

ANALYZING COMORBIDITY<sup>☆</sup>

*Bruce F. Pennington*

UNIVERSITY OF DENVER, USA

*Erik Willcutt and Soo Hyun Rhee*

UNIVERSITY OF COLORADO, USA

I. INTRODUCTION

- A. DEFINITION AND IMPORTANCE OF COMORBIDITY
- B. OVERVIEW OF CHAPTER

II. EXPLANATIONS OF COMORBIDITY

- A. ARTIFACTUAL EXPLANATIONS
- B. NON-ARTIFACTUAL EXPLANATIONS

III. METHODS FOR ANALYZING COMORBIDITY

- A. KLEIN AND RISO'S FAMILY PREVALENCE ANALYSES
- B. FAMILY PREVALENCE ANALYSES IN THE LITERATURE
- C. NEALE AND KENDLER MODEL FITTING APPROACH
- D. UNDERLYING DEFICITS APPROACH
- E. CONCLUSIONS

IV. ANALYSES OF SPECIFIC COMORBIDITIES

- A. READING DISABILITY AND SPEECH SOUND DISORDER
- B. READING DISABILITY AND ADHD
- C. CONDUCT DISORDER AND ADHD
- D. IMPLICATIONS FOR OTHER POSSIBLE PAIRS

V. MULTIFACTORIAL MODEL

REFERENCES

**I. Introduction**

A. DEFINITION AND IMPORTANCE OF COMORBIDITY

A fundamental question for psychology is how does atypical development relate to typical development. An adequate theory of development will need to

<sup>☆</sup> This work was supported by NIH grants MH38820, HD27802, HD04024, and DA13956.

43 account for both human universals *and* individual differences, hopefully with  
44 the same underlying mechanisms. So every example of atypical development  
45 poses both a challenge and an opportunity for developmental theory. In this  
46 chapter, we focus on a pervasive characteristic of atypical development,  
47 comorbidity among behavioral disorders. Comorbidity is relevant for develop-  
48 mental theory because it can provide insights into how behavioral disorders  
49 develop. Each disorder can be conceived of as having a particular develop-  
50 mental trajectory, in which some mechanisms underlying normal development  
51 are perturbed and many others are intact. The phenomenon of comorbidity often  
52 means that the developmental trajectories for different disorders intersect. These  
53 intersection points can be particularly informative about underlying mechan-  
54 isms. We hope to demonstrate how analyses of comorbidity may shed some  
55 light on these intersection points and hence the mechanisms that underlie both  
56 typical and atypical development.

57 Comorbidity simply means the co-occurrence in a single patient of two or  
58 more diagnoses (Feinstein, 1970). Because both the scientific and clinical value  
59 of a diagnostic construct depends in part on it providing a unifying explanation of  
60 the diverse signs and symptoms presented by a patient, unexplained comorbidity  
61 is a phenomenon that potentially poses problems for the explanatory value of  
62 diagnostic constructs. Perhaps the two comorbid disorders are simply different  
63 manifestations of the same underlying disease process, in which case only one  
64 diagnostic construct is needed. These different manifestations could be present at  
65 the same time or one could precede the other. For instance, only when the  
66 infectious agent responsible for syphilis (the spirochete bacteria) was discovered,  
67 could it be appreciated that the very different signs and symptoms of the three  
68 stages of this disease were all part of the same disorder. So progress in  
69 understanding the etiological and pathogenetic mechanisms that underlie  
70 syndromal collections of signs and symptoms can explain and ultimately  
71 eliminate comorbidities, because diagnostic boundaries are redrawn. It follows  
72 that comorbidity is more likely when diagnostic constructs are more descriptive  
73 than explanatory and less is known about underlying mechanisms, which is  
74 clearly the case for psychiatric diagnoses.

75 In fact, unlike much of the rest of medicine, current psychiatric nosologies,  
76 such as the DSM-IV or the ICD-10, contain diagnostic constructs that are  
77 *intentionally* just descriptive, because we do not yet know enough about  
78 underlying mechanisms to use them to define psychiatric disorders. Because  
79 earlier psychiatric nosologies were based on unproven assumptions about  
80 underlying mechanisms and because diagnostic definitions were not specific  
81 enough to be reliable across diagnosticians, developing reliable descriptive  
82 diagnostic categories was a scientific step *forward* for psychopathology research.  
83 But defining psychopathologies in terms of underlying mechanisms instead of  
84 just symptoms remains a key long-term goal of research on psychiatric disorders.

85 As we demonstrate in this chapter, analyzing comorbidity is one strategy for  
86 reaching that goal.

87 More specifically there are four main reasons why comorbidity is important for  
88 both research and clinical practice (Caron & Rutter, 1991; Klein, 1993, 2003;  
89 Klein & Riso, 1993). First, the presence of a comorbid disorder (e.g., anxiety)  
90 may influence the course and treatment of another disorder (e.g., depression).  
91 Second, if comorbidity is ignored, one may falsely conclude that some variable is  
92 associated with a given disorder (e.g., conduct problems in reading disability  
93 (RD)), when in fact the association is due to a comorbid condition (e.g., attention  
94 deficit hyperactivity disorder (ADHD)). Third, as discussed previously,  
95 comorbidity is a threat to the validity of diagnostic constructs. Finally, as we  
96 demonstrate in this chapter, analyses of comorbidity can also be a very useful  
97 “wedge” for prying apart underlying mechanisms, which in turn will allow us to  
98 develop more valid diagnostic constructs.

## 100 B. OVERVIEW OF CHAPTER

101  
102 In what follows, we first document that comorbidity is a pervasive  
103 phenomenon in both adult and child psychiatry, consider both artifactual and  
104 non-artifactual explanations of comorbidity, discuss genetic and cognitive  
105 methods for testing these explanations, provide examples of the application of  
106 these methods to specific, common comorbidities found in child psychopathology,  
107 explain the complex disease model and how it accounts for comorbidity,  
108 and consider implications for future research.

109 Extensive research documents the pervasiveness of comorbidity of psychiatric  
110 disorders, both in adults (see review by Clark, Watson, and Reynolds (1995) and  
111 children (see reviews by Caron and Rutter (1991) and by Angold, Costello, and  
112 Erkanli (1999)). For adults, more than half of individuals with one DSM  
113 diagnosis had at least one additional comorbid diagnosis in two different large  
114 national epidemiological studies: 60% in the Epidemiological Catchment Area  
115 (ECA) study (Robins, Locke, & Regier, 1991), and 56% in the National  
116 Comorbidity Survey (NCS) study (Kessler *et al.*, 1994). Moreover, those with  
117 comorbid disorders account for a large proportion of all diagnoses: 79% of all  
118 lifetime diagnoses and 82% of all 12-month diagnoses in the NCS survey.  
119 Finally, although pervasive, comorbidity is not random; some pairs of disorders  
120 co-occur much more frequently than others.

121  
122 For children, somewhat similar results have been found. In an epidemiological  
123 study in Puerto Rico (Bird *et al.*, 1988), almost half of children with one diagnosis  
124 had a second diagnosis. Several other studies have documented high rates of  
125 comorbidity among childhood psychiatric disorders (e.g., Jensen *et al.*, 1995;  
126 Steingard *et al.*, 1992). Again, some pairs of disorders, such as ADHD and

127 Conduct Disorder, CD, co-occur much more frequently than other pairs, such as  
128 CD and Anxiety disorder (Angold, Costello, & Erkanli, 1999).

## 131 II. Explanations of Comorbidity

132  
133 In what follows, we consider possible explanations for the phenomenon of  
134 comorbidity, dividing these into artifactual and non-artifactual explanations.  
135 Before doing that, it is useful to consider some other factors that influence the  
136 phenomenon of comorbidity. Klein and Riso (1993) made the important point  
137 that the concept of comorbidity presupposes that disorders are discrete  
138 categories, an assumption that has been hotly debated in the case of psychiatric  
139 disorders. Lilienfeld, Waldman, and Israel (1994) have argued that the term  
140 comorbidity is misleading when applied to psychiatric disorders because we do  
141 not know if they are discrete clinical entities. But even if psychiatric disorders are  
142 dimensional rather than discrete, covariation among the defining dimensions is an  
143 important phenomenon to understand. As we will see, some of the methods for  
144 analyzing comorbidity presented here do not require the assumption that  
145 psychiatric disorders are discrete categories.

146 Another factor that influences the phenomenon of comorbidity is whether the  
147 nosology employs hierarchical exclusion rules (Clark, Watson, & Reynolds,  
148 1995). For instance, in DSM-IV, a diagnosis of ADHD is precluded by a  
149 diagnosis of mental retardation or autism because the latter diagnoses are more  
150 severe and pervasive. But this exclusion assumes that we know that primary  
151 autism causes comorbid ADHD, which may not be correct. In DSM-III, there  
152 were many more such hierarchical exclusion rules than in DSM-IV and  
153 consequently the rates of comorbidity observed using DSM-III are lower than  
154 when using DSM-IV. Because many of the hierarchical exclusionary rules  
155 in DSM-III lacked a theoretical or empirical rationale, they were dropped in  
156 DSM-IV. This change in DSM criteria illustrates a broader point: it is hard for  
157 diagnostic criteria to remain purely descriptive. Implicit theories of disorders  
158 inevitably creep into their definition and relations with each other.

### 160 A. ARTIFACTUAL EXPLANATIONS

161  
162  
163 Although the phenomenon of comorbidity may signal an unappreciated causal  
164 relation between two disorders, it may also simply be an artifact of some kind.  
165 So before undertaking more extensive research to discover this possible causal  
166 relation, researchers must rule out artifactual explanations. Both Caron and  
167 Rutter (1991) and Klein and Riso (1993) discuss several artifactual explanations  
168 of comorbidity: chance, sampling bias, population stratification, definitional

169 overlap, and rater biases. We next briefly discuss each of these artifactual  
170 explanations and how they may be tested.

171 First of all, two disorders may co-occur simply by *chance*. The rate of such  
172 comorbidity is simply the product of their prevalences in the population. So, for  
173 two disorders A and B, each with a prevalence of 10%, the chance rate of  
174 comorbidity in the population will be 1%. If the rate of comorbidity in a  
175 population sample is significantly greater than 1%, then we can reject chance as  
176 the explanation. Both [Angold, Costello, and Erklani \(1999\)](#) and [Caron and Rutter \(1991\)](#)  
177 found that rates of comorbidity observed among several childhood  
178 disorders in epidemiological samples were significantly greater than what would  
179 be predicted by chance. [Angold, Costello, and Erkanli \(1999\)](#) performed a meta-  
180 analysis of epidemiological studies in which they computed the median odds  
181 ratio and 95% confidence intervals for pairs of disorders to test whether the rates  
182 of different comorbidities differed from chance and from each other. For instance,  
183 they found the median odds ratio for the comorbidity between ADHD and CD  
184 was 10.7 (confidence interval = 7.7–14.8), whereas that for Anxiety and CD was  
185 3.1 (confidence interval = 2.2–4.6). These results tell us each comorbidity is  
186 greater than chance would predict and that the rate of comorbidity between CD  
187 and ADHD is greater than that between CD and Anxiety.

188 Second, apparent comorbidity might be due to *sampling bias*, the best known  
189 example of which is Berkson's bias. [Berkson \(1946\)](#) showed that apparent  
190 comorbidities between otherwise independent disorders will arise in referred  
191 samples if the probability for referral of either or both disorders is less than one.  
192 In this case, comorbid individuals will be over-represented because their  
193 probability of being referred is a combined function of the referral rates of each of  
194 their disorders. A simpler way of putting this is that people with more problems  
195 are more likely to seek help. Therefore, referred or clinic samples will not provide  
196 reliable estimates of comorbidity, unless we know the population rates of each  
197 disorder and the referral rates and biases affecting the clinic in question. If  
198 known, these parameters could be used to estimate the actual comorbidity from  
199 the observed comorbidity, but usually not all these parameters are known.

200 Third, apparent comorbidity might be due to *population stratification*.  
201 Although the risk factors for each disorder A and B are in fact independent in  
202 the population as a whole, they may co-occur in certain strata of the population. If  
203 our test of comorbidity is performed on that strata, then we will falsely conclude  
204 that comorbidity between A and B happens more frequently than by chance. For  
205 instance, non-random or assortative mating by individuals with disorders A and B  
206 will produce apparent comorbidity in their offspring, if both disorders are  
207 familial. Such non-random mating appears to explain the comorbidity between  
208 depression and alcoholism ([Merikangas, 1982](#)). As a second example of  
209 population stratification, [Caron and Rutter \(1991\)](#) discuss the apparent  
210 comorbidity between depression and conduct disorder in children. In this case,

211 depression in parents acts in different ways to create an increased risk for each  
212 disorder in offspring: parental depression is both a genetic and environmental risk  
213 factor for depression in a child and parental depression increases marital discord,  
214 which is an environmental risk factor for conduct disorder in the child.

215 Fourth, *definitional overlap* could produce artifactual comorbidity. If some of  
216 the defining symptoms for disorders A and B are the same, then individuals with  
217 those overlapping symptoms will be more likely to be comorbid than if the  
218 defining symptoms did not overlap. If one still finds comorbidity after deleting  
219 the overlapping symptoms, then one can reject this artifactual explanation. But  
220 the converse is not necessarily the case because deleting symptoms changes the  
221 definition of each disorder.

222 Fifth, *rater biases* or halo effects can produce artifactual comorbidity. If the  
223 ratings for both disorders A and B are provided by the same informant, such as a  
224 teacher or parent, then the rater's concern about the child's true disorder A may  
225 lead them to endorse more symptoms of disorder B, thus producing comorbidity.

226

227

#### B. NON-ARTIFACTUAL EXPLANATIONS

228

229 [Neale and Kendler \(1995\)](#) presented the quantitative specifications of Klein  
230 and Riso's models, describing 13 comorbidity models providing the most  
231 comprehensive set of possible explanations for comorbidity. The first of these  
232 models is the Chance model described previously, and the other 12 models are  
233 non-artifactual explanations for comorbidity (see [Figure 1](#)).

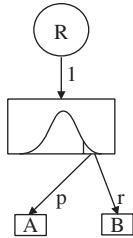
234 In [Figure 1](#), the latent variable "R" refers to the multifactorial liability for each  
235 disorder (e.g.,  $R_A$  = multifactorial liability for disorder A,  $R_B$  = multifactorial  
236 liability for disorder B). The liability distributions with the thresholds in the  
237 boxes are simply another way of representing the multifactorial liability for each  
238 disorder. (Note that the path coefficient from the latent variable "R" and the  
239 liability distributions with the thresholds is always 1.) The individuals who cross  
240 the threshold in the liability distribution manifest disorder A or B.

241 All of the Neale and Kendler comorbidity models are versions of the  
242 continuous liability threshold model, which assumes that there is a continuous  
243 liability distribution of multifactorial causes (genetic and/or environmental  
244 causes) for a disorder, and that a disorder occurs if an individual crosses a  
245 particular threshold in that liability distribution. The 12 non-artifactual  
246 explanations for comorbidity can be divided into four groups of related models:  
247 alternate forms, multiformity (six models), three independent disorders, and  
248 correlated liabilities (four models).

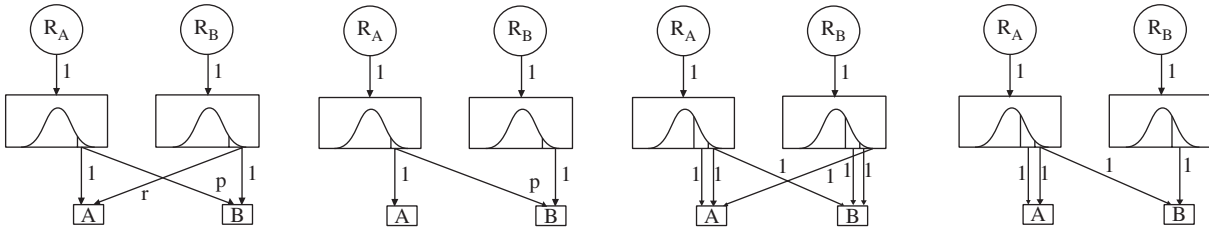
249 The alternate forms model hypothesizes that comorbidity occurs because the  
250 two comorbid disorders are alternate manifestations of a single liability. For  
251 individuals who cross a particular threshold in that single liability distribution,  
252 the probability of having disorder A is  $p$ , and the probability of having disorder B

253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294

Alternate Forms Model



Multiformity Models



Random Multiformity Model

Random Multiformity of A Model

Extreme Multiformity Model

Extreme Multiformity of A Model

Fig. 1. Neale and Kendler models  $R$  is a latent variable that refers to the multifactorial liability for each disorder. The latent  $R$ s for disorder A or B are independent unless connected by a line or lines. The liability distribution is a normal curve with a threshold (or thresholds) on the extreme high end. Those falling above the threshold have the disorder A or B or both, and are represented by the boxes labeled A or B.

