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

* This work was supported by NIH grants MH38820, HD27802, HD04024, and DA13956.
account for both human universals and individual differences, hopefully with
the same underlying mechanisms. So every example of atypical development
poses both a challenge and an opportunity for developmental theory. In this
chapter, we focus on a pervasive characteristic of atypical development, comorbidity among behavioral disorders. Comorbidity is relevant for develop-
mental theory because it can provide insights into how behavioral disorders
develop. Each disorder can be conceived of as having a particular develop-
mental trajectory, in which some mechanisms underlying normal development
are perturbed and many others are intact. The phenomenon of comorbidity often
means that the developmental trajectories for different disorders intersect. These
intersection points can be particularly informative about underlying mechan-
isms. We hope to demonstrate how analyses of comorbidity may shed some
light on these intersection points and hence the mechanisms that underlie both
typical and atypical development.

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

In fact, unlike much of the rest of medicine, current psychiatric nosologies,
such as the DSM-IV or the ICD-10, contain diagnostic constructs that are
intentionally just descriptive, because we do not yet know enough about
underlying mechanisms to use them to define psychiatric disorders. Because
earlier psychiatric nosologies were based on unproven assumptions about
underlying mechanisms and because diagnostic definitions were not specific
enough to be reliable across diagnosticians, developing reliable descriptive
diagnostic categories was a scientific step forward for psychopathology research.
But defining psychopathologies in terms of underlying mechanisms instead of
just symptoms remains a key long-term goal of research on psychiatric disorders.
As we demonstrate in this chapter, analyzing comorbidity is one strategy for reaching that goal.

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

B. OVERVIEW OF CHAPTER

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

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

For children, somewhat similar results have been found. In an epidemiological study in Puerto Rico (Bird et al., 1988), almost half of children with one diagnosis had a second diagnosis. Several other studies have documented high rates of comorbidity among childhood psychiatric disorders (e.g., Jensen et al., 1995; Steingard et al., 1992). Again, some pairs of disorders, such as ADHD and
Conduct Disorder, CD, co-occur much more frequently than other pairs, such as CD and Anxiety disorder (Angold, Costello, & Erkanli, 1999).

II. Explanations of Comorbidity

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

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

A. ARTIFACTUAL EXPLANATIONS

Although the phenomenon of comorbidity may signal an unappreciated causal relation between two disorders, it may also simply be an artifact of some kind. So before undertaking more extensive research to discover this possible causal relation, researchers must rule out artifactual explanations. Both Caron and Rutter (1991) and Klein and Riso (1993) discuss several artifactual explanations of comorbidity: chance, sampling bias, population stratification, definitional
overlap, and rater biases. We next briefly discuss each of these artifactual
explanations and how they may be tested.

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

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

Third, apparent comorbidity might be due to population stratification.
Although the risk factors for each disorder A and B are in fact independent in
the population as a whole, they may co-occur in certain strata of the population. If
our test of comorbidity is performed on that strata, then we will falsely conclude
that comorbidity between A and B happens more frequently than by chance. For
instance, non-random or assortative mating by individuals with disorders A and B
will produce apparent comorbidity in their offspring, if both disorders are
familial. Such non-random mating appears to explain the comorbidity between
depression and alcoholism (Merikangas, 1982). As a second example of
population stratification, Caron and Rutter (1991) discuss the apparent
comorbidity between depression and conduct disorder in children. In this case,
depression in parents acts in different ways to create an increased risk for each
disorder in offspring: parental depression is both a genetic and environmental risk
factor for depression in a child and parental depression increases marital discord,
which is an environmental risk factor for conduct disorder in the child.

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

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

**B. NON-ARTIFICIAL EXPLANATIONS**

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

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

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

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

Correlated Liabilities Model

A causes B Model

Reciprocal Causation Model

Fig. 1. Continued.
is $r$. This means that both disorders share a single liability, and that one person manifests disorder A while another person manifests disorder B because of chance or risk factors that vary across individuals. A gene by environment interaction where the environmental risk factor is specific to an individual is an example of how comorbidity may occur through alternate forms. If two individuals have the same overall liability but are exposed to different person-specific environmental risks, the first individual may manifest disorder A while the second individual manifests disorder B. A gene by environment interaction that replicates across individuals would not be an example of the alternate forms model.

