Understanding the Comorbidity Between Dyslexia and Attention-Deficit/Hyperactivity Disorder

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Dyslexia and attention-deficit/hyperactivity disorder (ADHD) are 2 of the most prevalent complex neurodevelopmental disorders of childhood, each affecting approximately 5% of the population in the United States. These disorders are also each comorbid with speech sound disorder and language impairment. Understanding the nature of the comorbidity among these disorders could lead to advances in developmental theory, a deeper understanding of the genetic and brain mechanisms that cause disability, a more refined diagnostic classification scheme, and new treatments and interventions for children with these disorders. As part of this special issue of *Topics in Language Disorders*, this review focuses on the comorbidity between dyslexia and ADHD. It provides a review of the known etiological mechanisms that underlie each disorder. It describes the reconceptualization of these disorders using a multiple deficit model and provides a synopsis of recent studies that illustrate a cohesive approach to investigating the causes of comorbidity. Future directions are discussed in the context of expanding these approaches to the comorbidity among all 4 disorders. **Key words:** *ADHD*, *attention-deficit/hyperactivity disorder*, *comorbidity*, *dyslexia*, *genetics*, *reading disability*

THIS SPECIAL ISSUE of *Topics in Language Disorders* (Vol. 32[3]) is devoted to providing a better understanding of the factors that underlie the comorbidity between attention-deficit/hyperactivity disorder (ADHD) and various neurodevelopmental disorders of childhood, namely, speech sound disorder (SSD), specific language impairment (SLI), and dyslexia. This article focuses specifically on the comorbidity between dyslexia and attention-deficit/hyperactivity disorder (ADHD), two of the most prevalent complex neurobehavioral disorders in the United States, each affecting approximately 5% of children in the population (*DSM-IV-TR* [*Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition–Text Revision*], American Psychiatric Association [APA], 2000).

Although we acknowledge that some researchers and educational professionals may define reading disability to include children whose primary deficits are in reading comprehension, but that is not the focus of this article. We are using the definition of dyslexia adopted by the International Dyslexia Association and the National Institute of Child Health and Human Development in 2002, which characterizes dyslexia as difficulty with accurate and/or fluent word recognition

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and by poor spelling and decoding abilities. Although some may disagree, a more specific definition has definite advantages; it allows for greater homogeneity when selecting a group of children with the disorder, which, in turn, increases the probability of finding specific cognitive and genetic factors that influence that disorder.

The comorbidity between dyslexia and ADHD has been well established. Dyslexia and ADHD co-occur more frequently than expected by chance, with 25%–40% of children with one disorder meeting criteria for the other (August & Garfinkel, 1990; Semrud-Clikeman et al., 1992; Willcutt & Pennington, 2000b). Understanding the nature and causes of the comorbidity between dyslexia and ADHD has been a central focus of cognitive and developmental neuroscience research for some time. The rapid development of behavior genetic and, especially, molecular approaches (including gene-sequencing techniques) over the past few decades has accelerated the field's appreciation for the complexity of the relationship between these two disorders.

Although understanding the factors leading to the comorbidity between dyslexia and ADHD is an important goal in its own right, it is important to place this relationship in a wider context. As highlighted in the introductory article of this special issue of *Topics in Language Disorders*, one important reason to explore the relationship between dyslexia and ADHD is the significant overlap that already has been established between dyslexia, SSD, and SLI. If dyslexia, SSD, and SLI share common underlying etiologies, either at the cognitive or genetic level, and if dyslexia and ADHD share a similar relationship, then there is a theoretical possibility that ADHD also may contribute to the manifestation of SSD and SLI. For basic neuroscience and clinical researchers alike, shedding light on how and why these four disorders (ADHD, SSD, SLI, and dyslexia) overlap within individuals is an overarching and exciting goal.

Various factors contribute to the complexity of studying the relation between dyslexia and ADHD. First, both disorders are behaviorally defined, and there is variability in how these definitions are operationalized. Second, the disorders can manifest maximally at different ages, which often requires a longitudinal approach to investigate their relations. Third, there is a developmental course for each disorder, which causes the nature and severity of the behavioral symptoms to change gradually over time. The changes that occur over the course of development require a careful approach to the selection of measures used to characterize each disorder at different ages so that appropriate sensitivity and specificity is maintained.