295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336

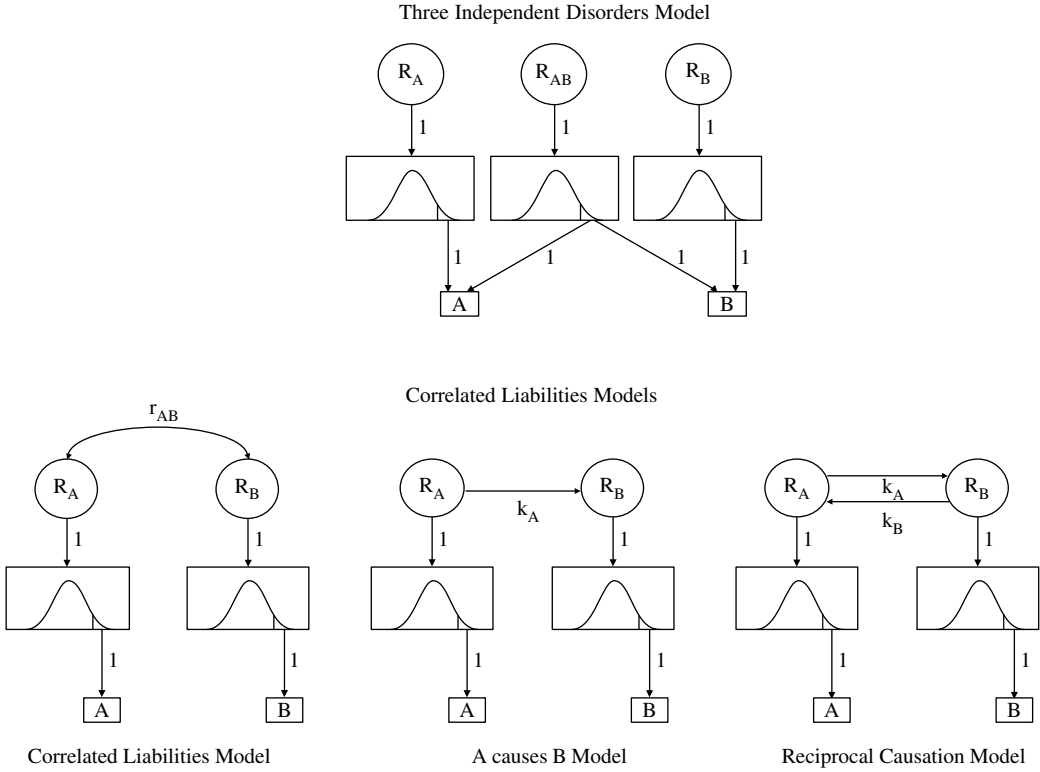


Fig. 1. Continued.

337 is  $r$ . This means that both disorders share a single liability, and that one person  
338 manifests disorder A while another person manifests disorder B because of  
339 chance or risk factors that vary across individuals. A gene by environment  
340 interaction where the environmental risk factor is specific to an individual is  
341 an example of how comorbidity may occur through alternate forms. If two  
342 individuals have the same overall liability but are exposed to different person-  
343 specific environmental risks, the first individual may manifest disorder A while  
344 the second individual manifests disorder B. A gene by environment interaction  
345 that replicates across individuals would not be an example of the alternate forms  
346 model.

347 In multiformity models, an individual who has one disorder is at an increased risk  
348 for having the second disorder, despite not having an elevated liability for the  
349 second disorder. Although having a disorder without having the liability for it may  
350 seem contradictory, it is important to remember that behavioral disorders are  
351 defined at the level of symptoms, whereas liability is defined in terms of underlying  
352 etiological mechanisms. So, sometimes the symptoms of a disorder can be produced  
353 without the usual underlying etiological mechanisms being present. Two of the  
354 multiformity models, the random multiformity of A and random multiformity of B  
355 models illustrate this possibility. They are the “phenocopy” model often discussed  
356 in the literature. The “phenocopy” model hypothesizes that the first disorder  
357 produces a copy of the second disorder; hence, the first disorder is primary whereas  
358 the second disorder is secondary. For example, [Pennington, Groisser, and Welsh \(1993\)](#)  
359 suggested that reading disability might lead to the phenotypic manifestation  
360 of ADHD in the absence of etiological influences typically associated with ADHD  
361 in isolation. One can readily imagine that a child might appear to be inattentive or  
362 hyperactive in the classroom due to the frustration elicited by difficulties with  
363 reading, rather than as a consequence of the neurocognitive difficulties that are  
364 typically associated with ADHD in the absence of RD.

365 According to the three independent disorders model, comorbidity occurs  
366 because the comorbid disorder is a disorder that is separate from either disorder  
367 occurring alone. It is sometimes referred to as the “subtype” hypothesis in the  
368 literature.

369 The four correlated liabilities models share the idea that there is a continuous  
370 relation between the liability to one disorder and the liability to the second  
371 disorder. An increase in liability for one disorder is correlated with the increase in  
372 liability for the second disorder. (In contrast, in the multiformity models, a  
373 change in liability for one disorder has absolutely no effect on the second disorder  
374 unless an individual crosses the threshold for the first disorder and is actually  
375 affected by the disorder.) The relation between the liability of the two disorders  
376 occurs via a significant correlation between the risk factors (correlated liabilities)  
377 or a direct causal relation between the manifest phenotypes of the two disorders  
378 (A causes B, B causes A, or reciprocal causation).

379 Although the [Neale and Kendler \(1995\)](#) models are a major contribution to the  
380 comorbidity literature because they are the most complete set of models yet  
381 proposed and because they are specified quantitatively, they nonetheless have some  
382 limitations. Specifically, they do not include a neural or a cognitive level, they are  
383 not explicitly developmental, they only deal with pairwise comorbidities, and some  
384 of them can be difficult to distinguish empirically, even with ideal (simulated)  
385 data sets. Most of these limitations are apparent in the sections that follow.

386

387

388

### III. Methods for Analyzing Comorbidity

389

390 Given the importance of discriminating the correct comorbidity model among  
391 many alternatives, a series of studies ([Rhee \*et al.\*, 2003, 2004a,b,c](#)) examined  
392 whether various methods testing alternative comorbidity models are valid. In all  
393 studies, simulations were conducted to test the validity of the common methods  
394 used to test alternative comorbidity models.

395 Data were simulated for each of the 13 Neale and Kendler comorbidity models;  
396 in these simulated data, the true cause of comorbidity is known. Then, analyses  
397 commonly used to test the alternative comorbidity models were conducted on  
398 each of the 13 simulated datasets. If a particular analysis is valid, the predicted  
399 result should be found in the data simulated for the comorbidity model, and the  
400 predicted result should not be found in data simulated for other comorbidity  
401 models (i.e., the particular analysis should discriminate a particular comorbidity  
402 model from alternative hypotheses).

403

404

#### A. KLEIN AND RISO'S FAMILY PREVALENCE ANALYSES

405

406 For each comorbidity model, [Klein and Riso \(1993\)](#) presented a set of  
407 predictions regarding the prevalence of disorders in the relatives of different  
408 groups of probands. They presented a comprehensive set of predictions  
409 comparing the prevalence of disorder A-only, disorder B-only, and disorder  
410 AB (i.e., both disorders) among the relatives of probands with A-only, B-only,  
411 AB, and controls. Several studies have used these predictions to test alternative  
412 comorbidity models (e.g., [Donaldson \*et al.\*, 1997](#); [Riso \*et al.\*, 1996](#);  
413 [Wickramaratne & Weissman, 1993](#)).

414 Most of Klein and Riso's predictions were validated by the simulation results, in  
415 that most of their predicted results matched the results in the simulated datasets.  
416 However, there were several notable differences between the predicted results and  
417 results obtained in the simulated datasets. Some of Klein and Riso's predictions  
418 were not obtained in the simulated results because of lack of power in the  
419 simulated datasets. Another reason for the discrepancy between the predicted  
420 results and the results in the simulated dataset was the predictions' lack of

421 consideration of all possible pathways for the comorbid disorder, notably the fact  
422 that there will be some individuals who have both disorders A and B due to chance.

#### 423 B. FAMILY PREVALENCE ANALYSES IN THE LITERATURE

425 Many other researchers (e.g., [Biederman et al., 1992](#); [Bierut et al., 1998](#)) have  
426 conducted a subset of the Klein and Riso analyses or analyses very similar to  
427 those presented by [Klein and Riso \(1993\)](#) without testing their comprehensive set  
428 of predictions. Most of the studies in the literature have focused on three  
429 comorbidity models: (a) the alternate forms model (i.e., the two comorbid  
430 disorders are alternate manifestations of the same underlying liability); (b) the  
431 correlated liabilities model (i.e., there is a significant correlation between the  
432 liabilities for the two models); and (c) the three independent disorders model (i.e.,  
433 the comorbid disorder is a third disorder that is etiologically distinct from either  
434 disorder occurring alone).

435 The results of the study ([Rhee et al., 2003](#)) examining the validity of family  
436 prevalence analyses found in the literature indicate that although some analyses  
437 validly discriminate the alternate forms model from other comorbidity models,  
438 the analyses testing the correlated liabilities model and the three independent  
439 disorders model did not discriminate them from other comorbidity models. In  
440 many cases, although the predicted results were consistent with a particular  
441 comorbidity model, they were also consistent with several alternative  
442 comorbidity models.

#### 443 C. NEALE AND KENDLER MODEL FITTING APPROACH

444 [Neale and Kendler \(1995\)](#) described 13 alternative models. They illustrated the  
445 probabilities for the four combinations of disease state (neither A nor B; A but not  
446 B; B but not A; both A and B) for each comorbidity model, then illustrated the  
447 probabilities for the ten combinations of affected or unaffected status for pairs of  
448 relatives for each comorbidity model (e.g., neither A nor B in relative 1 and neither  
449 A nor B in relative 2; both A and B in relative 1, and A only in relative 2). The data  
450 that are analyzed in the Neale and Kendler model fitting approach are simply the  
451 frequency tables for the number of relative pairs in each possible combination  
452 of disease state. The observed cell frequencies are compared to the expected  
453 cell frequencies (i.e., the probabilities for the ten combinations of affected or  
454 unaffected status for pairs of relatives) in each comorbidity model. The  
455 comorbidity model with the smallest difference between the observed cell  
456 frequencies and the expected cell frequencies is chosen as the best fitting model.

457 In general, the Neale and Kendler model fitting approach discriminated the  
458 following classes of models reliably: the alternate forms model, the random  
459 multiformity models (i.e., random multiformity, random multiformity of A, and  
460 multiformity of B).

463 random multiformity of B), the extreme multiformity models (i.e., extreme  
464 multiformity, extreme multiformity of A, and extreme multiformity of B), the  
465 three independent disorders model, and the correlated liabilities models (i.e.,  
466 correlated liabilities, A causes B, B causes A, and the reciprocal causation).  
467 Discrimination within these classes of models was poorer. Results from  
468 simulations varying the prevalences of the comorbid disorders indicate that the  
469 ability to discriminate between models becomes poorer as the prevalences of the  
470 disorders decreases, and suggests the importance of considering the issue of  
471 power when conducting these analyses.

472

473

#### D. UNDERLYING DEFICITS APPROACH

474

475 Several researchers have tested alternative comorbidities by comparing the  
476 underlying neuropsychological deficits of the two comorbid disorders in  
477 individuals with neither disorder, A only, B only, and both A and B. So, unlike  
478 the family prevalence approaches just discussed, this method examines groups of  
479 unrelated individuals. For example, Pennington, Groisser, and Welsh (1993)  
480 examined the comorbidity between reading disability and ADHD, comparing the  
481 underlying deficits associated with reading disability (i.e., phonological  
482 processes) and the underlying deficits associated with ADHD (i.e., executive  
483 functioning) in individuals with neither disorder, reading disability only, ADHD  
484 only, and both reading disability and ADHD. Most of the researchers using this  
485 approach have made predictions for 5 of the 13 Neale and Kendler comorbidity  
486 models. In addition to the three models often tested using family prevalence  
487 analyses in the literature (i.e., alternate forms, correlated liabilities, and three  
488 independent disorders), researchers have made predictions regarding the random  
489 Q1 multiformity of A or random multiformity of B models (i.e., an individual who  
490 has one disorder is at an increased risk for having the second disorder, although  
491 he or she may not have an elevated liability for the second disorder).

492 Given adequate power, the method of examining the underlying deficits of  
493 comorbid disorders can distinguish between all 13 Neale and Kendler comorbidity  
494 models, except the random multiformity, extreme multiformity, and three  
495 independent disorders models. As the sample sizes decreased and the magnitude  
496 of correlation between the underlying deficits and the symptom scores decreased,  
497 the ability to discriminate the correct comorbidity model from alternative  
498 hypotheses decreased. Again, the issue of power should be considered carefully.

499

500

#### E. CONCLUSIONS

501

502 Although most of Klein and Riso's family prevalence analyses were valid,  
503 there were notable discrepancies between their predicted results and results found  
504 in the simulated datasets. Some of the family prevalence analyses found in

505 the literature were valid predictors of the alternate forms model, but none were  
506 valid predictors of the correlated liabilities or three independent disorders  
507 models. The Neale and Kendler model fitting approach and the method of  
508 examining the underlying deficits of comorbid disorders discriminated between  
509 several comorbidity models reliably, suggesting that these two methods may be  
510 the most useful methods found in the literature. Especially encouraging is the fact  
511 that some of the models that cannot be distinguished well using the Neale and  
512 Kendler model fitting approach can be distinguished well by examining the  
513 underlying deficits of comorbid disorders, and vice versa. The best approach may  
514 be a combination of these two methods. However, simulation results suggest that  
515 the issue of power should be considered carefully.

#### 517 **IV. Analyses of Specific Comorbidities**

519 In this section, we present analyses of three specific comorbidities commonly  
520 found among childhood disorders: between speech sound disorder (SSD) and  
521 reading disability, between RD and ADHD, and between ADHD and conduct  
522 disorder (CD). These examples were chosen because each individual disorder has  
523 a high prevalence among children and each comorbidity has received enough  
524 empirical attention to make a review worthwhile. Not incidentally, these were  
525 also comorbidities that we have studied.

527 Of these three comorbidities, perhaps the most surprising one is that between  
528 RD and ADHD because we think of these disorders as being cognitively distinct.  
529 RD is usually conceptualized as a kind of language disorder, involving a problem  
530 in phonological development and ADHD is usually conceptualized as a kind of  
531 executive disorder, involving a problem in the development of inhibitory control  
532 (Pennington, 2002). Hence, the comorbidity between RD and ADHD qualifies as  
533 an example of what Angold, Costello, and Erkanli (1999) call “heterotypic  
534 comorbidity” in which the comorbidity is between disorders from different  
535 diagnostic groupings. In contrast, homotypic comorbidity is between disorders  
536 from the same diagnostic grouping. The frequently studied comorbidities among  
537 anxiety disorders or between depression and dysthymia are good examples of  
538 homotypic comorbidity. The other two comorbidities that we present here,  
539 between RD and SSD, and between ADHD and CD can be considered examples  
540 of homotypic comorbidities because RD and SSD are both language disorders  
541 and ADHD and CD are both externalizing disorders. Of course, as Angold,  
542 Costello, and Erkanli (1999) point out, the distinction between homotypic and  
543 heterotypic comorbidity is not completely clear-cut because it presupposes that  
544 we already have an adequate scientific understanding of these disorders.

545 It is also interesting to note that research on each of these three comorbidities  
546 has rejected an initially favored and seemingly intuitive explanation. For the

547 comorbidity between SSD and RD, this favored hypothesis (severity) was an  
548 example of the alternate forms model, in which the two disorders share the same  
549 liability distribution but are different phases or expressions of that liability. On  
550 this hypothesis, the etiology shared by SSD and RD disrupts phonological  
551 development, which then manifests as speech problems in the preschool years  
552 and as reading problems in the school years. For RD and ADHD, the initially  
553 favored hypothesis for this counterintuitive comorbidity was that it was either an  
554 artifact or a phenocopy (multiformity of RD). In either of these cases, the  
555 underlying liabilities for pure RD and ADHD would be distinct. For ADHD and  
556 CD, one favored hypothesis was the three independent disorders model, in which  
557 the combination of ADHD and CD was a distinct disorder from either ADHD or  
558 CD alone. This hypothesis was favored because there were distinct correlates of  
559 comorbid ADHD + CD compared to each disorder in isolation. So research on  
560 each of these three comorbidities has produced some counterintuitive results,  
561 which have led us to new models of how disorders develop and why they are  
562 comorbid.

563

564

#### A. READING DISABILITY AND SPEECH SOUND DISORDER

565

566 From some perspectives, it does not make sense that SSD and RD should be  
567 comorbid. SSD (Shriberg, Tomblin, & McSweeney, 1999) involves difficulties in  
568 the preschool development of *spoken* language, specifically problems with the  
569 accurate (and therefore intelligible) production of speech sounds in spoken words  
570 (it is distinct from stuttering or mutism). RD, or dyslexia, manifests at school age  
571 with difficulty in learning *written* language, specifically printed word recognition  
572 and spelling (see IDA and NICHD working definition of dyslexia, Dickman,  
573 2003). In the past, RD has been conceptualized as a visual disorder (Orton, 1925)  
574 and SSD has been conceptualized as an auditory or motor disorder. So, from these  
575 perspectives, each disorder would appear to require a different neurobiological  
576 origin. But as discussed earlier, if each disorder is viewed as a kind of language  
577 disorder, then their comorbidity is less surprising and could be called homotypic.  
578 However, as we will see, we have had to reject our initial favored hypothesis for  
579 their comorbidity, the severity variant of the alternate forms hypothesis.

580

#### 1. *Symptom Overlap Between SSD and RD*

582 Children with early speech/language problems are at increased risk for later  
583 literacy problems (Aram, Ekelman, & Nation, 1984; Bishop & Adams, 1990;  
584 Catts et al., 2002; Hall & Tomblin, 1978; Magnusson & Naucler, 1990; Rutter &  
585 Mawhood, 1991; Scarborough & Dobrich, 1990; Snowling & Stackhouse, 1983;  
586 Snowling, Bishop, & Stothard, 2000; Tomblin, Freese, & Records, 1992)  
587 and individuals with literacy problems retrospectively report increased rates of  
588 earlier speech and language problems (Hallgren, 1950; Rutter & Yule, 1975).

589 Moreover, the latter association is not limited to retrospective reports because  
590 young children selected for family risk for dyslexia or RD and followed  
591 prospectively also have higher rates of preschool speech and language problems  
592 than controls (Gallagher, Frith, and Snowling, 2000; Gilger *et al.*, 1994; Lyytinen  
593 *et al.*, 2002; Pennington & Lefly, 2001; Scarborough, 1990). But these previous  
594 studies have rarely distinguished SSD from specific language impairment (SLI),  
595 which is defined by deficits in semantics and syntax. So, it is less clear which  
596 subtypes (or components) of SSD *per se* presage which kinds of later literacy  
597 problems.