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

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

The four correlated liabilities models share the idea that there is a continuous relation between the liability to one disorder and the liability to the second disorder. An increase in liability for one disorder is correlated with the increase in liability for the second disorder. (In contrast, in the multiformity models, a change in liability for one disorder has absolutely no effect on the second disorder unless an individual crosses the threshold for the first disorder and is actually affected by the disorder.) The relation between the liability of the two disorders occurs via a significant correlation between the risk factors (correlated liabilities) or a direct causal relation between the manifest phenotypes of the two disorders (A causes B, B causes A, or reciprocal causation).
Although the Neale and Kendler (1995) models are a major contribution to the comorbidity literature because they are the most complete set of models yet proposed and because they are specified quantitatively, they nonetheless have some limitations. Specifically, they do not include a neural or a cognitive level, they are not explicitly developmental, they only deal with pairwise comorbidities, and some of them can be difficult to distinguish empirically, even with ideal (simulated) data sets. Most of these limitations are apparent in the sections that follow.

III. Methods for Analyzing Comorbidity

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

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

A. KLEIN AND RISO’S FAMILY PREVALENCE ANALYSES

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

Most of Klein and Riso’s predictions were validated by the simulation results, in that most of their predicted results matched the results in the simulated datasets. However, there were several notable differences between the predicted results and results obtained in the simulated datasets. Some of Klein and Riso’s predictions were not obtained in the simulated results because of lack of power in the simulated datasets. Another reason for the discrepancy between the predicted results and the results in the simulated dataset was the predictions’ lack of
consideration of all possible pathways for the comorbid disorder, notably the fact that there will be some individuals who have both disorders A and B due to chance.

B. FAMILY PREVALENCE ANALYSES IN THE LITERATURE

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

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

C. NEALE AND KENDLER MODEL FITTING APPROACH

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

In general, the Neale and Kendler model fitting approach discriminated the following classes of models reliably: the alternate forms model, the random multiformity models (i.e., random multiformity, random multiformity of A, and
random multiformity of B), the extreme multiformity models (i.e., extreme multiformity, extreme multiformity of A, and extreme multiformity of B), the three independent disorders model, and the correlated liabilities models (i.e., correlated liabilities, A causes B, B causes A, and the reciprocal causation). Discrimination within these classes of models was poorer. Results from simulations varying the prevalences of the comorbid disorders indicate that the ability to discriminate between models becomes poorer as the prevalences of the disorders decreases, and suggests the importance of considering the issue of power when conducting these analyses.

D. UNDERLYING DEFICITS APPROACH

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

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

E. CONCLUSIONS

Although most of Klein and Riso’s family prevalence analyses were valid, there were notable discrepancies between their predicted results and results found in the simulated datasets. Some of the family prevalence analyses found in
the literature were valid predictors of the alternate forms model, but none were valid predictors of the correlated liabilities or three independent disorders models. The Neale and Kendler model fitting approach and the method of examining the underlying deficits of comorbid disorders discriminated between several comorbidity models reliably, suggesting that these two methods may be the most useful methods found in the literature. Especially encouraging is the fact that some of the models that cannot be distinguished well using the Neale and Kendler model fitting approach can be distinguished well by examining the underlying deficits of comorbid disorders, and vice versa. The best approach may be a combination of these two methods. However, simulation results suggest that the issue of power should be considered carefully.