It should be noted that these factors apply more broadly as well, complicating the task of investigating the relations among SSD, SLI, dyslexia, and ADHD. Despite these challenges, recent research designs have allowed for exploration of the relationships among various combinations of these disorders at both the phenotypic (i.e., behavioral and cognitive manifestations) and genetic (i.e., molecular) levels of analysis. These studies have led to important theoretical shifts in how these disorders are conceptualized and what their overlap might tell us about the nature of typical and atypical development.

In keeping with the overall goals of this special issue, this article is divided into five parts. The first section defines dyslexia and ADHD at the symptom level and discusses some of the ramifications of having each of these disorders. The second section provides an overview of the cognitive and genetic factors involved in each disorder. The third section briefly describes the utility of studying comorbidity. The fourth section describes some of the approaches used to understand the comorbidity between dyslexia and ADHD, as well as some recent findings. The article ends with a section discussing potential future directions, in light of the additional comorbidities of these two disorders with SSD and SLI.

Definitions

Dyslexia is a learning disability that is of neurobiological origin. Individuals with

dyslexia have difficulties with accurate and/or fluent word recognition and spelling, despite adequate instruction and intelligence and intact sensory abilities (Lyon, Shaywitz, & Shaywitz, 2003). These difficulties typically result from a deficit in the phonological component of language and it is often unexpected in relation to other cognitive abilities. Secondary consequences may include problems in reading comprehension and reduced reading experience that can impede growth of vocabulary and background knowledge.

Research suggests that dyslexia represents the lower end of a normal distribution of word reading ability; as such, diagnosing someone with dyslexia requires setting a somewhat arbitrary cutoff on a continuous variable. A typical cutoff of -1.5 standard deviations below the mean for age on a single word decoding test identifies approximately 7% of the population as having dyslexia. There is a slight male predominance in population samples (1.5–3:1), with the gender difference being larger in referred samples (3–6:1) (Rutter, Caspi, Fergusson, Horwood, & Goodman, 2004; Smith et al., 2001). This difference between population and referred samples may be due to the fact that boys come to clinical attention more often than girls, often because they have higher rates of comorbid externalizing disorders, including ADHD (Willcutt & Pennington, 2000a). Although some children may learn to read after intensive remediation, the disorder is lifelong, with reading fluency problems having substantial effects on educational achievement and vocation.

Attention-deficit/hyperactivity disorder has undergone various changes in definition over the years, but in the current edition of the *DSM-IV* (APA, 1994) it is characterized as maladaptive levels of inattention (predominantly inattentive type), hyperactivity-impulsivity (predominantly hyperactive–impulsive type), or both inattention and hyperactivity–impulsivity (combined type). Children must meet criteria for at least six of nine symptoms within each type to qualify for that diagnosis. Children also must have symptoms of the disorder before age 7 and in at least

two settings. Symptom ratings are often obtained from both parents and teachers in the form of questionnaires, with most of these using the *DSM-IV* or *DSM-IV*-like criteria. Similar to dyslexia, there is a male predominance in reported ADHD symptoms, with a gender ratio of approximately 1.7–3:1 reported in a recent Norwegian study (Ullebo, Posserud, Heiervang, Obel, & Gillberg, 2011). This estimate was based on parent report. This is consistent with a population-based study conducted in Missouri, USA, where the gender ratio was 2.28:1 (Ramtekkar, Reiersen, Todorov, & Todd, 2010). Interestingly, the gender ratio based on teacher ratings in the Norwegian study was higher, with estimates as high as 6.2: 1 (male to female) for the combined subtype.

Ramifications and associated outcomes of dyslexia and ADHD

Specific costs in terms of broader outcomes have also been documented for dyslexia and ADHD. Each is associated with academic, social, and occupational impairment and higher risk for a range of important emotional, behavioral, and psychosocial difficulties (Boetsch, Green, & Pennington, 1996; Daniel et al., 2006; Goldston et al., 2007). These, in turn, lead to significant public health costs (Schnoes, Reid, Wagner, & Marder, 2006).