## 599 2. *Cognitive and Etiological Overlap Between SSD and RD*

600 The large majority of children with problems in printed word recognition (i.e.,  
601 dyslexia or RD) have deficits on measures of phonological processing (Wagner &  
602 Torgesen, 1987), including measures of both explicit (i.e., phoneme awareness)  
603 and implicit (i.e., phonological memory and rapid serial naming) phonological  
604 processing. There is also accumulating evidence that many children with speech  
605 and language problems have phonological processing problems, such as deficits  
606 on measures of phoneme awareness and phonological memory (Bird & Bishop,  
607 1992; Bird, Bishop, & Freeman, 1995; Bishop, North, & Donlan, 1995;  
608 Clarke-Klein & Hodson, 1995; Edwards & Lahey, 1998; Kamhi *et al.*, 1988;  
609 Leonard, 1982; Lewis & Freebairn, 1992; Montgomery, 1995).

610 Support for a shared etiology for SSD and RD has been provided by Lewis and  
611 colleagues (Lewis, 1990, 1992; Lewis, Ekelman, & Aram, 1989), who found that  
612 SSD and RD are co-familial. We have found that SSD and RD are coheritable as  
613 well (Tunick & Pennington, 2002).

614 The etiological and cognitive overlap between SSD and RD suggests a  
615 parsimonious *severity* hypothesis, namely that many cases of SSD and RD lie on  
616 a severity continuum in which shared etiological risk factors lead to a shared  
617 underlying phonological deficit. If the phonological deficit is severe enough, it  
618 first produces SSD and then later RD. So, according to the severity hypothesis,  
619 SSD and RD are alternate forms of the same underlying liability expressed at  
620 different points in development. If it is less severe, it does not produce  
621 diagnosable SSD (though it may lead to subclinical speech production problems),  
622 but it does produce later RD, because reading requires more mature phonological  
623 representations than does speech. So this hypothesis posits that RD without  
624 earlier SSD is a less severe variant of SSD and has a less extreme threshold on the  
625 same liability distribution. To account for children with SSD who do not develop  
626 later RD, the severity hypothesis must posit that they have a subtype of SSD that  
627 is not caused by an underlying phonological deficit. The already documented  
628 etiological and cognitive overlap between SSD and RD supports this severity  
629 hypothesis. But because SSD has not been clearly distinguished from SLI in  
630

631 previous etiological and cognitive studies, other possible hypotheses can explain  
632 the relation between SSD and RD.

633

### 634 3. *Hypotheses to Explain SSD/RD Comorbidity*

635 In an NIH grant application, one of us (BFP) once proposed five competing  
636 hypotheses (all but one of which were single cognitive deficit hypotheses) to  
637 account for the comorbidity of SSD and RD (see [Figure 2](#)). These hypotheses  
638 were generated without knowledge of the [Klein and Risso \(1993\)](#) hypotheses,  
639 yet all but one of them (cognitive phenocopy) corresponds to one of their  
640 hypotheses. These hypotheses were generated by crossing two distinctions: a  
641 common vs. distinct etiology and a common vs. distinct cognitive phenotype.  
642 These five hypotheses were: (1) severity (both etiology and cognitive phenotype  
643 are shared, but comorbid children have a more severe phonological deficit); (2)  
644 pleiotropy (a shared etiology leads to two distinct cognitive phenotypes, which  
645 co-occur in comorbid children); (3) cognitive phenocopy or genetic heterogen-  
646 eity (distinct etiologies lead to a shared cognitive phenotype, thus producing  
647 comorbidity); (4) cross-assortment or non-random mating (both the etiology and  
648 cognitive phenotypes are distinct, but individuals with SSD (or RD) are more  
649 likely to select mates with RD (or SSD), thus transmitting risk alleles for both  
650 disorders to their children); and (5) synergy, in which the etiologies and cognitive  
651 phenotypes of SSD and RD are distinct, but comorbidity between SSD and *SLI*  
652 produces later RD. The severity and pleiotropy hypotheses correspond to  
653 different versions of [Klein and Riso's \(1993\)](#) alternate forms hypothesis; synergy  
654 is similar to the three independent disorders hypothesis; and assortment is an  
655 example of the population stratification hypothesis, as discussed earlier.

656

### 657 4. *Tests of the Five Hypotheses*

658 To distinguish these five hypotheses, three questions need to be addressed. (1)  
659 Do SSD and RD share a common genetic etiology? (2) Do they share an  
660 underlying cognitive phenotype? (3) Is there assortative mating between  
661 individuals with SSD and those with RD? In what follows, we present what is  
662 known about the answers to these questions.

663 First, there is now stronger evidence for a shared genetic etiology between RD  
664 and SSD, which rejects hypotheses 3–5, all of which posit distinct etiologies for  
665 RD and SSD. Two groups have now tested whether some of the risk loci already  
666 identified for RD are risk loci for SSD. Several replicated risk loci or QTLs for  
667 RD have been identified, on chromosomes 1p, 2p, 3p–q, 6p, 15q, and 18p ([Fisher  
& DeFries, 2002](#)). Stein and colleagues found that SSD is linked to the RD locus  
668 on chromosome 3 ([Stein et al., 2004](#)). They tested several related phenotypes,  
669 including SSD itself, phonological memory, phonological awareness, and  
670 reading. All of these phenotypes were linked to the RD risk locus on  
671 chromosome 3, indicating that this locus affects phonological development and  
672

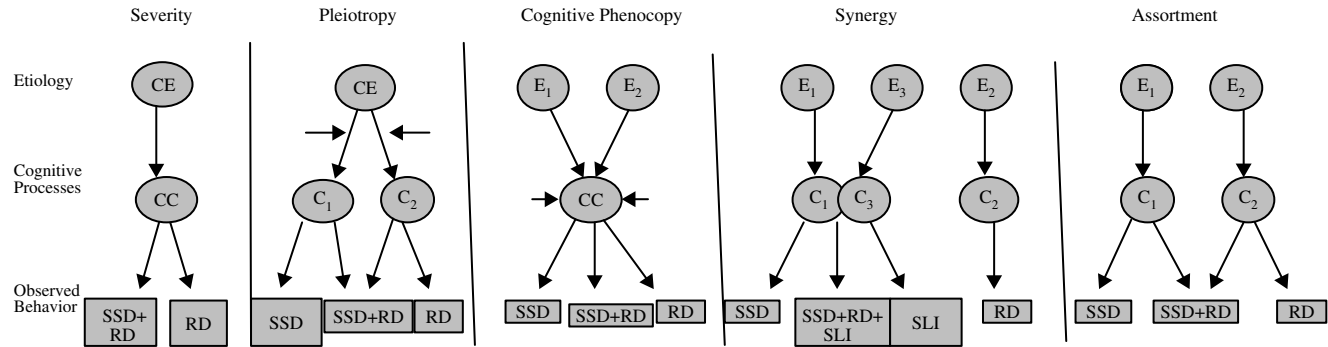


Fig. 2. Schematic representation of five hypotheses. E = Common Etiology; CC = Common Cognitive Phenotype; E<sub>1</sub>, E<sub>2</sub>, E<sub>3</sub> = Specific etiologies; C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub> = Specific cognitive phenotypes. Horizontal arrows indicate influence of additional chance factors.

673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714

715 contributes to the comorbidity between SSD and RD. We have also found that  
716 SSD is linked to RD risk loci on chromosomes 6 and 15, and perhaps 1 (Smith  
717 *et al.*, 2003). We also tested multiple phenotypes, including SSD itself,  
718 phonological memory, and phonological awareness, all of which provided  
719 evidence for linkage.

720 The second test of these five hypotheses is whether RD and SSD share an  
721 underlying cognitive deficit. To perform this test, we examined preliteracy skills,  
722 including phoneme awareness, in a large sample of preschool children with SSD  
723 (Raitano *et al.*, 2004). Because we were also interested in whether the cognitive  
724 deficit in SSD varied by subtype, we divided the sample along two dimensions,  
725 presence vs. absence of SLI, and a persistent speech disorder vs. a speech  
726 disorder that has now normalized. We found that a phoneme awareness deficit  
727 was pervasive across the four resulting subtypes of SSD, although its severity  
728 varied in an additive fashion as a function of each subtype dimension. Those with  
729 SLI had a worse phonological awareness deficit than those without SLI; those  
730 with a persistent speech disorder had a worse phonological awareness deficit than  
731 those whose speech problems had normalized. A similar pattern of results was  
732 found for alphabet knowledge. Intriguingly, the SSD group had a less pronounced  
733 deficit in rapid serial naming. So the results of this study, along with other  
734 evidence reviewed earlier, indicate a shared underlying phonological deficit in  
735 SSD and RD, and that this shared deficit is found in all four subtypes of SSD.  
736 Thus, the results of this second test reject the phenocopy hypothesis and only  
737 partially support the severity hypothesis, which requires a fairly common subtype  
738 of SSD *without* a phonological deficit. The fact that the phonological awareness  
739 deficit is not restricted to the group with both SSD and SLI is also inconsistent  
740 with the predictions of the synergy hypothesis, which is also contradicted by the  
741 genetic results just discussed.

742 To address the third question regarding assortative mating, we examined the  
743 parents in our large sample of children with SSD (Tunick *et al.*, in preparation).  
744 Relative to control parents, parents of SSD probands reported higher rates of both  
745 speech and reading problems, indicating that SSD was familial in this sample and  
746 that SSD and RD were co-familial. We also found similar results in the siblings  
747 of probands; they had higher rates of speech problems and worse scores on  
748 preliteracy measures than controls. These results indicate an etiological overlap  
749 between SSD and RD, consistent with the studies discussed earlier. In contrast,  
750 we found low rates of cross-assortment in these parents. Moreover, SSD  
751 probands with comorbid preliteracy problems rarely came from cross-assorted  
752 parents. So we did not find support for the assortment hypothesis.

753 In sum the results of these three tests reject all but the severity hypothesis. But  
754 despite the fact that the severity hypothesis garners some support from these data  
755 and that of previous studies reviewed earlier, there are still significant challenges  
756 to how it accounts for the nature of the comorbidity between SSD and RD.

757 The severity hypothesis proposes that SSD and RD are comorbid because they  
758 share etiological risk factors (some of which are genetic) and these lead to a  
759 shared phonological deficit, which is more *severe* in children with comorbid SSD  
760 and RD than children with RD only. To account for SSD children who do not  
761 become RD, the severity hypothesis must postulate a subtype of SSD with a  
762 distinct etiology and a different underlying cognitive deficit. If SSD children  
763 without later RD nonetheless have an underlying phonological deficit, the  
764 severity hypothesis must be seriously questioned. But the results of [Raitano et al.](#)  
765 [\(2004\)](#) just discussed suggest there is not a common subtype of SSD without a  
766 phonological deficit. Clearer evidence on this point is provided by long-term  
767 follow-up study ([Snowling, Bishop, & Stothard, 2000](#)) of SSD children initially  
768 identified by Bishop at preschool age. These researchers found there were former  
769 SSD children with a persistent deficit in phoneme awareness in adolescence who  
770 are nonetheless normal readers. Both these results are inconsistent with the  
771 severity hypothesis.

772 **Q2** Subsequent data from Tunick (2004) also questions the severity hypothesis.  
773 Her project involved two comparisons of SSD and RD, one between probands at  
774 age 5 and one between siblings of probands around age 8. The goal of the proband  
775 comparison was to test which deficits are shared and specific to each disorder  
776 before the onset of literacy instruction. The sibling comparison tested the  
777 familiarity of these patterns and whether they persist to a later age.

778 Because both SSD and RD vary in the severity of the symptoms that define  
779 them diagnostically, it is important to compare SSD and RD groups that are  
780 similar in severity. Consequently, Tunick matched the SSD and RD proband  
781 groups on severity, as well as on age and gender. The 23 SSD probands were  
782 selected from the entire sample of SSD probands in our current study so as to  
783 match the 23 RD probands from our earlier longitudinal study of children at high  
784 family risk for RD ([Pennington & Lefly, 2001](#)). The RD probands were all the  
785 children in the high family risk group who were later diagnosed as RD at follow-  
786 up. For the sibling comparison, Tunick recruited a separate sample of RD siblings  
787 and matched them to a subset of our current sample of SSD siblings on (1)  
788 proband sibling's diagnostic severity, (2) their own diagnostic severity, and (3)  
789 age and gender.

790 The comparison of the profiles of phonological processing deficits in probands  
791 and siblings tests the severity hypothesis, which predicts similar profiles in each  
792 disorder, with greater impairment in the SSD group. We examined three  
793 phonological processing constructs: phonological awareness, phonological  
794 memory, and rapid serial naming. In the proband comparison, somewhat  
795 different measures of the same constructs had been used with each group, so their  
796 z-scores relative to matched controls were used to compare the SSD and RD  
797 proband groups. In the sibling comparison, the same measures were used in each  
798 group. We found that SSD and RD probands shared a deficit of similar magnitude

799 (relative to their controls) on the phonological awareness composite, but had  
800 significantly different profiles overall, producing a significant group  $\times$  domain  
801 interaction. The interaction arose because the SSD proband group performed  
802 significantly better than the RD proband group on the rapid serial naming  
803 composite and non-significantly worse score on the phonological memory  
804 composite. This interaction replicated in the sibling comparison, in which the  
805 *same* measures of these constructs were used in each group. The relative strength  
806 on rapid serial naming measures in both SSD groups is a somewhat surprising  
807 finding, given that one would expect a slower articulatory rate in SSD. So, it will  
808 be important to replicate this result in another SSD sample. But this finding could  
809 help explain why not all SSD children develop later RD, despite having a  
810 phonological awareness deficit. In sum, Tunick's (2004) results do not support  
811 the predictions of the single deficit, severity model because the phonological  
812 awareness deficit is not more severe in the SSD groups and because the profiles of  
813 phonological deficits are not parallel.

814 These difficulties with the severity hypothesis led us to develop an alternative  
815 *multiple* cognitive deficit model of RD and SSD, which is presented later in this  
816 chapter. In this multiple deficit model, comorbidity between these two disorders  
817 arises from partially overlapping genetic risk factors (i.e., correlated liabilities)  
818 that lead to a shared cognitive deficit (in phonological representations), which  
819 interacts with other non-shared cognitive deficits to produce the symptoms that  
820 distinguish the two disorders.

821 The severity and the multiple deficit hypotheses make competing predictions  
822 about the literacy outcome of children with SSD. The severity hypothesis predicts  
823 (1) that SSD children who do not develop later RD (SSD-only children) have a  
824 distinct form of SSD without an underlying phonological deficit, and (2) that SSD  
825 children who do develop later RD (comorbid children) have a more severe  
826 phonological deficit than both RD children without earlier SSD (RD-only  
827 children) and RD children in general (because only about 30% of RD children  
828 had earlier SSD). In contrast, the multiple deficit hypothesis predicts (1) that  
829 SSD-only children have a phonological deficit but compensate for it via other  
830 cognitive protective factors, and (2) that comorbid children will not necessarily  
831 have a more severe phonological deficit than RD-only children or RD children in  
832 general, but they must have an additional cognitive risk factor to explain why  
833 they have RD.

834

835

#### B. READING DISABILITY AND ADHD

836

837 RD and ADHD are two of the most common disorders of childhood, each  
838 occurring in approximately five percent of the population (e.g., [American](#)  
839 [Psychiatric Association, 2000](#)). ADHD and RD also co-occur significantly more  
840 frequently than expected by chance; 25–40% of individuals with ADHD also

841 meet criteria for RD (e.g., (Dykman & Ackerman, 1991; Semrud-Clikeman *et al.*,  
842 1992), whereas 15–40% of individuals with RD meet criteria for ADHD (Gilger,  
843 Pennington, & DeFries, 1992; Shaywitz, Fletcher, & Shaywitz, 1995; Willcutt &  
844 Pennington, 2000a,b).

845

### 846 1. *Artifactual Explanations for Comorbidity Between RD and ADHD*

847 Most of the artifactual explanations for comorbidity described previously can  
848 be rejected for RD/ADHD comorbidity. RD and ADHD co-occur more  
849 frequently than expected by chance in both samples ascertained from clinics  
850 (e.g., Semrud-Clikeman *et al.*, 1992) and non-referred samples recruited from the  
851 community (e.g., Fergusson & Horwood, 1992; Willcutt & Pennington, 2000a,b;  
852 Willcutt *et al.*, in press a,b). Because RD is assessed by cognitive tests whereas  
853 ADHD is assessed by behavioral ratings, the relation between RD and ADHD  
854 cannot be explained by shared method variance. Similarly, the symptoms of RD  
855 and ADHD as defined in the fourth edition of the *Diagnostic and Statistical*  
856 *Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 1994,  
857 2000) do not overlap.

858 According to the cross-assortment hypothesis, an individual with RD is more  
859 likely to have a child with an individual with ADHD than would be expected by  
860 chance based on population base rates of RD and ADHD. In a family study of the  
861 biological relatives of children with ADHD, Faraone *et al.* (1993) found that  
862 comorbidity between learning disabilities and ADHD was best explained by  
863 cross-assortment. However, this result was not replicated in later studies (Doyle  
864 *et al.*, 2001; Friedman *et al.*, 2003), suggesting that cross-assortment is not likely  
865 to explain the majority of cases of comorbid RD and ADHD.

866 The rater-bias hypothesis is somewhat more difficult to test, and the possibility  
867 remains that parents or teachers may be more likely to endorse ADHD symptoms  
868 on a rating scale when they know that the child is experiencing difficulty in  
869 learning to read. However, results from our population-based twin study of RD  
870 and ADHD indicate that in addition to higher ratings of inattention symptoms by  
871 parents and teachers, children with RD report greater attentional difficulties than  
872 children without RD on self-report measures (Willcutt, Chhabildas, &  
873 Pennington, 1998). Although the rater-bias hypothesis cannot be conclusively  
874 rejected based on these results, these data suggest it is unlikely to provide a  
875 sufficient explanation for all cases of comorbidity between RD and ADHD.