IV. Analyses of Specific Comorbidities

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

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

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

A. READING DISABILITY AND SPEECH SOUND DISORDER

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

1. Symptom Overlap Between SSD and RD

Children with early speech/language problems are at increased risk for later literacy problems (Aram, Ekelman, & Nation, 1984; Bishop & Adams, 1990; Catts et al., 2002; Hall & Tomblin, 1978; Magnusson & Naucler, 1990; Rutter & Mawhood, 1991; Scarborough & Dobrich, 1990; Snowling & Stackhouse, 1983; Snowling, Bishop, & Stothard, 2000; Tomblin, Freese, & Records, 1992) and individuals with literacy problems retrospectively report increased rates of earlier speech and language problems (Hallgren, 1950; Rutter & Yule, 1975).
Moreover, the latter association is not limited to retrospective reports because young children selected for family risk for dyslexia or RD and followed prospectively also have higher rates of preschool speech and language problems than controls (Gallagher, Frith, and Snowling, 2000; Gilger et al., 1994; Lyytinen et al., 2002; Pennington & Lefly, 2001; Scarborough, 1990). But these previous studies have rarely distinguished SSD from specific language impairment (SLI), which is defined by deficits in semantics and syntax. So, it is less clear which subtypes (or components) of SSD *per se* presage which kinds of later literacy problems.

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

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

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

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

3. Hypotheses to Explain SSD/RD Comorbidity

In an NIH grant application, one of us (BFP) once proposed five competing
hypotheses (all but one of which were single cognitive deficit hypotheses) to
account for the comorbidity of SSD and RD (see Figure 2). These hypotheses
were generated without knowledge of the Klein and Risso (1993) hypotheses,
yet all but one of them (cognitive phenocopy) corresponds to one of their
hypotheses. These hypotheses were generated by crossing two distinctions: a
common vs. distinct etiology and a common vs. distinct cognitive phenotype.
These five hypotheses were: (1) severity (both etiology and cognitive phenotype
are shared, but comorbid children have a more severe phonological deficit); (2)
pleiotropy (a shared etiology leads to two distinct cognitive phenotypes, which
coccur in comorbid children); (3) cognitive phenocopy or genetic heterogeneity (distinct etiologies lead to a shared cognitive phenotype, thus producing
comorbidity); (4) cross-assortment or non-random mating (both the etiology and
cognitive phenotypes are distinct, but individuals with SSD (or RD) are more
likely to select mates with RD (or SSD), thus transmitting risk alleles for both
disorders to their children); and (5) synergy, in which the etiologies and cognitive
phenotypes of SSD and RD are distinct, but comorbidity between SSD and SLI
produces later RD. The severity and pleiotropy hypotheses correspond to
different versions of Klein and Riso’s (1993) alternate forms hypothesis; synergy
is similar to the three independent disorders hypothesis; and assortment is an
example of the population stratification hypothesis, as discussed earlier.

4. Tests of the Five Hypotheses

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

First, there is now stronger evidence for a shared genetic etiology between RD
and SSD, which rejects hypotheses 3–5, all of which posit distinct etiologies for
RD and SSD. Two groups have now tested whether some of the risk loci already
identified for RD are risk loci for SSD. Several replicated risk loci or QTLs for
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
on chromosome 3 (Stein et al., 2004). They tested several related phenotypes,
including SSD itself, phonological memory, phonological awareness, and
reading. All of these phenotypes were linked to the RD risk locus on
chromosome 3, indicating that this locus affects phonological development and
Fig. 2. Schematic representation of five hypotheses. E = Common Etiology; CC = Common Cognitive Phenotype; $E_1,E_2,E_3$ = Specific etiologies; $C_1,C_2,C_3$ = Specific cognitive phenotypes. Horizontal arrows indicate influence of additional chance factors.
contributes to the comorbidity between SSD and RD. We have also found that SSD is linked to RD risk loci on chromosomes 6 and 15, and perhaps 1 (Smith et al., 2003). We also tested multiple phenotypes, including SSD itself, phonological memory, and phonological awareness, all of which provided evidence for linkage.