In addition to the difficulties across domains associated with dyslexia or ADHD individually, various studies have found that comorbidity is often a marker for a more severe manifestation of a disorder. For example, in comparison to children with ADHD or dyslexia alone, children with comorbid dyslexia and ADHD exhibit a more extensive and severe profile of neuropsychological weaknesses and have a stronger genetic loading for both dyslexia and ADHD (Willcutt, 2009; Willcutt et al., 2007b). What is particularly striking is the significant interaction between dyslexia and ADHD that is found in terms of functional impairment. As can be seen in Figure 1, children who meet criteria for both dyslexia and ADHD are at
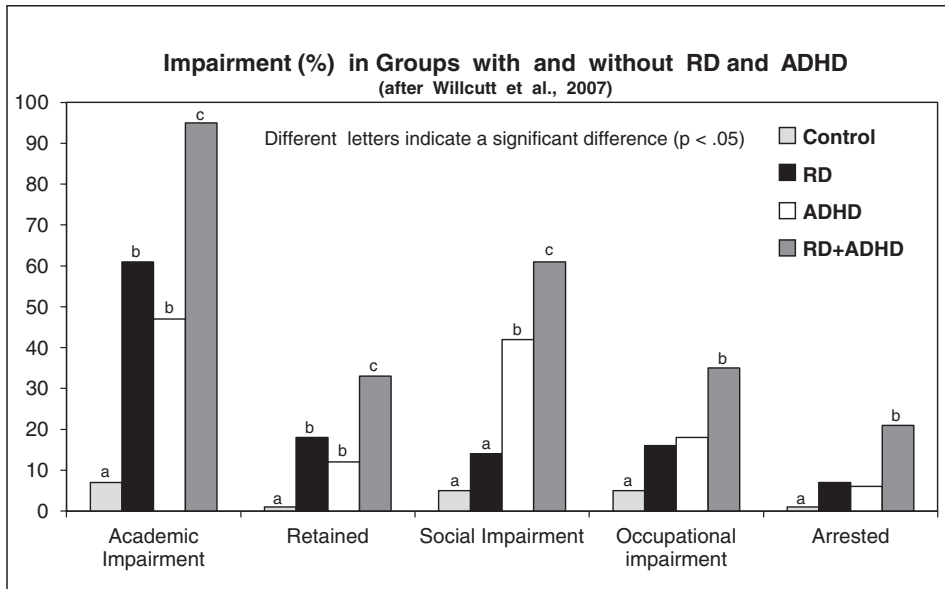
Impairment (%) in Groups with and without RD and ADHD
(after Willcutt et al., 2007)

Different letters indicate a significant difference (p < .05)

Figure 1. Impairment (%) in groups with and without dyslexia and ADHD. Information from Willcutt et al. (2007).

significantly higher risk of being retained in school, and of having academic and social impairment, compared with children with either condition in isolation. Children with dyslexia and ADHD also exhibit significantly higher rates of legal difficulties and occupational impairment than controls (Willcutt et al., 2007b). In addition to the scientific advancement in understanding the comorbidity between these two disorders, there are significant clinical implications for doing so. High rates of comorbidity complicate clinical assessment, diagnosis, and treatment planning, and may compromise interpretation of research studies. Clarifying the etiology of each specific weakness and their covariance can help to improve classification models and may eventually facilitate more accurate diagnoses and improved methods for early detection and prevention.

ETIOLOGICAL MECHANISMS IMPLICATED IN DYSLEXIA AND ADHD

Investigating the factors that may influence comorbidity between dyslexia and ADHD requires an understanding of the etiological and cognitive mechanisms involved in the manifestation of each disorder separately. Over the past few decades, an extensive literature on reading acquisition and dyslexia has emerged, with a well-elaborated story unfolding by integrating findings across multiple levels of analysis. Attention-deficit/hyperactivity disorder has also been the focus of intense investigation, with numerous researchers attempting to identify the genetic and environmental etiologies, as well as cognitive endophenotypes, contributing to the ADHD symptoms. An extensive review of these two disorders is beyond what can be summarized in this article, but a brief synopsis of each disorder is provided below, as a foundation for the discussion regarding the etiology of their comorbidity.