876

### 877 2. *Competing Explanations for True Comorbidity Between RD and ADHD*

878 Three of Neale and Kendler's (1995) competing explanations have received  
879 at least some support in previous studies of comorbidity between RD and ADHD.  
880 These models include the phenocopy (multiformity of A) hypothesis (e.g.,  
881 Pennington, Groisser, & Welsh, 1993), the three independent disorders  
882 hypothesis (e.g., Rucklidge & Tannock, 2002), and the correlated liabilities

883 (common etiology) hypothesis (e.g., Willcutt, Pennington, & DeFries, 2000,  
884 Willcutt et al. in press a,b). We consider each.

885

886 *a. The Phenocopy Hypothesis.* Pennington et al. (1993) described results in  
887 a small sample of children with RD and ADHD that suggested that RD might lead  
888 to the phenotypic manifestation of ADHD in the absence of the etiological  
889 influences typically associated with ADHD in isolation. They reached this  
890 conclusion because the group with ADHD without RD exhibited a significant  
891 deficit on measures of executive functions, whereas the group with ADHD and  
892 RD exhibited the phonological processing difficulties that are characteristic of  
893 RD, but did not have deficits in executive functioning. Subsequent data from  
894 larger samples, however, generally failed to support the phenocopy hypothesis.  
895 Instead, these studies suggest that the comorbid group exhibits the additive  
896 combination of the neuropsychological weaknesses associated with RD and  
897 ADHD when they occur separately (e.g., Nigg et al., 1998; Rucklidge &  
898 Tannock, 2002; Seidman et al., 2001; Willcutt, in press; Willcutt et al., 2001).

899

900 *b. The Three Independent Disorders Hypothesis.* This model suggests that  
901 comorbid RD + ADHD is a third disorder that is due at least in part to etiological  
902 factors that are distinct from those that increase susceptibility to RD or ADHD  
903 alone. Therefore, this hypothesis predicts that the comorbid group will exhibit a  
904 different pattern of neurocognitive deficits or other external correlates than would  
905 be predicted based on the additive combination of the deficits associated with  
906 each disorder when it occurs alone. Rucklidge and Tannock (2002) found that the  
907 comorbid group performed significantly worse than the RD-only and ADHD-  
908 only groups on measures of color naming, providing some support for this  
909 hypothesis. In contrast, other studies found that the RD + ADHD group  
910 exhibited the additive combination of the deficits associated with each individual  
911 disorder (e.g., Pisecco et al., 2001; Swanson, Mink, & Bocian, 1999; Willcutt  
912 et al., 2001), suggesting that additional research is needed.

913

914 *c. The Correlated Liabilities Hypothesis.* Finally, a series of studies tested if  
915 the relation between RD and ADHD is attributable to common etiological  
916 influences that increase susceptibility to both disorders. Because this model has  
917 received the strongest support in previous studies, we describe these results in  
918 more detail in Section IV.B.3.

919

### 920 3. Behavioral Genetic Studies of RD and ADHD

921 *a. Family Studies.* Family studies provide a first step toward understanding  
922 the genetic and environmental risk factors for RD, ADHD, and their comorbidity.  
923 A family study compares the rate of a disorder in the biological relatives of  
924 individuals with and without the disorder. If a disorder occurs more often among

925 the family members of individuals with the disorder, this suggests that familial  
926 factors play a role in the etiology of the disorder.

927 Biological family members of children with RD are 4–8 times more likely to  
928 meet criteria for RD than family members of children without RD (Gilger,  
929 Pennington, & DeFries, 1991). Similarly, 30–40% of the full siblings of children  
930 with ADHD also meet criteria for ADHD, a rate that is 6–8 times higher than the  
931 rate in siblings of children without ADHD (Faraone, Biederman, & Friedman,  
932 2000). Thus, RD and ADHD are each clearly familial, and results from our  
933 laboratory suggest that the two disorders co-occur in the same families more  
934 frequently than expected by chance. Although these results should be interpreted  
935 with caution until they can be replicated in an independent sample, they are  
936 consistent with the hypothesis that RD and ADHD are attributable to common  
937 familial risk factors.

938  
939 *b. Twin Studies.* The fact that RD and ADHD are significantly familial  
940 suggests that each disorder may be influenced by genes, but family data are not  
941 conclusive. Because members of intact biological families share both genetic and  
942 family environmental influences, other methods such as twin studies are  
943 necessary to disentangle the relative contributions of genes and environment.  
944 By comparing the similarity of identical twins, who share all of their genes, to  
945 fraternal twins, who share half of their segregating genes on average, twin studies  
946 are able to estimate the extent to which a trait is due to genetic or environmental  
947 influences. The influence of genes is quantified by estimating *heritability*, a  
948 number ranging from 0 (no genetic influences at all) to 1 (entirely due to genetic  
949 influences) that provides an index of the extent to which a trait is attributable to  
950 genes. Environmental risk factors can be subdivided into *shared* and *non-shared*  
951 environmental influence. Shared environmental influences are those that similarly  
952 influence members of a family, thereby increasing the similarity of individuals  
953 within a family in comparison to unrelated individuals in the populations. In  
954 contrast, non-shared environmental influences describe events that affect the two  
955 twins differently and lead to differences among individuals in a family.

956 Twin studies indicate that the heritability of RD is about 0.60, suggesting that  
957 genetic influences account for approximately 60% of the reading deficit in  
958 children and adolescents with RD (e.g., Wadsworth *et al.*, 2002). ADHD is even  
959 more highly heritable (0.75–0.80), indicating that genetic influences play an  
960 even larger role in the development of ADHD.

961 Based on the finding that both RD and ADHD are significantly heritable,  
962 several studies have used twin data to test if the same genetic influences  
963 contribute to both RD and ADHD. Gilger, Pennington, & DeFries (1992)  
964 conducted cross-concordance analyses in a small sample of twins selected for  
965 RD, and found that ADHD and RD were primarily attributable to independent  
966 genetic factors. However, a statistical trend suggested that children with

967 comorbid RD and ADHD might represent an etiological subtype, providing  
968 tentative support for the three independent disorders model. The authors  
969 concluded that although most cases of RD or ADHD were not attributable to the  
970 same genetic influences, some cases of comorbid RD and ADHD might represent  
971 a separate disorder with a genetic etiology distinct from that associated with  
972 either diagnosis in isolation.

973 Light et al. (1995) and Stevenson et al. (1993) expanded upon the findings of  
974 Gilger, Pennington, and DeFries (1992) by conducting more powerful multiple  
975 regression analyses to estimate the bivariate heritability of ADHD and reading  
976 (Light et al., 1995) or spelling difficulties (Stevenson et al., 1993). In a sample  
977 of twins selected because at least one member of the pair met criteria for RD,  
978 Light et al. (1995) found significant bivariate heritability for RD and ADHD  
979 ( $h_{g(RD/ADHD)}^2 = 0.45$ ), suggesting that common genetic influences increase  
980 susceptibility to both disorders. In a separate community sample of twins,  
981 Stevenson et al. (1993) reported that the bivariate heritability of spelling deficits  
982 and ADHD was positive and similar whether probands were selected due to  
983 spelling difficulties ( $h_{g(Spell/ADHD)}^2 = 0.21$ ) or elevations of ADHD symptoms  
984 ( $h_{g(ADHD/Spell)}^2 = 0.15$ ), but these estimates of bivariate heritability were not  
985 statistically significant. Thus, these initial studies provided tentative support for  
986 the hypothesis that comorbidity between reading or spelling disability and  
987 ADHD may be attributable to common genetic influences, but the findings were  
988 somewhat inconclusive.

989

990 c. *The Importance of ADHD Symptom Dimensions.* The etiology of  
991 comorbidity between RD and ADHD becomes clearer when symptoms of  
992 ADHD are subdivided into dimensions of inattention symptoms and hyperactiv-  
993 ity–impulsivity symptoms as described in the fourth edition of the *Diagnostic and*  
994 *Statistical Manual of Mental Disorders (DSM-IV)*. Phenotypic analyses suggest  
995 that RD and other learning difficulties are more strongly associated with  
996 inattention symptoms than hyperactivity–impulsivity symptoms (e.g., Willcutt  
997 & Pennington, 2000a,b). Bivariate twin analyses indicate that the correlation  
998 between reading difficulties and inattention symptoms is almost entirely due to  
999 common genetic influences, whereas the lower correlation between reading and  
1000 hyperactivity–impulsivity is primarily due to environmental influences (Willcutt  
1001 et al., in press a,b; Willcutt et al., 2003; Willcutt, Pennington, & DeFries, 2000).

1002 In summary, family and twin studies indicate that RD and ADHD are each  
1003 familial and highly heritable. Bivariate twin analyses indicate that comorbidity  
1004 between RD and ADHD is primarily due to common genetic influences, but  
1005 suggest that these common genes are more strongly associated with inattention  
1006 than hyperactivity–impulsivity. In Section IV.B.4 we review initial studies that  
1007 have begun to search the genome to identify the specific genes that lead to the  
1008 development of RD, ADHD, and their comorbidity.

#### 4. Candidate Gene and Linkage Studies of RD and ADHD

Although an estimated 99.9% of the deoxyribonucleic acid (DNA) sequence that comprises the human genetic code is identical among all people, the genetic sequence varies at tens of thousands of locations across the remaining 0.1% of the human genome. These individual differences in the genetic code may lead to differences in protein production, which may then lead to individual differences in early brain development or adult brain functioning if the sequence difference occurs in a gene that is expressed in the central nervous system. Candidate gene analysis and linkage analysis are two primary methods that are used to identify the approximate location of genes that may contain sequence differences that influence disorders such as ADHD and RD.

*a. Candidate Gene Studies.* The candidate gene approach is extremely useful if previous research has identified specific physiological processes that are involved in a disorder. For example, based on evidence that ADHD is associated with dysfunction in the dopamine neurotransmitter system (e.g., Volkow *et al.*, 1998), nearly 100 candidate gene studies have tested if ADHD is associated with genes that influence dopamine or other related neurotransmitters, and significant associations have been reported for 15 different candidate genes (reviewed by Willcutt, *in press*). However, virtually all of these results have been replicated inconsistently or await independent replication, and each of these genes appears to account for a relatively small proportion of the total variance in ADHD symptoms in the population (e.g., Faraone *et al.*, 2001; Maher *et al.*, 2002).

Plausible candidate genes for RD have proved to be more difficult to identify, primarily because our understanding of the pathophysiology of RD is less advanced. Therefore, most molecular genetic studies of RD have conducted family-based linkage analyses, an alternative approach to identify regions of the genome that may contain genes that increase susceptibility to a disorder.

*b. Linkage Studies.* Linkage analysis takes advantage of the fact that alleles of genes that are close together on the same chromosome tend to be transmitted together across many generations, whereas alleles of genes that are far apart become separated over time due to recombination during meiosis (see Fisher and DeFries (2002) or Pennington (2002) for more information on linkage analysis). Linkage analysis typically does not identify the specific gene that is associated with increased risk for a disorder. Instead, this approach allows researchers to identify specific regions of the genome that may contain susceptibility loci for a disorder, and these regions can then be targeted for more extensive analysis.

Significant linkage for RD has been reported and replicated on chromosomes 1, 2, 3, 6, 15, and 18 (see review by Fisher and DeFries (2002)). The most consistent result, obtained in five independent samples, suggests that a gene on chromosome 6p21 leads to difficulties in reading, spelling, and a variety of other

1051 reading-related language measures (e.g., [Cardon et al., 1994, 1995](#); [Gayan et al.,](#)  
1052 [1999](#)). In addition to these six replicated linkage regions, it is likely that ongoing  
1053 linkage studies will identify additional loci in the future.

1054 Linkage studies of ADHD tell a similar story. In addition to the 15 genes  
1055 identified by candidate gene studies, linkage studies have identified more than 10  
1056 additional regions of the genome that may contain genes that increase risk for  
1057 ADHD ([Bakker et al., 2003](#); [Ogdie et al., 2003](#); [Willcutt et al., 2002](#)). However,  
1058 only a single region on chromosome 5p13 was significant in both genome scans  
1059 that have been published ([Bakker et al., 2003](#); [Ogdie et al., 2003](#)), and neither of  
1060 these genome scans detected linkage in the regions of most of the known  
1061 candidate genes for ADHD.

1062 The results of candidate gene and linkage studies underscore two important  
1063 points about the etiology of RD and ADHD. First, it is clear that multiple genetic  
1064 and environmental risk factors are involved in the etiology of both disorders.  
1065 Second, each of these risk factors has a relatively small effect on the final  
1066 phenotype. Therefore, whereas each risk factor leads to a small increase in  
1067 susceptibility to the disorder, few or none are necessary or sufficient to cause RD or  
1068 ADHD. These small effect sizes and inconsistent results across studies are not  
1069 unique to RD and ADHD, a similar pattern is apparent in genetic studies of other  
1070 complex psychopathologies such as schizophrenia (e.g., [Riley & McGuffin, 2000](#)),  
1071 additive behaviors (e.g., [Crabbe, 2002](#)), and bipolar disorder (e.g., [Craddock &](#)  
1072 [Jones, 2001](#)). In light of the complexity of these results, it is plausible that some of  
1073 these genes may specifically increase risk for RD or ADHD, whereas others may  
1074 have more general effects that increase risk for both disorders, sometimes resulting  
1075 in comorbidity. In Section V we turn to studies that attempted to identify the genes  
1076 that contribute to comorbidity by increasing risk for both RD and ADHD.

1077

### 1078 5. *Linkage Studies of Comorbidity Between RD and ADHD*

1079 Linkage studies of comorbidity between RD and ADHD have begun to identify  
1080 chromosomal regions that may contain a gene that increases risk for both  
1081 disorders ([Loo et al., 2004](#); [Willcutt et al., 2003, 2002](#)). In the first of these  
1082 studies, [Willcutt et al. \(2003, 2002\)](#) reported that the well-replicated quantitative  
1083 trait locus for RD on chromosome 6p21 also increases susceptibility to ADHD. In  
1084 a somewhat different approach, [Loo et al. \(2004\)](#) screened the entire genome for  
1085 genes that influence ADHD or RD in a sample of sibling pairs selected because  
1086 both siblings met criteria for ADHD. Their results suggest that regions of  
1087 chromosomes 16p and 17q may contain genes that increase susceptibility to both  
1088 RD and ADHD. In contrast, their results also revealed several regions that were  
1089 linked specifically to ADHD or RD.

1090 Thus, although several of these results await independent replication,  
1091 existing data provide the strongest support for the hypothesis that comorbidity  
1092 between RD and ADHD is due, at least, in part to a common genetic etiology.

1093 Although the specific functions of the genes that lead to comorbidity between  
1094 RD and ADHD are unknown, one plausible model suggests that these shared  
1095 genetic risk factors may cause a developmental change in a single  
1096 pathophysiological substrate, and that this change then increases risk for  
1097 both RD and ADHD. In this model the final phenotypic expression of this  
1098 common susceptibility is then influenced by other genetic and environmental  
1099 risk factors. Therefore, in some individuals this common risk factor would be  
1100 expressed as RD alone, some individuals would meet criteria for ADHD  
1101 alone, and some would meet criteria for both RD and ADHD. An important  
1102 step in validating this hypothesis is to identify a neuropsychological deficit or  
1103 other pathophysiological marker that reflects the common genetic risk for RD  
1104 and ADHD (Willcutt *et al.*, in press a,b). Measures of this neurocognitive  
1105 weakness may then facilitate future molecular genetic studies of RD, ADHD,  
1106 and their comorbidity.

### 1107 C. CONDUCT DISORDER AND ADHD

1108  
1109  
1110 Conduct disorder (CD) and ADHD also occur together in 30–50% of the cases  
1111 in both epidemiological and clinical samples (Biederman, Newcorn, & Sprich,  
1112 1991). The results of studies examining the etiology of comorbidity between  
1113 ADHD and CD vary a great deal.

#### 1114 1. Phenotypic Tests

1115  
1116 Many studies in the literature address whether the three independent disorders  
1117 model (i.e., ADHD + CD is a third, independent disorder, or an etiological  
1118 distinct subtype) explains the comorbidity between ADHD and CD. Although  
1119 several researchers have noted the similarities between ADHD children with and  
1120 without CD, including similarities in neurological “soft signs” and pre- and peri-  
1121 natal complications (e.g., August & Stewart, 1983), physical anomalies (e.g.,  
1122 August & Stewart, 1983; McGee, Williams, & Silva, 1984), and average  
1123 intelligence (e.g., August & Stewart, 1983; Loney & Milich, 1982; McGee,  
1124 Williams, & Silva, 1984), more researchers have noted the differences between  
1125 ADHD children with and without CD and suggested that the two groups should  
1126 be classified as two different types of ADHD. A similar idea is that CD with and  
1127 without ADHD may constitute two different etiological types. In 1993, Moffitt  
1128 presented her developmental taxonomy model of antisocial behavior, suggesting  
1129 two categories of antisocial behavior that are distinct in etiology. The first  
1130 category includes individuals who are antisocial at every stage of life (i.e., life-  
1131 course-persistent), and the second category includes individuals who are  
1132 antisocial only during adolescence (i.e., adolescence-limited). Moffitt noted  
1133 that one of the risk characteristics in individuals with life-course-persistent  
1134 antisocial behavior is hyperactivity.