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

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

In sum the results of these three tests reject all but the severity hypothesis. But despite the fact that the severity hypothesis garners some support from these data and that of previous studies reviewed earlier, there are still significant challenges to how it accounts for the nature of the comorbidity between SSD and RD.
The severity hypothesis proposes that SSD and RD are comorbid because they share etiological risk factors (some of which are genetic) and these lead to a shared phonological deficit, which is more severe in children with comorbid SSD and RD than children with RD only. To account for SSD children who do not become RD, the severity hypothesis must postulate a subtype of SSD with a distinct etiology and a different underlying cognitive deficit. If SSD children without later RD nonetheless have an underlying phonological deficit, the severity hypothesis must be seriously questioned. But the results of Raitano et al. (2004) just discussed suggest there is not a common subtype of SSD without a phonological deficit. Clearer evidence on this point is provided by long-term follow-up study (Snowling, Bishop, & Stothard, 2000) of SSD children initially identified by Bishop at preschool age. These researchers found there were former SSD children with a persistent deficit in phoneme awareness in adolescence who are nonetheless normal readers. Both these results are inconsistent with the severity hypothesis.

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

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

The comparison of the profiles of phonological processing deficits in probands and siblings tests the severity hypothesis, which predicts similar profiles in each disorder, with greater impairment in the SSD group. We examined three phonological processing constructs: phonological awareness, phonological memory, and rapid serial naming. In the proband comparison, somewhat different measures of the same constructs had been used with each group, so their z-scores relative to matched controls were used to compare the SSD and RD proband groups. In the sibling comparison, the same measures were used in each group. We found that SSD and RD probands shared a deficit of similar magnitude.
(relative to their controls) on the phonological awareness composite, but had significantly different profiles overall, producing a significant group × domain interaction. The interaction arose because the SSD proband group performed significantly better than the RD proband group on the rapid serial naming composite and non-significantly worse score on the phonological memory composite. This interaction replicated in the sibling comparison, in which the same measures of these constructs were used in each group. The relative strength on rapid serial naming measures in both SSD groups is a somewhat surprising finding, given that one would expect a slower articulatory rate in SSD. So, it will be important to replicate this result in another SSD sample. But this finding could help explain why not all SSD children develop later RD, despite having a phonological awareness deficit. In sum, Tunick’s (2004) results do not support the predictions of the single deficit, severity model because the phonological awareness deficit is not more severe in the SSD groups and because the profiles of phonological deficits are not parallel.

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

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

B. READING DISABILITY AND ADHD

RD and ADHD are two of the most common disorders of childhood, each occurring in approximately five percent of the population (e.g., American Psychiatric Association, 2000). ADHD and RD also co-occur significantly more frequently than expected by chance; 25–40% of individuals with ADHD also
meet criteria for RD (e.g., (Dykman & Ackerman, 1991; Semrud-Clikeman et al., 1992), whereas 15–40% of individuals with RD meet criteria for ADHD (Gilger, Pennington, & DeFries, 1992; Shaywitz, Fletcher, & Shaywitz, 1995; Willcutt & Pennington, 2000a,b).

1. Artifactual Explanations for Comorbidity Between RD and ADHD

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

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

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

2. Competing Explanations for True Comorbidity Between RD and ADHD

Three of Neale and Kendler's (1995) competing explanations have received at least some support in previous studies of comorbidity between RD and ADHD. These models include the phenocopy (multiformity of A) hypothesis (e.g., Pennington, Groisser, & Welsh, 1993), the three independent disorders hypothesis (e.g., Rucklidge & Tannock, 2002), and the correlated liabilities
(common etiology) hypothesis (e.g., Willcutt, Pennington, & DeFries, 2000, Willcutt et al. in press a,b). We consider each.

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

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

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

3. Behavioral Genetic Studies of RD and ADHD

a. Family Studies. Family studies provide a first step toward understanding the genetic and environmental risk factors for RD, ADHD, and their comorbidity. A family study compares the rate of a disorder in the biological relatives of individuals with and without the disorder. If a disorder occurs more often among
the family members of individuals with the disorder, this suggests that familial factors play a role in the etiology of the disorder.