Dyslexia

Genetics

Like all behaviorally defined disorders, the cause of dyslexia is multifactorial and is associated with multiple genes and environmental risk factors. Dyslexia is familial and moderately heritable (Pennington & Olson,

2005). It has been linked to nine risk loci (DYX1–DYX9) through replicated linkage studies, (Fisher & DeFries, 2002; McGrath, Smith, & Pennington, 2006), although not every study has replicated these results (Ludwig et al., 2008; Meaburn, Harlaar, Craig, Schalkwyk, & Plomin, 2008). Genetic methods have more recently identified 6 candidate genes (DYX1C1 in the DYX1 locus on chromosome 15q21; DCDC2 and KIAA0319 in the DYX2 locus on chromosome 6p21; C2Orf3 and MRPL19 in the DYX3 locus on chromosome 2p16–p15; and ROBO1 in the DYX5 locus on chromosome 3p12–q12). The role of these genes in brain development also has been under investigation (Kere, 2011). Work in animals has shown that DYX1C1, DCDC2, KIAA0319, and ROBO1 affect neuronal migration and axon guidance and coregulate each other. Very little is known about the functions of the two DYX3 candidate genes.

Neural substrates

Reading is a linguistic skill, and as such, it should involve brain structures used in oral language; additional brain areas that subserve visual-object processing also should be involved, as well as association cortex that maps the relationship between these two domains. Many investigations using structural and functional neuroimaging have been performed in individuals with dyslexia, with a certain amount of convergence obtained in the results. Functional imaging studies have shown aberrant activation patterns in a dominant (usually left) hemisphere distributed language network (Demonet, Taylor, & Chaix, 2004; Shaywitz & Shaywitz, 2005). Two posterior left hemisphere regions have shown consistent underactivation: a temporoparietal region believed to be critical for phonological processing and phoneme–grapheme conversion, and an occipitotemporal region, which is thought to participate in whole word recognition. In addition, abnormal activation has also been shown in left inferior frontal gyrus, although this is sometimes seen as overactivation rather than underactivation. These findings have been confirmed in a recent quantitative meta-analysis of imaging studies, where potential confounds, such as the similarity of in-scanner reading tasks, were taken into account (Richlan, Kronbichler, & Wimmer, 2009). It should be noted that, in these types of studies, it is not always clear whether the differences in activation between groups reflect deviancy versus delay. Researchers describe their findings using terms such as "aberrant," but due to the lack of longitudinal studies following both dyslexic and nondyslexic children, it is difficult to know whether the patterns observed at one time point are actually deviant, or just a reflection of immaturity.

Whether abnormal activation patterns are a cause or a correlate of reading difficulty, or potentially arise from reading inexperience, also has been a source of debate. Findings from studies that have used reading age comparison groups to control for reading experience generally support the view that brain changes are associated with dyslexia from an early age. Specifically, results show abnormal activation in people with dyslexia, with underactivation in left temporoparietal regions relative to both chronological-age and reading-age controls (Hoeft et al., 2006, 2007). Although the purpose of using a reading-age-matched comparison group is to rule out the confound of reading experience as a source of the difference between groups, it does not rule out other potential confounds. A younger reading-age-matched group will have the same reading level, by definition, but will likely differ from the dyslexic group on other language-related variables (e.g., vocabulary level, syntactical processing ability, working memory). Thus, differences in activation during functional imaging tasks may actually reflect, in part, the influence of these other factors, even if the task is specifically a reading task.