1135 Systematic reviews of studies examining ADHD only, CD only, and both  
1136 ADHD and CD have reached differing conclusions. [Lynam \(1996\)](#) conducted a  
1137 review of studies examining differences in children with hyperactivity–  
1138 impulsivity–attention problems only, conduct problems only, and both  
1139 hyperactivity–impulsivity, attention and conduct problems, and concluded that  
1140 a “psychopathic deficit” is the underlying pathology for both kinds of symptoms  
1141 in children with both sets of problems (comorbid children), but not in children  
1142 with only one set of problems occurring alone. One of the main reasons for this  
1143 conclusion was the finding that comorbid children have unique deficits (e.g., a  
1144 distinct social information-processing pattern and qualitatively different errors on  
1145 a continuous performance task) not found in children with problems only in  
1146 hyperactivity–impulsivity–attention or conduct. In addition, some of these  
1147 unique deficits (e.g., lowered autonomic reactivity) are also found in adult  
1148 psychopathic individuals. [Jensen, Martin, and Cantwell \(1997\)](#) also conducted a  
1149 systematic review of studies examining the differences among children with  
1150 ADHD only, CD only, and ADHD + CD. Given several characteristics of  
1151 children of ADHD + CD (e.g., earlier age of onset, greater male–female sex  
1152 ratio, lower IQs, increased learning/reading difficulties), Jensen, Watanabe,  
1153 Richters, Cortes, Roper, and Liu concluded that there is enough evidence for a  
1154 new diagnostic entity or a sub-classification of ADHD: ADHD, aggressive type.

1155 Subsequently, [Waschbusch \(2002\)](#) conducted a meta-analysis of studies  
1156 examining children with hyperactive-impulsive-attention problems only, con-  
1157 duct problems only, or both kinds of problems. Waschbusch found several  
1158 differences between comorbid children and children with only one kind of  
1159 problem. For example, comorbid children had more severe conduct problems,  
1160 lower verbal IQ scores, more peer difficulties, and more adult offending than the  
1161 children with only one kind of problem or controls. However, [Waschbusch](#)  
1162 [\(2002\)](#) concluded that there was little evidence that comorbid children have  
1163 deficits that are not also present to some degree in children with only one kind  
1164 of problem. Also interesting is the fact that the general pattern of results found  
1165 in studies reviewed by Waschbusch (i.e., the comorbid group was the most  
1166 impaired on deficits that are also present in the other two groups) is the pattern  
1167 expected when the correlated liabilities model is the correct comorbidity model  
1168 ([Rhee \*et al.\*, 2004](#)).

1169 Other alternative accounts of the comorbidity between ADHD and CD have  
1170 been proposed based on phenotypic data. A longitudinal study examining ADHD  
1171 and CD symptoms ([Taylor \*et al.\*, 1996](#)) reported that the outcome of the  
1172 ADHD + CD group was similar to the ADHD only group and rejected the three  
1173 independent disorders model. They also reported that childhood ADHD symptoms  
1174 in the absence of CD symptoms predicted CD symptoms in adolescence, whereas  
1175 childhood CD symptoms did not predict ADHD symptoms in adolescence. They  
1176 concluded that ADHD symptoms are the major developmental risk factor and that

1177 CD symptoms are epiphenomenal (i.e., support for the random multiformity of  
1178 ADHD model).

1179 A study examining the correlates of ADHD only, CD only, and ADHD + CD  
1180 children (Schachar & Tannock, 1995) reported that ADHD only was associated  
1181 with cognitive deficits, greater developmental delays, and greater reading  
1182 problems, the CD only group had been exposed to significantly greater  
1183 environmental adversity and had more severe problems in arithmetic, and that  
1184 the ADHD + CD group had the correlates of both the ADHD only and the CD  
1185 only groups. Given these results, they rejected the alternate forms model and the  
1186 three independent disorders model. They asserted ADHD + CD is a hybrid of  
1187 pure ADHD and pure CD and that comorbidity between ADHD and CD occurs  
1188 because the risk factors for one disorder increase the probability of the risk  
1189 factors for the second disorder.

1190 In sum, phenotypic tests of the comorbidity between ADHD and CD have  
1191 reached conflicting conclusions. We next examine whether behavior genetic tests  
1192 can help resolve this conflict.  
1193

1194

1195

## 1195 2. Behavior Genetic Tests

1196 Faraone and his colleagues (Biederman *et al.*, 1992; Faraone, Biederman, &  
1197 Monuteaux, 2000; Faraone *et al.*, 1991, 1997) took a different approach in testing  
1198 the three independent disorders model in a series of family studies. They  
1199 compared the risk for ADHD, CD, and ADHD + CD in the relatives of probands  
1200 with ADHD only and ADHD + CD and reported two major results in all four  
1201 studies. First, the risk of CD was greater in relatives of probands with  
1202 ADHD + CD than in relatives of probands with ADHD only. Second, there was  
1203 significant cosegregation of ADHD and CD (having one disorder increased the  
1204 likelihood of having the other disorder) in the relatives of probands with  
1205 ADHD + CD. Given these results, they concluded that ADHD only and  
1206 ADHD + CD are etiologically distinct disorders (i.e., support for the three  
1207 independent disorders model).

1208 Given the evidence of support for the three independent disorders model in the  
1209 literature, Holmes *et al.* (2002) considered the possibility of etiological  
1210 heterogeneity in their examination of the association between the DRD4 gene  
1211 and ADHD. Evidence of association was not found in the total sample, but  
1212 significant association was found between the DRD4 gene and ADHD plus  
1213 conduct problems.

1214 Several multivariate behavior genetic studies using the twin method (Nadder  
1215 *et al.*, 1998, 2002; Scarborough & Dobrich, 1990; Silberg *et al.*, 1996; Thapar,  
1216 Harrington, & McGuffin, 2001; Waldman *et al.*, 2001; Willcutt *et al.*, 1995)  
1217 examined whether comorbidity between ADHD and CD is due to shared genetic  
1218 influences. All of these studies found a substantial overlap between the genetic

1219 influences on ADHD and the genetic influences on CD (i.e., support for the  
1220 correlated liabilities model).

1221 In a subsequent study (Rhee *et al.*, 2004c), we examined a wide range of  
1222 alternative models explaining the comorbidity between ADHD and CD. As  
1223 mentioned previously, a series of simulation studies (Rhee *et al.*, 2003, 2004b)  
1224 showed that the Neale and Kendler model fitting approach does a better job of  
1225 validly discriminating the three independent disorders model from other  
1226 Q3 comorbidity models than family prevalence analyses, such as the ones used in  
1227 Faraone, Biederman, Lehman, Keenan, Norman and Seidman (2000).

1228 All 13 alternative comorbidity models were tested in a twin sample enriched  
1229 with individuals with ADHD or academic difficulties, with 110 monozygotic twin  
1230 pairs and 182 dizygotic twin pairs. Of these models, several did not fit the data  
1231 well and could be rejected; the three independent disorders model was one of  
1232 these models. The models that fit the data and could not be rejected were random  
1233 multiformity, random multiformity of B, extreme multiformity, extreme  
1234 multiformity of B, correlated liabilities, A causes B, B causes A, and reciprocal  
1235 causation. The best fitting model was the extreme multiformity of B model,  
1236 which suggests that being affected by CD leads to increased risk for manifesting  
1237 ADHD. A simulation study examining the validity of the Neale and Kendler  
1238 model fitting approach found that mistakes in discrimination within and between  
1239 the multiformity models and the correlated liabilities are common in small  
1240 samples. Therefore, it is difficult to interpret this result as support for the extreme  
1241 multiformity of B model as the “correct” hypothesis for the comorbidity between  
1242 ADHD and CD. However, these results provide evidence against the three  
1243 independent disorders model and support the results of the several twin studies  
1244 concluding that there are significant shared genetic influences between ADHD  
1245 and CD.

1246

### 1247 3. *Summary of Evidence Regarding Comorbidity of ADHD and CD*

1248 In conclusion, the existing evidence regarding the causes of comorbidity  
1249 between ADHD and CD is not consistent. Reviews of studies evaluating the three  
1250 independent disorders model by examining the correlates or underlying deficits in  
1251 groups of children with ADHD + CD, ADHD only, and CD only have reached  
1252 different conclusions, with Jensen, Martin and Cantwell (1997), Lynam (1996)  
1253 supporting the three independent disorders model and Waschbusch (2002) and  
1254 others concluding that there is little evidence for the three independent disorders  
1255 model. Family studies examining the risk of ADHD and CD in relatives of  
1256 probands with ADHD + CD, ADHD only, CD only, and controls conclude  
1257 support for the three independent disorders model, but a simulation study (Rhee  
1258 *et al.*, 2003) suggests that the analyses used in these studies are not valid tests of  
1259 the three independent disorders model. Several studies have found support for  
1260 other models for the comorbidity between ADHD and CD, including random

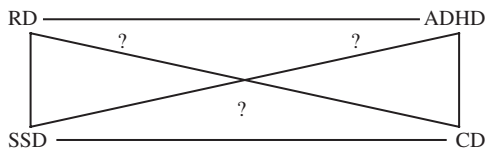
1261 multiformity of ADHD, risk factors for one disorder increasing the probability of  
 1262 risk factors for another disorder (a model not discussed by Neale and Kendler),  
 1263 and the correlated liabilities model. Our recent study, which is the only study to  
 1264 examine a wide range of comorbidity models using the Neale and Kendler model  
 1265 fitting approach (which has been validated by a simulation study), suggests that  
 1266 correlated liabilities is a more likely cause of the comorbidity between ADHD  
 1267 and CD rather than Three Independent Disorders. Given the conflicting results in  
 1268 the literature, more studies examining the comorbidity between ADHD and CD  
 1269 using valid analytical approaches need to be conducted.

#### 1271 D. IMPLICATIONS FOR OTHER POSSIBLE PAIRS

1272  
 1273 We have reviewed what is known about the explanations for three of the  
 1274 possible six comorbidities among four common childhood disorders: RD, SSD,  
 1275 ADHD, and CD. At this point the reader may wonder what is known about the  
 1276 other three possible pairwise comorbidities among these four disorders.

1277 We can depict the relations among these four disorders graphically (Figure 3).  
 1278 Each disorder is at the vertex of a rectangle and each comorbidity is a line  
 1279 connecting two vertices. More generally, the number of pairwise comorbidities  
 1280 among  $n$  disorders is  $(n^2 - n)/2$ . For instance, if one studied eight disorders,  
 1281 there would be 28 possible comorbidities. If we have only studied a subset of the  
 1282 possible comorbidities among a set of disorders, as is true in Figure 3, what we  
 1283 have already learned could place some constraints on possible solutions for  
 1284 the unknown comorbidities.

1285 One possibility discussed by Angold, Costello, and Erkanli (1999) is that of  
 1286 “epiphenomenal” comorbidity. That is, if there are robust pairwise comorbidities  
 1287 between disorders A and B and between disorders B and C, the expected rate of  
 1288 co-occurrence of disorders A and C will be the product of these two other  
 1289 comorbidity rates. If this product is greater than the product of the prevalences of  
 1290 A and C, we will observe a comorbidity rate that appears greater than chance, but  
 1291 which is in fact mediated by the other two comorbidities. In other words, there is  
 1292 no relation between A and C independent of their relation to B. Angold, Costello,  
 1293 and Erkanli (1999) present evidence that the apparent comorbidity between CD  
 1294



1295  
 1296  
 1297  
 1298  
 1299  
 1300  
 1301 *Fig. 3. Pairwise comorbidities among four disorders. RD = reading disability; SSD = speech*  
 1302 *sound disorder; ADHD = attention deficit hyperactivity disorder; CD = conduct disorder.*

1303 and anxiety was epiphenomenal because it derived from the comorbidities  
1304 between CD and depression, and depression and anxiety. So some of the many  
1305 non-artifactual comorbidities observed among DSM-IV diagnoses are likely to be  
1306 epiphenomenal and we can winnow them from the list of comorbidities requiring  
1307 a deeper explanation.

1308 There are other ways in which what we have already learned could place  
1309 constraints on less-studied comorbidities. For instance, if we had found that SSD  
1310 was a risk factor for RD and that RD was a risk factor for ADHD (the causal model),  
1311 then it would follow logically that SSD would be a risk factor for ADHD. Or, if we  
1312 had found that the alternate forms model fit both the comorbidity between SSD and  
1313 RD, and RD and ADHD, then we would expect there to be non-artifactual  
1314 comorbidity between SSD and ADHD that also fits the alternate forms model.

1315 Given what has actually been found about the three studied comorbidities in  
1316 [Figure 3](#), namely that each fits the correlated liabilities model, there are not sure  
1317 predictions for the three less-studied comorbidities. Even if there is a partial  
1318 etiological overlap between SSD and RD, and RD and ADHD, it does not  
1319 necessarily follow that the liabilities between SSD and ADHD will be correlated.

1320 What do we actually know empirically about the three less-studied  
1321 comorbidities in [Figure 3](#)? In two studies, isolated SSD is not comorbid with  
1322 ADHD, whereas SSD + LI is ([Beitchman, Peterson, & Clegg, 1988](#); McGrath  
1323 *et al.*, in preparation). Thus, isolated SSD may be etiologically and cognitively  
1324 distinct from ADHD. We do not know of studies examining the relation between  
1325 isolated SSD and CD, but it is well known that CD is associated with weaker  
1326 language skills (e.g., [Moffitt, 1993](#)). RD and CD are comorbid ([Hinshaw, 1992](#)),  
1327 but some research ([Willcutt & Pennington, 2000a,b](#)) finds this comorbidity is no  
1328 long present once ADHD is controlled, so there may not be a direct comorbidity  
1329 between RD and CD. Instead, it may be epiphenomenal. A twin study  
1330 ([Trzesniewski, Moffitt, & Caspi, submitted](#)) of this relation found evidence for  
1331 a different possibility. While this study found there was a genetic overlap  
1332 between ADHD and CD, consistent with earlier studies reviewed earlier, the  
1333 relation between RD and CD was mediated environmentally.

1334 In sum, as we learn more about comorbidities, we will be able to say more about  
1335 developmental pathways from risk factors to outcomes, including where these  
1336 pathways overlap and where they are distinct. This brings us to a more general  
1337 model for thinking about relations between disorders.

1338

1339

1340

1341

## V. Multifactorial Model

1342 So what has research on these three comorbidities taught us about the  
1343 development of disorders more generally? One lesson is that single etiology  
1344 models of disorders do not seem to be adequate to account for either their

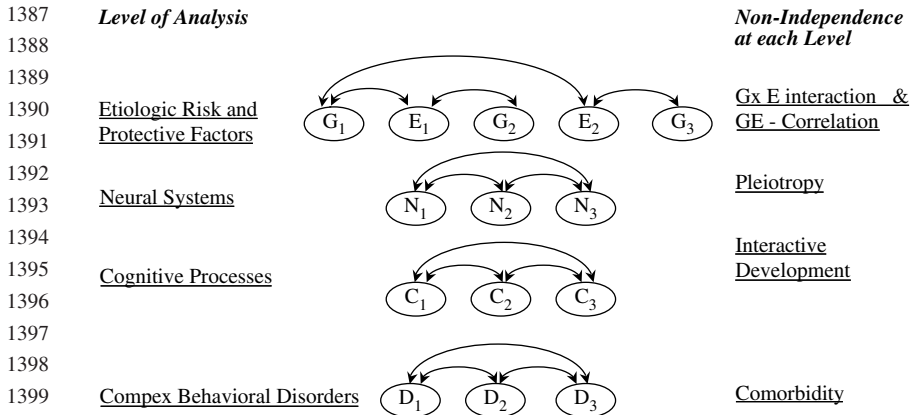
1345 development or comorbidity. We have yet to find a behaviorally defined disorder  
1346 with a single necessary and sufficient etiology. The emerging etiological model for  
1347 such disorders is probabilistic and multifactorial. But the prevailing cognitive  
1348 model has often been deterministic and focused on a single cognitive cause, such  
1349 as the phonological deficit in RD. So there is a potential contradiction in our  
1350 frameworks for understanding such disorders that needs to be resolved. Another  
1351 lesson is that a frequently supported explanation for comorbidity is correlated  
1352 liabilities, specifically shared genetic risk factors. A third lesson is some disorders  
1353 may be developmental precursors of later disorders, although usually an additional  
1354 risk factor determines whether a child with the precursor disorder develops the  
1355 later disorders. In this final section, we present a model that incorporates these  
1356 lessons and is probabilistic and multifactorial at all levels of analysis.

1357 Similar to the complex disease model in medicine (Sing & Reilly, 1993), this  
1358 model includes six key proposals:

- 1359 (1) The etiology of complex behavioral disorders is multifactorial and  
1360 involves the interaction of multiple risk and protective factors, which can be  
1361 either genetic or environmental.
- 1362 (2) No single etiological factor is sufficient for a disorder, and few may be  
1363 necessary.
- 1364 (3) These risk and protective factors alter the development of psychological  
1365 functions necessary for normal development, thus producing the behavioral  
1366 symptoms that define these disorders.
- 1367 (4) Few, if any, single cognitive risk factors are sufficient for a disorder,  
1368 although some may be necessary.
- 1369 (5) Consequently, comorbidity among complex behavioral disorders is to be  
1370 expected because of shared etiologic and cognitive risk factors.
- 1371 (6) The liability distribution for a given disease is often continuous and  
1372 quantitative, rather than being discrete and categorical, so that the threshold for  
1373 having the disorder is somewhat arbitrary.
- 1374

1375 So there are normally distributed individual differences in the behavioral  
1376 dimensions (such as speech, reading, attention, and socially appropriate  
1377 behavior) that define disorders. Those with a disorder fall beyond a somewhat  
1378 arbitrary threshold on an extreme end of these distributions. The etiology of these  
1379 individual differences is multifactorial, both across the whole distribution and at  
1380 the extremes, and the etiologies of different behavioral dimensions partly overlap,  
1381 producing cognitive overlap between dimensions and disorders.

