries, J. C., Fulker, D. W., & Plomin, R. (1995a). Cognitive ability and academic achievement in the Colorado adoption project: A multivariate genetic analysis of parent-offspring and sibling data. *Behavior Genetics, 25,* 1–15.

Wadsworth, S. J., DeFries, J. C., Fulker, D. W., & Plomin, R. (1995b). Covariation among measures of cognitive ability and academic achievement in the Colorado Adoption Project: Sibling analysis. *Personality and Individual Differences, 18,* 63–73.

Wadsworth, S. J., Knopik, V. S., & DeFries, J. C. (2004). Reading disability in boys and girls: No evidence for a differential genetic etiology. *Reading & Writing, 13,* 133–145.

Willcutt, E. G., DeFries, J. C., Pennington, B. F., Smith, S. D., Cardon, L. R., & Olson, R. K. (2003). Genetic etiology of comorbid reading difficulties and ADHD. In R. Plomin, J. C. DeFries, I. W. Craig, & P. McGuffin (Eds.), *Behavioral genetics in the postgenomic era* (pp. 227–246). Washington, DC: American Psychological Association.

Wolf, M., & Bowers, P. (2000). The question of naming-speed deficits in developmental reading disability: An introduction to the double-deficit hypothesis. *Journal of Learning Disabilities, 33,* 322–324.

Zondervan, K. T., & Cardon, L. R. (2004). The complex interplay among factors that influence allelic association. *Nature Reviews Genetics, 5,* 89–100.

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