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

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

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

Based on the finding that both RD and ADHD are significantly heritable, several studies have used twin data to test if the same genetic influences contribute to both RD and ADHD. Gilger, Pennington, & DeFries (1992) conducted cross-concordance analyses in a small sample of twins selected for RD, and found that ADHD and RD were primarily attributable to independent genetic factors. However, a statistical trend suggested that children with
comorbid RD and ADHD might represent an etiological subtype, providing tentative support for the three independent disorders model. The authors concluded that although most cases of RD or ADHD were not attributable to the same genetic influences, some cases of comorbid RD and ADHD might represent a separate disorder with a genetic etiology distinct from that associated with either diagnosis in isolation.

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

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

In summary, family and twin studies indicate that RD and ADHD are each familial and highly heritable. Bivariate twin analyses indicate that comorbidity between RD and ADHD is primarily due to common genetic influences, but suggest that these common genes are more strongly associated with inattention than hyperactivity–impulsivity. In Section IV.B.4 we review initial studies that have begun to search the genome to identify the specific genes that lead to the 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
reading-related language measures (e.g., Cardon et al., 1994, 1995; Gayan et al., 1999). In addition to these six replicated linkage regions, it is likely that ongoing linkage studies will identify additional loci in the future.

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

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

5. Linkage Studies of Comorbidity Between RD and ADHD

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

Thus, although several of these results await independent replication, existing data provide the strongest support for the hypothesis that comorbidity between RD and ADHD is due, at least, in part to a common genetic etiology.
Although the specific functions of the genes that lead to comorbidity between RD and ADHD are unknown, one plausible model suggests that these shared genetic risk factors may cause a developmental change in a single pathophysiological substrate, and that this change then increases risk for both RD and ADHD. In this model the final phenotypic expression of this common susceptibility is then influenced by other genetic and environmental risk factors. Therefore, in some individuals this common risk factor would be expressed as RD alone, some individuals would meet criteria for ADHD alone, and some would meet criteria for both RD and ADHD. An important step in validating this hypothesis is to identify a neuropsychological deficit or other pathophysiological marker that reflects the common genetic risk for RD and ADHD (Willcutt et al., in press a,b). Measures of this neurocognitive weakness may then facilitate future molecular genetic studies of RD, ADHD, and their comorbidity.

C. CONDUCT DISORDER AND ADHD

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

1. Phenotypic Tests

Many studies in the literature address whether the three independent disorders model (i.e., ADHD + CD is a third, independent disorder, or an etiological distinct subtype) explains the comorbidity between ADHD and CD. Although several researchers have noted the similarities between ADHD children with and without CD, including similarities in neurological “soft signs” and pre- and perinatal complications (e.g., August & Stewart, 1983), physical anomalies (e.g., August & Stewart, 1983; McGee, Williams, & Silva, 1984), and average intelligence (e.g., August & Stewart, 1983; Loney & Milich, 1982; McGee, Williams, & Silva, 1984), more researchers have noted the differences between ADHD children with and without CD and suggested that the two groups should be classified as two different types of ADHD. A similar idea is that CD with and without ADHD may constitute two different etiological types. In 1993, Moffitt presented her developmental taxonomy model of antisocial behavior, suggesting two categories of antisocial behavior that are distinct in etiology. The first category includes individuals who are antisocial at every stage of life (i.e., life-course-persistent), and the second category includes individuals who are antisocial only during adolescence (i.e., adolescence-limited). Moffitt noted that one of the risk characteristics in individuals with life-course-persistent antisocial behavior is hyperactivity.
Systematic reviews of studies examining ADHD only, CD only, and both ADHD and CD have reached differing conclusions. Lynam (1996) conducted a review of studies examining differences in children with hyperactivity–impulsivity–attention problems only, conduct problems only, and both hyperactivity–impulsivity, attention and conduct problems, and concluded that a “psychopathic deficit” is the underlying pathology for both kinds of symptoms in children with both sets of problems (comorbid children), but not in children with only one set of problems occurring alone. One of the main reasons for this conclusion was the finding that comorbid children have unique deficits (e.g., a distinct social information-processing pattern and qualitatively different errors on a continuous performance task) not found in children with problems only in hyperactivity–impulsivity–attention or conduct. In addition, some of these unique deficits (e.g., lowered autonomic reactivity) are also found in adult psychopathic individuals. Jensen, Martin, and Cantwell (1997) also conducted a systematic review of studies examining the differences among children with ADHD only, CD only, and ADHD + CD. Given several characteristics of children of ADHD + CD (e.g., earlier age of onset, greater male–female sex ratio, lower IQs, increased learning/reading difficulties), Jensen, Watanabe, Richters, Cortes, Roper, and Liu concluded that there is enough evidence for a new diagnostic entity or a sub-classification of ADHD: ADHD, aggressive type.