1382 Applying the model to the three comorbidities reviewed here, each individual  
1383 disorder (SSD, RD, ADHD, and CD) has its own profile of risk factors (both  
1384 etiologic and cognitive), with some of these risk factors being shared by pairs of  
1385 disorders, resulting in comorbidity.  
1386



1401 *Fig. 4. Multifactorial model. G = genetic risk or protective factor, E = environmental risk or*  
 1402 *protective factor, N = neural system, C = cognitive process, D = disorder.*

1403

1404

1405 **Figure 4** illustrates this multifactorial model, which is also discussed in  
 1406 **Pennington (in press)**. There are four levels of analysis in this diagram: etiologic,  
 1407 neural, cognitive, and symptom, where clusters of symptoms define complex  
 1408 behavioral disorders. For any such complex behavioral disorder, it is expected  
 1409 there will be more risk and protective factors than the five shown here.  
 1410 Bidirectional connections at each level indicate that constructs are not  
 1411 independent. For instance, at the etiologic level, there are likely to be gene–  
 1412 environment interactions and correlations. At the neural level, a single genetic or  
 1413 environmental risk factor will often affect more than one neural system  
 1414 (pleiotropy). Even if the risk factor initially only affects one neural system, this  
 1415 alteration will likely have downstream effects on the development of other neural  
 1416 systems. At the cognitive level, constructs are correlated because their  
 1417 developmental pathways overlap and because cognition is interactive. Overlap  
 1418 at the cognitive level leads to comorbidity at the symptom level. So, although a  
 1419 single deficit model conceptualizes the relation between disorders in terms of  
 1420 double dissociations, the multiple deficit model conceptualizes this relation in  
 1421 terms of partial overlap. At the symptom level, there is comorbidity (i.e., greater  
 1422 than chance co-occurrence) of complex behavioral disorders. Omitted from the  
 1423 diagram are the causal connections *between* levels of analyses, some of which  
 1424 would include feedback loops from behavior to brain or even to etiology. The  
 1425 existence and strength of these various causal connections must be determined  
 1426 empirically. The weights of the connections between levels of analysis will tell us  
 1427 to what extent different etiological and cognitive factors contribute to  
 1428 comorbidity at the symptom level.

1429 It is also apparent that a similar but expanded model could be proposed for  
 1430 species-typical cognitive development, which results from the interaction of a  
 1431 largely shared genome (99.9% the same across unrelated humans) and species-  
 1432 typical environments. So in principle the same model could account for both  
 1433 typical and atypical development. Indeed, a complete account of any given  
 1434 developmental disorder will need to explain the many aspects of development  
 1435 that proceed typically as well as the few that go awry.

1436 This model makes it clear that achieving a complete understanding of the  
 1437 development of disorders like SSD, RD, ADHD, or CD will be very difficult  
 1438 because of the multiple pathways and interactions involved. But this kind of  
 1439 model is needed because it is becoming increasingly clear that there are shared  
 1440 processes at the etiologic, neural, and cognitive levels across such disorders.

1441

1442

1443

1444

## ACKNOWLEDGEMENTS

1445 **Q5** A portion of this chapter has been published in Rhee, S. H., Hewitt, J. K., Corley, R. P., &  
 1446 Stallings, M. C. (submitted). Comorbidity. In B. Everitt & D. C. Howell (Eds.), *Encyclopedia of*  
 1447 *Behavioral Statistics*. London: Wiley.

1448

1449

1450

## REFERENCES

- 1451 American Psychiatric Association. (1994). *American Psychiatric Association Diagnostic and*  
 1452 *Statistical Manual of Mental Disorders* (4th ed.). Washington, DC: American Psychiatric  
 1453 Association.
- 1454 American Psychiatric Association. (2000). *American Psychiatric Association Diagnostic and*  
 1455 *Statistical Manual of Mental Disorders* (4th ed.). American Psychiatric Association:  
 1456 Washington, DC, Text Revision.
- 1457 Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology*  
 1458 *and Psychiatry*, 40, 57–87.
- 1459 Aram, D. M., Ekelman, B. L., & Nation, J. E. (1984). Preschoolers with language disorders: 10  
 1460 years later. *Journal of Speech and Hearing Research*, 27, 232–244.
- 1461 August, G. J., & Stewart, M. A. (1983). Familial subtypes of childhood hyperactivity. *Journal of*  
 1462 *Nervous Mental Disorders*, 171, 362–368.
- 1463 **Q6** Bakker, S. C., van der Meulen, E. M., Buitelaar, J. K., Sandkuijl, L. A., Pauls, D. L., Monsuur,  
 1464 A. J. *et al.* (2003). A whole-genome scan in 164 Dutch sib pairs with attention-deficit/  
 1465 hyperactivity disorder: Suggestive evidence for linkage on chromosomes 7p and 15q.  
 1466 *American Journal of Human Genetics*, 72, 1251–1260.
- 1467 Beitchman, J. H., Peterson, M., & Clegg, M. (1988). Speech and language impairment and  
 1468 psychiatric disorder: The relevance of family demographic variables. *Child Psychiatry and*  
 1469 *Human Development*, 18, 191–207.
- 1470 Berkson, J. (1946). Limitations of the application of fourfold table analysis to hospital data.  
*Biometrics*, 2, 47–51.
- Biederman, J., Newcorn, J., & Sprich, S. (1991). Comorbidity of attention deficit hyperactivity  
 disorder with conduct, depressive, anxiety, and other disorders. *American Journal of*  
*Psychiatry*, 148, 564–577.

- 1471 **Q7**Biederman, J., Faraone, S. V., Keenan, K., Benjamin, J., Krifcher, B., Moore, C. et al. (1992).  
 1472 Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder.  
 1473 Patterns of comorbidity in probands and relatives psychiatrically and pediatrically referred  
 1474 samples. *Archives of General Psychiatry*, *49*, 728–738.
- 1474 **Q8**Bierut, L. J., Dinwiddie, S. H., Begleiter, H., Crowe, R. R., Hesselbrock, V., Nurnberger, J. I. Jr.  
 1475 et al. (1998). Familial transmission of substance dependence: Alcohol, marijuana, cocaine,  
 1476 and habitual smoking: A report from the Collaborative Study on the Genetics of Alcoholism.  
 1477 *Archives of General Psychiatry*, *55*, 982–988.
- 1478 Bird, J., & Bishop, D. (1992). Perception and awareness of phonemes in phonologically  
 1479 impaired children. *European Journal of Disorders in Communication*, *27*, 289–311.
- 1480 Bird, J., Bishop, D. V., & Freeman, N. H. (1995). Phonological awareness and literacy  
 1481 development in children with expressive phonological impairments. *Journal of Speech and  
 1482 Hearing Research*, *38*, 446–462.
- 1482 **Q9**Bird, H., Canino, G., Rubio-Stipec, M., Gould, M., Ribera, J., Sesman, M. et al. (1988).  
 1483 Estimates of the prevalence of childhood maladjustment in a community survey in Puerto  
 1484 Rico: The use of combined measures. *Archives of General Psychiatry*, *45*, 1120–1126.
- 1485 Bishop, D. V., & Adams, C. (1990). A prospective study of the relationship between specific  
 1486 language impairment, phonological disorders and reading retardation. *Journal of Child  
 1487 Psychology and Psychiatry*, *31*, 1027–1050.
- 1488 Bishop, D. V., North, T., & Donlan, C. (1995). Genetic basis of specific language impairment:  
 1489 Evidence from a twin study. *Developmental and Medical Child Neurology*, *37*, 56–71.
- 1489 Cardon, L. R., Smith, S. D., Fulker, D. W., Kimberling, W. J., Pennington, B. F., & DeFries, J. C.  
 1490 (1994). Quantitative trait locus for reading disability on chromosome 6. *Science*, *266*,  
 1491 276–279.
- 1492 Cardon, L. R., Smith, S. D., Fulker, D. W., Kimberling, W. J., Pennington, B. F., & DeFries, J. C.  
 1493 (1995). Quantitative trait locus for reading disability: Correction. *Science*, *268*, 1553.
- 1493 Caron, C., & Rutter, M. (1991). Comorbidity in child psychopathology: Concepts, issues and  
 1494 research strategies. *Journal of Child Psychology and Psychiatry*, *32*, 1063–1080.
- 1495 Catts, H. W., Fey, M. E., Tomblin, J. B., & Zhang, X. (2002). A longitudinal investigation of  
 1496 reading outcomes in children with language impairments. *Journal of Speech, Language, and  
 1497 Hearing Research*, *45*, 1142–1157.
- 1498 Clark, L. A., Watson, D., & Reynolds, S. (1995). Diagnosis and classification of  
 1499 psychopathology: Challenges to the current system and future directions. *Annual Review  
 1500 of Psychology*, *46*, 121–153.
- 1500 Clarke-Klein, S., & Hodson, B. W. (1995). A phonologically based analysis of misspellings by  
 1501 third graders with disordered-phonology histories. *Journal of Speech, and Hearing  
 1502 Research*, *38*, 839–849.
- 1503 Crabbe, J. C. (2002). Genetic contributions to addiction. *Annual Review of Psychology*, *53*,  
 1504 435–462.
- 1504 Craddock, N., & Jones, I. (2001). Molecular genetics of bipolar disorder. *British Journal of  
 1505 Psychiatry*, *178*(Suppl. 41), S128–S133.
- 1506 Dickman, G. E. (2003). The nature of learning disabilities through the lens of reading research.  
 1507 *Perspectives: The International Dyslexia Association*, *29*, 4–8.
- 1508 Donaldson, S. K., Klein, D. N., Riso, L. P., & Schwartz, J. E. (1997). Comorbidity between  
 1509 dysthymic and major depressive disorders: A family study analysis. *Journal of Affective  
 1510 Disorders*, *42*, 103–111.
- 1510 Doyle, A. E., Faraone, S. V., DuPre, E. P., & Biederman, J. (2001). Separating attention deficit  
 1511 hyperactivity disorder and learning disabilities in girls: A familial risk analysis. *American  
 1512 Journal of Psychiatry*, *158*, 1666–1672.

- 1513 Dykman, R. A., & Ackerman, P. T. (1991). Attention deficit disorder and specific reading  
1514 disability: Separate but often overlapping disorders. *Journal of Learning Disabilities*, 24,  
1515 96–103.
- 1516 Edwards, J., & Lahey, M. (1998). Nonword repetitions in children with specific language  
1517 impairment: Exploration of some explanations for their inaccuracies. *Applied Psycholin-*  
1518 *guistics*, 19, 279–309.
- 1519 Faraone, S. V., Biederman, J., & Friedman, D. (2000). Validity of DSM-IV subtypes of  
1520 attention-deficit/hyperactivity disorder: A family study perspective. *Journal of the American*  
1521 *Academy of Child and Adolescent Psychiatry*, 39, 300–307.
- 1522 Faraone, S. V., Biederman, J., Keenan, K., & Tsuang, M. T. (1991). A family-genetic study of  
1523 girls with DSM-III attention deficit disorder. *American Journal of Psychiatry*, 148, 112–117.
- 1524 Faraone, S. V., Biederman, J., Jetton, J. G., & Tsuang, M. T. (1997). Attention deficit disorder  
1525 and conduct disorder: Longitudinal evidence for a familial subtype. *Psychological*  
1526 *Medicine*, 27, 291–300.
- 1527 Faraone, S. V., Biederman, J., Lehman, B. K., Keenan, K., Norman, D., Seidman, L. J. *et al.*  
1528 (1993). Evidence for the independent familial transmission of attention deficit hyperactivity  
1529 disorder and learning disabilities: Results from a family genetic study. *American Journal of*  
1530 *Psychiatry*, 150, 891–895.
- 1531 Faraone, S. V., Biederman, J., & Monuteaux, M. C. (2000). Attention-deficit disorder and  
1532 conduct disorder in girls: Evidence for a familial subtype. *Biological Psychiatry*, 48, 21–29.
- 1533 Faraone, S., Doyle, A., Mick, E., & Biederman, J. (2001). Meta-analysis of the association  
1534 between the 7-repeat allele of the dopamine D4 receptor gene and attention deficit  
1535 hyperactivity disorder. *American Journal of Psychiatry*, 158, 1052–1057.
- 1536 Feinstein, A. (1970). The pre-therapeutic classification of co-morbidity in chronic disease.  
1537 *Journal of Chronic Disease*, 23, 57–63.
- 1538 Fergusson, D. M., & Horwood, L. J. (1992). Attention deficit and reading achievement. *Journal*  
1539 *of Child Psychology and Psychiatry*, 33, 375–385.
- 1540 Fisher, S. E., & DeFries, J. C. (2002). Developmental dyslexia: Genetic dissection of a complex  
1541 cognitive trait. *Nature Reviews Neuroscience*, 3, 767–780.
- 1542 Friedman, M. C., Chhabildas, N., Budhiraja, N., Willcutt, E. G., & Pennington, B. F. (2003).  
1543 Etiology of the comorbidity between RD and ADHD: Exploration of the non-random mating  
1544 hypothesis. *American Journal of Medical Genetics*, 120B, 109–115.
- 1545 Gallagher, A., Frith, U., & Snowling, M. J. (2000). Precursors of literacy delay among children  
1546 at genetic risk of dyslexia. *Journal of Child Psychology and Psychiatry*, 41, 203–213.
- 1547 Q11 Gayan, J., Smith, S. D., Cherny, S. S., Cardon, L. R., Fulker, D. W., Brower, A. M. *et al.* (1999).  
1548 Quantitative-trait locus for specific language and reading deficits on chromosome 6p.  
1549 *American Journal of Human Genetics*, 64, 157–164.
- 1550 Gilger, J. W., Borecki, I. B., DeFries, J. C., & Pennington, B. F. (1994). Comingling and  
1551 segregation analysis of reading performance in families of normal reading probands.  
1552 *Behavioral Genetics*, 24, 345–355.
- 1553 Gilger, J., Pennington, B., & DeFries, J. (1991). Risk for reading disability as a function of  
1554 parental history in three family studies. *Reading and Writing: An Interdisciplinary Journal*,  
1555 3, 205–217.
- 1556 Gilger, J. W., Pennington, B. F., & DeFries, J. C. (1992). A twin study of the etiology of  
1557 comorbidity: Attention-deficit hyperactivity disorder and dyslexia. *Journal of the American*  
1558 *Academy of Child and Adolescent Psychiatry*, 31, 343–348.
- 1559 Hall, P. K., & Tomblin, J. B. (1978). A follow-up study of children with articulation and  
1560 language disorders. *Journal of Speech and Hearing Disorders*, 43, 227–241.
- 1561 Hallgren, B. (1950). Specific dyslexia: A clinical and genetic study. *Acta Psychiatrica*  
1562 *Neurologica Scandinavia*, 65(Suppl.), 1–287.

- 1555 Hinshaw, S. P. (1992). Externalizing behavior problems and academic underachievement in  
1556 childhood and adolescence: Causal relationships and underlying mechanisms. *Psychological*  
1557 *Bulletin*, *111*, 127–155.
- 1558 **Q12** Holmes, J., Payton, A., Barrett, J., Harrington, R., McGuffin, P., Owen, M. et al. (2002).  
1559 Association of DRD4 in children with ADHD and comorbid conduct problems. *American*  
1560 *Journal of Medical Genetics*, *114*, 150–153.
- 1561 Jensen, P. S., Martin, D., & Cantwell, D. P. (1997). Comorbidity in ADHD: Implications for  
1562 research, practice, and DSM-V. *Journal of the Academy of Child and Adolescent Psychiatry*,  
1563 *36*, 1065–1079.
- 1564 Jensen, P. S., Watanabe, H. K., Richters, J. E., Cortes, R., Roper, M., & Liu, S. (1995).  
1565 Prevalence of mental disorder in military children and adolescents: Findings from a two-  
1566 stage community survey. *Journal of the Academy of Child and Adolescent Psychiatry*, *34*,  
1567 1514–1524.
- 1568 Kamhi, A. G., Catts, H. W., Mauer, D., Apel, K., & Gentry, B. F. (1988). Phonological and  
1569 spatial processing abilities in language- and reading-impaired children. *Journal of Speech*  
1570 *and Hearing Disorders*, *53*, 316–327.
- 1571 Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S. et al.  
1572 **Q13** (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United  
1573 States. Results from the National Comorbidity Survey. *Archives of General Psychiatry*, *51*,  
1574 8–19.
- 1575 Klein, D. F. (1993). False suffocation alarms, spontaneous panics, and related conditions. An  
1576 integrative hypothesis. *Archives of General Psychiatry*, *50*, 306–317.
- 1577 Klein, D. N. (2003). Patients' versus informants' reports of personality disorders in predicting  
1578  $7\frac{1}{2}$ -year outcome in outpatients with depressive disorders. *Psychological Assessment*, *15*,  
1579 216–222.
- 1580 Klein, D. N., & Riso, L. (1993). Psychiatric disorders: Problems of boundaries and comorbidity.  
1581 In C. G. Costello (Ed.), *Basic issues in psychopathology* (pp. 19–66). New York: Guilford  
1582 Press.
- 1583 Leonard, L. B. (1982). Phonological deficits in children with developmental language  
1584 impairment. *Brain and Language*, *16*, 73–86.
- 1585 Lewis, B. A. (1990). Familial phonological disorders: Four pedigrees. *Journal of Speech and*  
1586 *Hearing Disorders*, *55*, 160–170.
- 1587 Lewis, B. (1992). Genetics in speech disorders. *Clinical Communication Disorders*, *2*, 48–58.
- 1588 Lewis, B. A., Ekelman, B. L., & Aram, D. M. (1989). A familial study of severe phonological  
1589 disorders. *Journal of Speech and Hearing Research*, *32*, 713–724.
- 1590 Lewis, B. A., & Freebairn, L. (1992). Residual effects of preschool phonology disorders in  
1591 grade school, adolescence, and adulthood. *Journal of Speech and Hearing Research*, *35*,  
1592 819–831.
- 1593 Light, J. G., Pennington, B. F., Gilger, J. W., & DeFries, J. C. (1995). Reading disability and  
1594 hyperactivity disorder: Evidence for a common genetic etiology. *Developmental*  
1595 *Neuropsychology*, *11*, 323–335.
- 1596 Lilienfeld, S., Waldman, I., & Israel, A. (1994). Critical examination of the use of the term and  
1597 concept of comorbidity in psychopathology research. *Clinical Psychology and Scientific*  
1598 *Practice*, *1*, 71–83.
- 1599 Loney, J., & Milich, R. (1982). Hyperactivity, inattention, and aggression in clinical practice.  
1600 In M. Wolraich & D. Routh (Eds.), *Advances in developmental and behavioral pediatrics*  
1601 (Vol. 3, pp. 113–147). Greenwich, CT: JAI Press.
- 1602 Loo, S. K., Fisher, S. E., Francks, C., Ogdie, M. N., MacPhie, I. L., Yang, M. et al. (2004).  
1603 **Q14** Genome-wide scan of reading ability in affected sibling pairs with attention-deficit/  
1604 hyperactivity disorder: Unique and shared genetic effects. *Molecular Psychiatry*, *9*, 485–493.

- 1597 Lynam, D. R. (1996). Early identification of chronic offenders: Who is the fledgling  
1598 psychopath? *Psychological Bulletin*, *120*, 209–234.
- 1599 Q15 Lyytinen, H., Ahonen, T., Eklund, K., Guttorm, T. K., Laakso, M. L., Leinone, S. *et al.* (2002).  
1600 Developmental pathways of children with and without familial risk for dyslexia during the  
1601 first years of life. *Developmental Neuropsychology*, *20*, 535–554.
- 1602 Magnusson, E., & Naucler, K. (1990). Reading and spelling in language disordered children-  
1603 linguistic and metalinguistic pre-requisites: A report on a longitudinal study. *Clinical*  
*Linguistics and Phonetics*, *4*, 49–61.
- 1604 Maher, B. S., Marazita, M. L., Ferrell, R. E., & Vanyukov, M. M. (2002). Dopamine system  
1605 genes and attention deficit hyperactivity disorder: A meta-analysis. *Psychiatric Genetics*, *12*,  
1606 207–215.
- 1607 McGee, R., Williams, S., & Silva, P. A. (1984). Behavioral and developmental characteristics of  
1608 aggressive, hyperactive and aggressive-hyperactive boys. *Journal of the American Academy*  
*of Child Psychiatry*, *23*, 270–279.
- 1609 Merikangas, K. (1982). Assortative mating for psychiatric disorders and psychological traits.  
1610 *Archives of General Psychiatry*, *39*, 1173–1180.
- 1611 Moffitt, T. E. (1993). Adolescence-limited and life-course-persistent antisocial behavior:  
1612 A developmental taxonomy. *Psychological Review*, *100*, 674–701.
- 1613 Montgomery, J. W. (1995). Sentence comprehension in children with specific language  
1614 impairment: The role of phonological working memory. *Journal of Speech and Hearing*  
*Research*, *38*, 187–199.
- 1615 Nadder, T. S., Rutter, M., Silberg, J. L., Maes, H. H., & Eaves, L. J. (2002). Genetic effects on  
1616 the variation and covariation of attention deficit-hyperactivity disorder (ADHD) and  
1617 oppositional-defiant disorder/conduct disorder (Odd/CD) symptomatology across informant  
1618 and occasion of measurement. *Psychological Medicine*, *32*, 39–53.
- 1619 Nadder, T. S., Silberg, J. L., Eaves, L. J., Maes, H. H., & Meyer, J. M. (1998). Genetic effects on  
1620 ADHD symptomatology in 7- to 13-year-old twins: Results from a telephone survey.  
1621 *Behavior Genetics*, *28*, 83–99.
- 1622 Neale, M. C., & Kendler, K. S. (1995). Models of comorbidity for multifactorial disorders.  
1623 *American Journal of Human Genetics*, *57*, 935–953.
- 1624 Nigg, J. T., Hinshaw, S. P., Carte, E. T., & Treuting, J. J. (1998). Neuropsychological correlates  
1625 of childhood attention-deficit/hyperactivity disorder: Explainable by comorbid disruptive  
1626 behavior or reading problems? *Journal of Abnormal Psychology*, *107*, 468–480.
- 1627 Ogdie, M. N., Macphie, I. L., Minassian, S. L., Yang, M., Fisher, S. E., Francks, C. *et al.* (2003).  
1628 A genomewide scan for attention-deficit/hyperactivity disorder in an extended sample:  
1629 Suggestive linkage on 17p11. *American Journal of Human Genetics*, *72*, 1268–1279.
- 1630 Orton, S. T. (1925). Word-blindness in school children. *Archives of Neurology and Psychiatry*,  
1631 *14*, 582–615.
- 1632 Pennington, B. F. (2002). *The development of psychopathology: Nature and nurture*. New York:  
1633 Guilford.
- 1634 Q17 Pennington, B. F. A multiple deficit model for understanding developmental disorders.  
1635 *Cognition*. in press.
- 1636 Pennington, B. F., Groisser, D., & Welsh, M. C. (1993). Contrasting cognitive deficits in  
1637 attention deficit hyperactivity disorder versus reading disability. *Developmental Psycho-*  
*1638*  
*1639*  
*1640*  
*1641*  
*1642*  
*1643*  
*1644*  
*1645*  
*1646*  
*1647*  
*1648*  
*1649*  
*1650*  
*1651*  
*1652*  
*1653*  
*1654*  
*1655*  
*1656*  
*1657*  
*1658*  
*1659*  
*1660*  
*1661*  
*1662*  
*1663*  
*1664*  
*1665*  
*1666*  
*1667*  
*1668*  
*1669*  
*1670*  
*1671*  
*1672*  
*1673*  
*1674*  
*1675*  
*1676*  
*1677*  
*1678*  
*1679*  
*1680*  
*1681*  
*1682*  
*1683*  
*1684*  
*1685*  
*1686*  
*1687*  
*1688*  
*1689*  
*1690*  
*1691*  
*1692*  
*1693*  
*1694*  
*1695*  
*1696*  
*1697*  
*1698*  
*1699*  
*1700*  
*1701*  
*1702*  
*1703*  
*1704*  
*1705*  
*1706*  
*1707*  
*1708*  
*1709*  
*1710*  
*1711*  
*1712*  
*1713*  
*1714*  
*1715*  
*1716*  
*1717*  
*1718*  
*1719*  
*1720*  
*1721*  
*1722*  
*1723*  
*1724*  
*1725*  
*1726*  
*1727*  
*1728*  
*1729*  
*1730*  
*1731*  
*1732*  
*1733*  
*1734*  
*1735*  
*1736*  
*1737*  
*1738*  
*1739*  
*1740*  
*1741*  
*1742*  
*1743*  
*1744*  
*1745*  
*1746*  
*1747*  
*1748*  
*1749*  
*1750*  
*1751*  
*1752*  
*1753*  
*1754*  
*1755*  
*1756*  
*1757*  
*1758*  
*1759*  
*1760*  
*1761*  
*1762*  
*1763*  
*1764*  
*1765*  
*1766*  
*1767*  
*1768*  
*1769*  
*1770*  
*1771*  
*1772*  
*1773*  
*1774*  
*1775*  
*1776*  
*1777*  
*1778*  
*1779*  
*1780*  
*1781*  
*1782*  
*1783*  
*1784*  
*1785*  
*1786*  
*1787*  
*1788*  
*1789*  
*1790*  
*1791*  
*1792*  
*1793*  
*1794*  
*1795*  
*1796*  
*1797*  
*1798*  
*1799*  
*1800*  
*1801*  
*1802*  
*1803*  
*1804*  
*1805*  
*1806*  
*1807*  
*1808*  
*1809*  
*1810*  
*1811*  
*1812*  
*1813*  
*1814*  
*1815*  
*1816*  
*1817*  
*1818*  
*1819*  
*1820*  
*1821*  
*1822*  
*1823*  
*1824*  
*1825*  
*1826*  
*1827*  
*1828*  
*1829*  
*1830*  
*1831*  
*1832*  
*1833*  
*1834*  
*1835*  
*1836*  
*1837*  
*1838*  
*1839*  
*1840*  
*1841*  
*1842*  
*1843*  
*1844*  
*1845*  
*1846*  
*1847*  
*1848*  
*1849*  
*1850*  
*1851*  
*1852*  
*1853*  
*1854*  
*1855*  
*1856*  
*1857*  
*1858*  
*1859*  
*1860*  
*1861*  
*1862*  
*1863*  
*1864*  
*1865*  
*1866*  
*1867*  
*1868*  
*1869*  
*1870*  
*1871*  
*1872*  
*1873*  
*1874*  
*1875*  
*1876*  
*1877*  
*1878*  
*1879*  
*1880*  
*1881*  
*1882*  
*1883*  
*1884*  
*1885*  
*1886*  
*1887*  
*1888*  
*1889*  
*1890*  
*1891*  
*1892*  
*1893*  
*1894*  
*1895*  
*1896*  
*1897*  
*1898*  
*1899*  
*1900*  
*1901*  
*1902*  
*1903*  
*1904*  
*1905*  
*1906*  
*1907*  
*1908*  
*1909*  
*1910*  
*1911*  
*1912*  
*1913*  
*1914*  
*1915*  
*1916*  
*1917*  
*1918*  
*1919*  
*1920*  
*1921*  
*1922*  
*1923*  
*1924*  
*1925*  
*1926*  
*1927*  
*1928*  
*1929*  
*1930*  
*1931*  
*1932*  
*1933*  
*1934*  
*1935*  
*1936*  
*1937*  
*1938*  
*1939*  
*1940*  
*1941*  
*1942*  
*1943*  
*1944*  
*1945*  
*1946*  
*1947*  
*1948*  
*1949*  
*1950*  
*1951*  
*1952*  
*1953*  
*1954*  
*1955*  
*1956*  
*1957*  
*1958*  
*1959*  
*1960*  
*1961*  
*1962*  
*1963*  
*1964*  
*1965*  
*1966*  
*1967*  
*1968*  
*1969*  
*1970*  
*1971*  
*1972*  
*1973*  
*1974*  
*1975*  
*1976*  
*1977*  
*1978*  
*1979*  
*1980*  
*1981*  
*1982*  
*1983*  
*1984*  
*1985*  
*1986*  
*1987*  
*1988*  
*1989*  
*1990*  
*1991*  
*1992*  
*1993*  
*1994*  
*1995*  
*1996*  
*1997*  
*1998*  
*1999*  
*2000*  
*2001*  
*2002*  
*2003*  
*2004*  
*2005*  
*2006*  
*2007*  
*2008*  
*2009*  
*2010*  
*2011*  
*2012*  
*2013*  
*2014*  
*2015*  
*2016*  
*2017*  
*2018*  
*2019*  
*2020*  
*2021*  
*2022*  
*2023*  
*2024*  
*2025*  
*2026*  
*2027*  
*2028*  
*2029*  
*2030*  
*2031*  
*2032*  
*2033*  
*2034*  
*2035*  
*2036*  
*2037*  
*2038*  
*2039*  
*2040*  
*2041*  
*2042*  
*2043*  
*2044*  
*2045*  
*2046*  
*2047*  
*2048*  
*2049*  
*2050*  
*2051*  
*2052*  
*2053*  
*2054*  
*2055*  
*2056*  
*2057*  
*2058*  
*2059*  
*2060*  
*2061*  
*2062*  
*2063*  
*2064*  
*2065*  
*2066*  
*2067*  
*2068*  
*2069*  
*2070*  
*2071*  
*2072*  
*2073*  
*2074*  
*2075*  
*2076*  
*2077*  
*2078*  
*2079*  
*2080*  
*2081*  
*2082*  
*2083*  
*2084*  
*2085*  
*2086*  
*2087*  
*2088*  
*2089*  
*2090*  
*2091*  
*2092*  
*2093*  
*2094*  
*2095*  
*2096*  
*2097*  
*2098*  
*2099*  
*2100*  
*2101*  
*2102*  
*2103*  
*2104*  
*2105*  
*2106*  
*2107*  
*2108*  
*2109*  
*2110*  
*2111*  
*2112*  
*2113*  
*2114*  
*2115*  
*2116*  
*2117*  
*2118*  
*2119*  
*2120*  
*2121*  
*2122*  
*2123*  
*2124*  
*2125*  
*2126*  
*2127*  
*2128*  
*2129*  
*2130*  
*2131*  
*2132*  
*2133*  
*2134*  
*2135*  
*2136*  
*2137*  
*2138*  
*2139*  
*2140*  
*2141*  
*2142*  
*2143*  
*2144*  
*2145*  
*2146*  
*2147*  
*2148*  
*2149*  
*2150*  
*2151*  
*2152*  
*2153*  
*2154*  
*2155*  
*2156*  
*2157*  
*2158*  
*2159*  
*2160*  
*2161*  
*2162*  
*2163*  
*2164*  
*2165*  
*2166*  
*2167*  
*2168*  
*2169*  
*2170*  
*2171*  
*2172*  
*2173*  
*2174*  
*2175*  
*2176*  
*2177*  
*2178*  
*2179*  
*2180*  
*2181*  
*2182*  
*2183*  
*2184*  
*2185*  
*2186*  
*2187*  
*2188*  
*2189*  
*2190*  
*2191*  
*2192*  
*2193*  
*2194*  
*2195*  
*2196*  
*2197*  
*2198*  
*2199*  
*2200*  
*2201*  
*2202*  
*2203*  
*2204*  
*2205*  
*2206*  
*2207*  
*2208*  
*2209*  
*2210*  
*2211*  
*2212*  
*2213*  
*2214*  
*2215*  
*2216*  
*2217*  
*2218*  
*2219*  
*2220*  
*2221*  
*2222*  
*2223*  
*2224*  
*2225*  
*2226*  
*2227*  
*2228*  
*2229*  
*2230*  
*2231*  
*2232*  
*2233*  
*2234*  
*2235*  
*2236*  
*2237*  
*2238*  
*2239*  
*2240*  
*2241*  
*2242*  
*2243*  
*2244*  
*2245*  
*2246*  
*2247*  
*2248*  
*2249*  
*2250*  
*2251*  
*2252*  
*2253*  
*2254*  
*2255*  
*2256*  
*2257*  
*2258*  
*2259*  
*2260*  
*2261*  
*2262*  
*2263*  
*2264*  
*2265*  
*2266*  
*2267*  
*2268*  
*2269*  
*2270*  
*2271*  
*2272*  
*2273*  
*2274*  
*2275*  
*2276*  
*2277*  
*2278*  
*2279*  
*2280*  
*2281*  
*2282*  
*2283*  
*2284*  
*2285*  
*2286*  
*2287*  
*2288*  
*2289*  
*2290*  
*2291*  
*2292*  
*2293*  
*2294*  
*2295*  
*2296*  
*2297*  
*2298*  
*2299*  
*2300*  
*2301*  
*2302*  
*2303*  
*2304*  
*2305*  
*2306*  
*2307*  
*2308*  
*2309*  
*2310*  
*2311*  
*2312*  
*2313*  
*2314*  
*2315*  
*2316*  
*2317*  
*2318*  
*2319*  
*2320*  
*2321*  
*2322*  
*2323*  
*2324*  
*2325*  
*2326*  
*2327*  
*2328*  
*2329*  
*2330*  
*2331*  
*2332*  
*2333*  
*2334*  
*2335*  
*2336*  
*2337*  
*2338*  
*2339*  
*2340*  
*2341*  
*2342*  
*2343*  
*2344*  
*2345*  
*2346*  
*2347*  
*2348*  
*2349*  
*2350*  
*2351*  
*2352*  
*2353*  
*2354*  
*2355*  
*2356*  
*2357*  
*2358*  
*2359*  
*2360*  
*2361*  
*2362*  
*2363*  
*2364*  
*2365*  
*2366*  
*2367*  
*2368*  
*2369*  
*2370*  
*2371*  
*2372*  
*2373*  
*2374*  
*2375*  
*2376*  
*2377*  
*2378*  
*2379*  
*2380*  
*2381*  
*2382*  
*2383*  
*2384*  
*2385*  
*2386*  
*2387*  
*2388*  
*2389*  
*2390*  
*2391*  
*2392*  
*2393*  
*2394*  
*2395*  
*2396*  
*2397*  
*2398*  
*2399*  
*2400*  
*2401*  
*2402*  
*2403*  
*2404*  
*2405*  
*2406*  
*2407*  
*2408*  
*2409*  
*2410*  
*2411*  
*2412*  
*2413*  
*2414*  
*2415*  
*2416*  
*2417*  
*2418*  
*2419*  
*2420*  
*2421*  
*2422*  
*2423*  
*2424*  
*2425*  
*2426*  
*2427*  
*2428*  
*2429*  
*2430*  
*2431*  
*2432*  
*2433*  
*2434*  
*2435*  
*2436*  
*2437*  
*2438*  
*2439*  
*2440*  
*2441*  
*2442*  
*2443*  
*2444*  
*2445*  
*2446*  
*2447*  
*2448*  
*2449*  
*2450*  
*2451*  
*2452*  
*2453*  
*2454*  
*2455*  
*2456*  
*2457*  
*2458*  
*2459*  
*2460*  
*2461*  
*2462*  
*2463*  
*2464*  
*2465*  
*2466*  
*2467*  
*2468*  
*2469*  
*2470*  
*2471*  
*2472*  
*2473*  
*2474*  
*2475*  
*2476*  
*2477*  
*2478*  
*2479*  
*2480*  
*2481*  
*2482*  
*2483*  
*2484*  
*2485*  
*2486*  
*2487*  
*2488*  
*2489*  
*2490*  
*2491*  
*2492*  
*2493*  
*2494*  
*2495*  
*2496*  
*2497*  
*2498*  
*2499*  
*2500*  
*2501*  
*2502*  
*2503*  
*2504*  
*2505*  
*2506*  
*2507*  
*2508*  
*2509*  
*2510*  
*2511*  
*2512*  
*2513*  
*2514*  
*2515*  
*2516*  
*2517*  
*2518*  
*2519*  
*2520*  
*2521*  
*2522*  
*2523*  
*2524*  
*2525*  
*2526*  
*2527*  
*2528*  
*2529*  
*2530*  
*2531*  
*2532*  
*2533*  
*2534*  
*2535*  
*2536*  
*2537*  
*2538*  
*2539*  
*2540*  
*2541*  
*2542*  
*2543*  
*2544*  
*2545*  
*2546*  
*2547*  
*2548*  
*2549*  
*2550*  
*2551*  
*2552*  
*2553*  
*2554*  
*2555*  
*2556*  
*2557*  
*2558*  
*2559*  
*2560*  
*2561*  
*2562*  
*2563*  
*2564*  
*2565*  
*2566*  
*2567*  
*2568*  
*2569*  
*2570*  
*2571*  
*2572*  
*2573*  
*2574*  
*2575*  
*2576*  
*2577*  
*2578*  
*2579*  
*2580*  
*2581*  
*2582*  
*2583*  
*2584*  
*2585*  
*2586*  
*2587*  
*2588*  
*2589*  
*2590*  
*2591*  
*2592*  
*2593*  
*2594*  
*2595*  
*2596*  
*2597*  
*2598*  
*2599*  
*2600*  
*2601*  
*2602*  
*2603*  
*2604*  
*2605*  
*2606*  
*2607*  
*2608*  
*2609*  
*2610*  
*2611*  
*2612*  
*2613*  
*2614</*