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

Other alternative accounts of the comorbidity between ADHD and CD have been proposed based on phenotypic data. A longitudinal study examining ADHD and CD symptoms (Taylor et al., 1996) reported that the outcome of the ADHD + CD group was similar to the ADHD only group and rejected the three independent disorders model. They also reported that childhood ADHD symptoms in the absence of CD symptoms predicted CD symptoms in adolescence, whereas childhood CD symptoms did not predict ADHD symptoms in adolescence. They concluded that ADHD symptoms are the major developmental risk factor and that
CD symptoms are epiphenomenal (i.e., support for the random multiformity of ADHD model).

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

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

2. Behavior Genetic Tests

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

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

Several multivariate behavior genetic studies using the twin method (Nadder et al., 1998, 2002; Scarborough & Dobrich, 1990; Silberg et al., 1996; Thapar, Harrington, & McGuffin, 2001; Waldman et al., 2001; Willcutt et al., 1995) examined whether comorbidity between ADHD and CD is due to shared genetic influences. All of these studies found a substantial overlap between the genetic
influences on ADHD and the genetic influences on CD (i.e., support for the correlated liabilities model).

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

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

3. Summary of Evidence Regarding Comorbidity of ADHD and CD

In conclusion, the existing evidence regarding the causes of comorbidity between ADHD and CD is not consistent. Reviews of studies evaluating the three independent disorders model by examining the correlates or underlying deficits in groups of children with ADHD + CD, ADHD only, and CD only have reached different conclusions, with Jensen, Martin and Cantwell (1997), Lynam (1996) supporting the three independent disorders model and Waschbusch (2002) and others concluding that there is little evidence for the three independent disorders model. Family studies examining the risk of ADHD and CD in relatives of probands with ADHD + CD, ADHD only, CD only, and controls conclude support for the three independent disorders model, but a simulation study (Rhee et al., 2003) suggests that the analyses used in theses studies are not valid tests of the three independent disorders model. Several studies have found support for other models for the comorbidity between ADHD and CD, including random
multiformity of ADHD, risk factors for one disorder increasing the probability of risk factors for another disorder (a model not discussed by Neale and Kendler), and the correlated liabilities model. Our recent study, which is the only study to examine a wide range of comorbidity models using the Neale and Kendler model fitting approach (which has been validated by a simulation study), suggests that correlated liabilities is a more likely cause of the comorbidity between ADHD and CD rather than Three Independent Disorders. Given the conflicting results in the literature, more studies examining the comorbidity between ADHD and CD using valid analytical approaches need to be conducted.

D. IMPLICATIONS FOR OTHER POSSIBLE PAIRS

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

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

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

Fig. 3. Pairwise comorbidities among four disorders. RD = reading disability; SSD = speech sound disorder; ADHD = attention deficit hyperactivity disorder; CD = conduct disorder.
and anxiety was epiphenomenal because it derived from the comorbidities between CD and depression, and depression and anxiety. So some of the many non-artifactual comorbidities observed among DSM-IV diagnoses are likely to be epiphenomenal and we can winnow them from the list of comorbidities requiring a deeper explanation.