- 1639 Raitano, N. A., Pennington, B. F., Tunick, R. A., Boada, R., & Shriberg, L. D. (2004). Pre-  
 1640 literacy skills of subgroups of children with speech sound disorders. *Journal of Child*  
 1641 *Psychology and Psychiatry*, *45*, 821–835.
- 1642 Rhee, S., Hewitt, J., Corley, R., & Stallings, M. (2003). The validity of analyses testing the  
 1643 etiology of comorbidity between two disorders: A review of family studies. *Journal of Child*  
*Psychology and Psychiatry and Allied Disciplines*, *44*, 612–636.
- 1644 Rhee, S. H., Hewitt, J. K., Corley, R. P., Willcutt, E., & Pennington, B. (2004a). *Testing*  
 1645 *hypotheses regarding the causes of comorbidity: Examining the underlying deficits of*  
 1646 *comorbid disorders*. Unpublished manuscript.
- 1647 Rhee, S. H., Hewitt, J. K., Lessem, J. M., Stallings, M. C., Corley, R. P., & Neale, M. C.  
 1648 (2004b). The validity of the Neale and Kendler model-fitting approach in examining the  
 1649 etiology of comorbidity. *Behavior Genetics*, *34*, 251–265.
- 1649 Rhee, S., Willcutt, E., Hartman, C., Pennington, B., & DeFries, J. (2004c). *Test of alternative*  
 1650 *hypotheses explaining the comorbidity between attention-deficit/hyperactivity disorder and*  
 1651 *conduct disorders*. Paper Presented at the Behavior Genetics Association, Aix-en-Provence,  
 1652 France.
- 1652 Riley, B. P., & McGuffin, P. (2000). Linkage and associated studies of schizophrenia. *American*  
 1653 *Journal of Medical Genetics*, *97*, 23–44.
- 1654 Riso, L. P., Klein, D. N., Ferro, T., Kasch, K. L., Pepper, C. M., Schwartz, J. E. et al. (1996).  
 1655 <sup>Q18</sup> Understanding the comorbidity between early-onset dysthymia and cluster B personality  
 1656 disorders: A family study. *American Journal of Psychiatry*, *153*, 900–906.
- 1657 Robins, L., Locke, B., & Regier, D. (1991). An overview of psychiatric disorders in America. In  
 1658 L. Robins & B. Locke (Eds.), *Psychiatric disorders in America* (pp. 328–366). New York:  
 1659 Free.
- 1659 Rucklidge, J. J., & Tannock, R. (2002). Neuropsychological profiles of adolescents with  
 1660 ADHD: Effects of reading difficulties and gender. *Journal of Child Psychology and*  
 1661 *Psychiatry*, *43*, 988–1003.
- 1662 Rutter, M., & Mawhood, L. (1991). The long-term psychosocial sequelae of specific  
 1663 developmental disorders of speech and language. In M. Rutter & P. Casaer (Eds.),  
 1664 *Biological risk factors for psychosocial disorders* (pp. 233–259). Cambridge: Cambridge  
 1665 University Press.
- 1665 Rutter, M., & Yule, W. (1975). The concept of specific reading retardation. *Journal Child*  
 1666 *Psychology and Psychiatry*, *16*, 181–197.
- 1667 Scarborough, H. S. (1990). Very early language deficits in dyslexic children. *Child*  
 1668 *Development*, *61*, 1728–1743.
- 1668 Scarborough, H. S., & Dobrich, W. (1990). Development of children with early language delay.  
 1669 *Journal of Speech and Hearing Research*, *33*, 70–83.
- 1670 Schachar, R., & Tannock, R. (1995). Test of four hypotheses for the comorbidity of attention-  
 1671 deficit hyperactivity disorder and conduct disorder. *Journal of the Academy of Child and*  
 1672 *Adolescent Psychiatry*, *34*, 639–648.
- 1672 Seidman, L. J., Biederman, J., Monuteaux, M. C., Doyle, A. E., & Faraone, S. V. (2001).  
 1673 Learning disabilities and executive dysfunction in boys with attention-deficit/hyperactivity  
 1674 disorder. *Neuropsychology*, *15*, 544–556.
- 1675 Semrud-Clikeman, M., Biederman, J., Sprich-Buckminster, S., Lehman, B. K., Faraone, S. V.,  
 1676 & Norman, D. (1992). Comorbidity between ADDH and learning disability: A review and  
 1677 report in a clinically referred sample. *Journal of the American Academy of Child and*  
 1678 *Adolescent Psychiatry*, *31*, 439–448.
- 1678 Shaywitz, B. A., Fletcher, J. M., & Shaywitz, S. E. (1995). Defining and classifying learning  
 1679 disabilities and attention-deficit/hyperactivity disorder. *Journal of Child Neurology*,  
 1680 *10*(Suppl. 1), S50–S57.

- 1681 Shriberg, L. D., Tomblin, J. B., & McSweeney, J. L. (1999). Prevalence of speech delay in  
1682 6-year-old children and comorbidity with language impairment. *Journal of Speech,*  
1683 *Language, and Hearing Research, 42,* 1461–1481.
- 1684 Q19 Silberg, J., Rutter, M., Meyer, J., Maes, H., Hewitt, J., Simonoff, E. *et al.* (1996). Genetic and  
1685 environmental influences on the covariation between hyperactivity and conduct disturbance  
1686 in juvenile twins. *Journal of Child Psychology and Psychiatry, 37,* 803–816.
- 1687 Sing, C. F., & Reilly, S. L. (1993). Genetics of common diseases that aggregate, but do not  
1688 segregate in families. In C. F. Sing & C. L. Hanis (Eds.), *Genetics of cellular, individual,*  
1689 *family and population variability* (pp. 140–161). New York: Oxford University Press.
- 1690 Smith, S. D., Deffenbacher, K. E., Boada, R., Tunick, R. A., Raitano, N. A. & Pennington, B.  
1691 (2003). *Speech sound disorder is linked to dyslexia risk loci on chromosome 6 and 15.* Paper  
1692 Presented at the 53rd Annual Meeting of American Society for Human Genetics,  
1693 Los Angeles, CA. November.
- 1694 Snowling, M., Bishop, D. V., & Stothard, S. E. (2000). Is preschool language impairment a risk  
1695 factor for dyslexia in adolescence? *Journal of Child Psychology and Psychiatry, 41,*  
1696 587–600.
- 1697 Snowling, M., & Stackhouse, J. (1983). Spelling performance of children with developmental  
1698 verbal dyspraxia. *Developmental and Medical Child Neurology, 25,* 430–437.
- 1699 Q20 Stein, C. M., Schick, J. H., Gerry Taylor, H., Shriberg, L. D., Millard, C., Kundtz-Kludge, A.  
1700 *et al.* (2004). Pleiotropic effects of a chromosome 3 locus on speech-sound disorder and  
1701 reading. *American Journal of Human Genetics, 74,* 283–297.
- 1702 Steingard, R., Biederman, J., Doyle, A., & Sprich-Buckminster, S. (1992). Psychiatric  
1703 comorbidity in attention deficit disorder: Impact on the interpretation of Child Behavior  
1704 Checklist results. *Journal of the Academy of Child and Adolescent Psychiatry, 31,* 449–454.
- 1705 Stevenson, J., Pennington, B. F., Gilger, J. W., DeFries, J. C., & Gillis, J. J. (1993).  
1706 Hyperactivity and spelling disability: Testing for shared genetic etiology. *Journal of Child*  
1707 *Psychology and Psychiatry, 14,* 1137–1152.
- 1708 Swanson, H., Mink, J., & Bocian, K. (1999). Cognitive processing deficits in poor readers with  
1709 symptoms of reading disabilities and ADHD: More alike than different? *Journal of*  
1710 *Educational Psychology, 91,* 321–333.
- 1711 Taylor, E., Chadwick, O., Heptinstall, E., & Danckaerts, M. (1996). Hyperactivity and conduct  
1712 problems as risk factors for adolescent development. *Journal of the Academy of Child and*  
1713 *Adolescent Psychiatry, 35,* 1213–1226.
- 1714 Thapar, A., Harrington, R., & McGuffin, P. (2001). Examining the comorbidity of ADHD-  
1715 related behaviours and conduct problems using a twin study design. *British Journal of*  
1716 *Psychiatry, 179,* 224–229.
- 1717 Tomblin, J. B., Freese, P. R., & Records, N. L. (1992). Diagnosing specific language  
1718 impairment in adults for the purpose of pedigree analysis. *Journal of Speech and Hearing*  
1719 *Research, 35,* 832–843.
- 1720 Q21 Trzesniewski, K., Moffitt, T. E., & Caspi, A. Revisiting the association between reading  
1721 achievement and antisocial behavior: New evidence of an environmental explanation from a  
1722 twin study. *Child Development.* submitted.
- 1723 Q22 Tunick, R. A., Boada, R., Raitano, N. A., & Pennington, B. F. *Cofamiliarity of speech sound*  
1724 *disorder and reading disability.* in preparation.
- 1725 Tunick, R. A., & Pennington, B. F. (2002). The etiological relationship between reading  
1726 disability and phonological disorder. *Annals of Dyslexia, 52,* 75–95.
- 1727 Volkow, N. D., Wang, G. J., Fowler, J. S., Gatley, S. J., Logan, J., Ding, Y. S. *et al.* (1998).  
1728 Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral  
1729 methylphenidate. *American Journal of Psychiatry, 155,* 1325–1331.

- 1723 Wadsworth, S. J., Davis, C., Knopik, V., Willcutt, E., & DeFries, J. (2002). Genetics of reading  
1724 disabilities. *Proceedings of the 12th Postgraduate Course in Pediatric Neurology: Learning*  
1725 *Disabilities in Reading and Writing*, 23–36.
- 1726 Wagner, R. K., & Torgesen, J. K. (1987). The nature of phonological processing and its causal  
1727 role in the acquisition of reading skills. *Psychological Bulletin*, 101, 192–212.
- 1728 Waldman, I., Rhee, S., Levy, F., & Hay, D. (2001). Causes of the overlap among symptoms of  
1729 ADHD, oppositional defiant disorder, and conduct disorder. In F. Levy & D. Hay (Eds.),  
1730 *Attention, genes, and ADHD* (pp. 115–138). East Sussex, England: Brunner-Routledge.
- 1731 Waschbusch, D. A. (2002). A meta-analytic examination of comorbid hyperactive-impulsive-  
1732 attention problems and conduct problems. *Psychological Bulletin*, 128, 118–150.
- 1733 Wickramaratne, P. J., & Weissman, M. M. (1993). Using family studies to understand  
1734 comorbidity. *European Archives of Psychiatry and Clinical Neuroscience*, 243, 150–157.
- 1735 Willcutt, E. Genetics of ADHD. In D. Barch (Ed.), *Cognitive and affective neuroscience*  
1736 *psychopathology*. Oxford: Oxford University Press. in press.
- 1737 Willcutt, E., Chhabildas, N., & Pennington, B. (1998). *Psychiatric correlates of reading*  
1738 *disability*. Paper Presented at the Kansas Conference on Clinical Child Psychology,  
1739 Lawrence, KS.
- 1740 Willcutt, E. G., DeFries, J. C., Pennington, B. F., Smith, S. D., Cardon, L. R., & Olson, R. K.  
1741 (2003). Genetic etiology of comorbid reading difficulties and ADHD. In R. Plomin, J. C.  
1742 DeFries, I. W. Craig, & P. McGuffin (Eds.), *Behavioral genetics in the postgenomic era*  
1743 (pp. 227–246). Washington, DC: American Psychological Association.
- 1744 Willcutt, E. G., & Pennington, B. F. (2000a). Comorbidity of reading disability and attention  
1745 deficit/hyperactivity disorder: Differences by gender and subtype. *Journal of Learning*  
1746 *Disabilities*, 33, 179–191.
- 1747 Willcutt, E. G., & Pennington, B. F. (2000b). Psychiatric comorbidity in children and  
1748 adolescents with reading disability. *Journal of Child Psychology and Psychiatry*, 41,  
1749 1039–1048.
- 1750 Willcutt, E. G., Pennington, B. F., Boada, R., Oglie, J. S., Tunick, R. A., Chhabildas, N. A.  
1751 *et al.* (2001). A comparison of the cognitive deficits in reading disability and attention-  
1752 deficit/hyperactivity disorder. *Journal of Abnormal Psychology*, 110, 157–172.
- 1753 Willcutt, E., Pennington, B., Chhabildas, N., Olson, R., & Hulslander, J. Neuropsychological  
1754 analyses of comorbidity between RD and ADHD in search of the common deficit.  
1755 *Developmental Neuropsychology*. in press.
- 1756 Willcutt, E. G., Pennington, B. F., & DeFries, J. C. (2000). Twin study of the etiology of  
1757 comorbidity between reading disability and attention-deficit/hyperactivity disorder.  
1758 *American Journal of Medical Genetics*, 96, 293–301.
- 1759 Willcutt, E., Pennington, B., Olson, R., & DeFries, J. Understanding comorbidity: A twin study  
1760 of reading disability and attention deficit/hyperactivity disorder. *American Journal of*  
1761 *Medical Genetics (Neuropsychiatric Genetics)*. in press.
- 1762 Willcutt, E., Shyu, V., Green, P., & Pennington, B. (1995). *A twin study of the comorbidity of the*  
1763 *disruptive behavior disorders of childhood*. Paper Presented at the Society for Research in  
1764 Child Development, Indianapolis, IN.
- 1765 Willcutt, E. G., Pennington, B. F., Smith, S. D., Cardon, L. R., Gayan, J., Knopik, V. S., *et al.*  
1766 (2002). Quantitative trait locus for reading disability on chromosome 6p is pleiotropic for  
1767 attention-deficit/hyperactivity disorder. *American Journal of Medical Genetics*, 114,  
1768 260–268.

1765 **Author Queries**

1766

1767 *JOB NUMBER:* 9146

1768 *TITLE:* Analyzing Comorbidity

1769

1770

1771 **Q1** Kindly confirm edit of the sentence “(i.e., an individual who has one...  
1772 for the second disorder)”

1773 **Q2** Tunick (2004) is cited but not in the list. Kindly provide details.

1774 **Q3** Kindly note that Faraone, Biederman, Lehman, Keenan, Norman and  
1775 Seidman (2000) is cited but not in the list.

1776 **Q4** Kindly note that McGrath *et al.*, in preparation is cited but not in the list.

1777 **Q5** Kindly note that Rhee, S. H., Hewitt, J. K., Corley, R. P., & Stallings,  
1778 M. C. (submitted) is cited but not in list.

1779

1780 **Q6** Kindly provide complete author details for Bakker *et al.* (2003).

1781 **Q7** Kindly provide complete author details for Biederman *et al.* (1992).

1782

1783 **Q8** Kindly provide complete author details for Bierut *et al.* (1998).

1784 **Q9** Kindly provide complete author details for Bird *et al.* (1988).

1785 **Q10** Kindly provide complete authors details for Faraone *et al.* (1993).

1786 **Q11** Kindly provide complete authors detail for Gayan *et al.* (1999).

1787

1788 **Q12** Kindly provide complete authors detail for Holmes *et al.* (2002).

1789 **Q13** Kindly provide complete authors detail for Kessler *et al.* (1994).

1790 **Q14** Kindly provide complete authors detail for Loo *et al.* (2004).

1791 **Q15** Kindly provide complete authors detail for Lyytinen *et al.* (2002).

1792

1793 **Q16** Kindly provide complete authors detail for Ogdie *et al.* (2003).

1794 **Q17** Kindly update Pennington (in press)

1795 **Q18** Kindly provide complete authors detail for Riso (1996).

1796

1797 **Q19** Kindly provide complete authors detail for Silberg *et al.* (1996).

1798 **Q20** Kindly provide complete authors detail for Stein *et al.* (2004).

1799 **Q21** Kindly update Trzesniewski, Moffitt, and Caspi (submitted).

1800 **Q22** Kindly update Tunick *et al.* (in preparation)

1801

1802 **Q23** Kindly provide complete authors detail for Volkow *et al.* (1998).

1803 **Q24** Kindly update Willcutt (in press).

1804 **Q25** Kindly provide complete authors detail for Willcutt *et al.* (2001)

1805

1806 **Q26** Kindly update Willcutt *et al.* (in press).

1807 **Q27** Kindly update Willcutt *et al.* (in press).  
1808 **Q28** Kindly provide complete authors detail for Willcutt *et al.* (2002)  
1809  
1810  
1811  
1812  
1813  
1814  
1815  
1816  
1817  
1818  
1819  
1820  
1821  
1822  
1823  
1824  
1825  
1826  
1827  
1828  
1829  
1830  
1831  
1832  
1833  
1834  
1835  
1836  
1837  
1838  
1839  
1840  
1841  
1842  
1843  
1844  
1845  
1846  
1847  
1848