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

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

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

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

V. Multifactorial Model

So what has research on these three comorbidities taught us about the development of disorders more generally? One lesson is that single etiology models of disorders do not seem to be adequate to account for either their
development or comorbidity. We have yet to find a behaviorally defined disorder with a single necessary and sufficient etiology. The emerging etiological model for such disorders is probabilistic and multifactorial. But the prevailing cognitive model has often been deterministic and focused on a single cognitive cause, such as the phonological deficit in RD. So there is a potential contradiction in our frameworks for understanding such disorders that needs to be resolved. Another lesson is that a frequently supported explanation for comorbidity is correlated liabilities, specifically shared genetic risk factors. A third lesson is some disorders may be developmental precursors of later disorders, although usually an additional risk factor determines whether a child with the precursor disorder develops the later disorders. In this final section, we present a model that incorporates these lessons and is probabilistic and multifactorial at all levels of analysis.

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

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

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

Applying the model to the three comorbidities reviewed here, each individual disorder (SSD, RD, ADHD, and CD) has its own profile of risk factors (both etiologic and cognitive), with some of these risk factors being shared by pairs of disorders, resulting in comorbidity.
Figure 4 illustrates this multifactorial model, which is also discussed in Pennington (in press). There are four levels of analysis in this diagram: etiologic, neural, cognitive, and symptom, where clusters of symptoms define complex behavioral disorders. For any such complex behavioral disorder, it is expected there will be more risk and protective factors than the five shown here. Bidirectional connections at each level indicate that constructs are not independent. For instance, at the etiologic level, there are likely to be gene–environment interactions and correlations. At the neural level, a single genetic or environmental risk factor will often affect more than one neural system (pleiotropy). Even if the risk factor initially only affects one neural system, this alteration will likely have downstream effects on the development of other neural systems. At the cognitive level, constructs are correlated because their developmental pathways overlap and because cognition is interactive. Overlap at the cognitive level leads to comorbidity at the symptom level. So, although a single deficit model conceptualizes the relation between disorders in terms of double dissociations, the multiple deficit model conceptualizes this relation in terms of partial overlap. At the symptom level, there is comorbidity (i.e., greater than chance co-occurrence) of complex behavioral disorders. Omitted from the diagram are the causal connections between levels of analyses, some of which would include feedback loops from behavior to brain or even to etiology. The existence and strength of these various causal connections must be determined empirically. The weights of the connections between levels of analysis will tell us to what extent different etiological and cognitive factors contribute to comorbidity at the symptom level.
It is also apparent that a similar but expanded model could be proposed for species-typical cognitive development, which results from the interaction of a largely shared genome (99.9% the same across unrelated humans) and species-typical environments. So in principle the same model could account for both typical and atypical development. Indeed, a complete account of any given developmental disorder will need to explain the many aspects of development that proceed typically as well as the few that go awry.

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

ACKNOWLEDGEMENTS


REFERENCES


Nadder, T. S., Rutter, M., Silberg, J. L., Maes, H. H., & Eaves, L. J. (2002). Genetic effects on the variation and covariation of attention deficit-hyperactivity disorder (ADHD) and oppositional-defiant disorder/conduct disorder (Odd/CD) symptomatologies across informant and occasion of measurement. Psychological Medicine, 32, 39–53.


Willcutt, E., Pennington, B., Chhabildas, N., Olson, R., & Hulslander, J. Neuropsychological analyses of comorbidity between RD and ADHD in search of the common deficit. Developmental Neuropsychology. in press.


Willcutt, E., Pennington, B., Olson, R., & DeFries, J. Understanding comorbidity: A twin study of reading disability and attention deficit/hyperactivity disorder. American Journal of Medical Genetics (Neuropsychiatric Genetics). in press.


Author Queries

JOB NUMBER: 9146
TITLE: Analyzing Comorbidity

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Q17 Kindly update Pennington (in press)

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

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

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

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

Q22 Kindly update Tunick et al. (in preparation)

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

Q24 Kindly update Willcut (in press).

Q25 Kindly provide complete authors detail for Willcut et al. (2001)

Q26 Kindly update Willcut et al. (in press).
Q27  Kindly update Willcutt et al. (in press).

Q28  Kindly provide complete authors detail for Willcutt et al. (2002)