Family risk studies also have been used to disambiguate the direction of effect. Studies that have compared young children at risk for dyslexia with those not at risk have found activation abnormalities as well, in this case affecting a wider set of bilateral cortical and subcortical regions. These younger at-risk children do not always show consistent activation

patterns; rather, frontotemporal sites have been noted to be overactivated bilaterally, whereas left frontal gyri have shown underactivation. One hypothesis for the bilateral overactivation findings is that at-risk children in the early stages of reading acquisition may need to recruit homologous areas in the nondominant hemisphere in a compensatory manner (Bach et al., 2010; Specht et al., 2009). Overall, there is evidence of less specialized left hemisphere function for reading and phonological tasks in young children at risk for dyslexia compared to children who develop reading normally.

In addition to functional neuroimaging, other physiological methods have been used to investigate whether brain differences are a cause of dyslexia. For example, infants at family risk for dyslexia have shown abnormal event-related potentials in response to speech sounds from as early as the first month of life (Guttorm, Leppanen, Tolvanen, & Lyytinen, 2003). These aberrant neural responses predict language and dyslexia risk over several years (Been et al., 2008; Molfese, 2000). Even though one has to acknowledge that there are inconsistent findings across studies, and that reading experience also changes brain structure and function (i.e., effects are bidirectional), there is significant converging evidence at this point that temporoparietal abnormalities are more likely a cause than a result of reading failure.

Not all activation abnormalities or differences may be causal, however, especially in young children. An example of this may be the visual-word form area in the occipitotemporal region, where some researchers have hypothesized that underactivation differences in children may be driven by reduced exposure to print (van der Mark et al., 2009). This finding highlights the complex and interactive nature of the neural networks involved in reading acquisition; patterns of activation are likely to change because of endogenous and environmental factors and are likely to be dynamic in the context of development and intervention.

Structural imaging studies predate functional studies, but recent advances in imaging techniques have allowed for more refined investigations of the structural connectivity among brain regions. There has been a greater impetus for this approach from the hypotheses generated from functional studies, as they point to both posterior and anterior language networks being affected. This supports the possibility that dyslexia may be characterized as a disconnection syndrome. In addition, as noted previously, various candidate genes that are currently under investigation in dyslexia are known to be involved in neuronal migration and axon guidance, which offers at least some face validity that abnormal connectivity among critical regions may partly underlie the deficits seen in dyslexia.

Recent research exploring the white matter correlates of dyslexia using diffusion tensor imaging have specifically focused on local white matter changes (as indexed by fractional anisotropy) in children and adults with dyslexia in left temporoparietal regions and in the left inferior frontal gyrus (Carter et al., 2009; Dougherty et al., 2007; Nagy, Westerberg, & Klingberg, 2004; Odegard, Farris, Ring, McColl, & Black, 2009; Qiu, Tan, Zhou, & Khong, 2008; Richlan et al., 2009; Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010; Steinbrink et al., 2008). For example, work by Silani et al. (2005), which included both structural and functional imaging on the same cohort, has shown decreases in grey matter density in people with dyslexia that correspond to the key area of functional underactivation in the left medial temporal gyrus. Consistent with other studies using diffusion tensor imaging, findings also include white matter decreases in the left frontal and parietal portions of the arcuate fasciculus and other left hemisphere sites. Even structural differences in brain across reading groups are open to the criticism that they may be secondary to differences in reading experience. To counter this potential argument, a recent family risk study found decreased grey matter density in left hemisphere regions (e.g.,

temporoparietal, lingual gyrus, and occipi-totemporal areas) in at-risk children before the onset of reading instruction (Raschle, Chang, & Gaab, 2011).

Neuropsychological factors

For many years, a single-deficit phonological theory of dyslexia was most prominent; however, mounting evidence shows that, although phonological deficits are standard in individuals with dyslexia, a single phonological deficit is probably not sufficient to cause the disorder. Phonological deficits have been operationalized slightly differently across studies of dyslexia. They originally were indexed by problems in phonemic awareness, but more recently, there have been studies that have used speech perception and implicit tasks to show differences in individuals with dyslexia with regard to the nature of their underlying phonological representations (e.g., Boada & Pennington, 2006).

The accumulation of several findings across studies has led to the shift away from the single-deficit phonological theory of dyslexia. Some of the more compelling arguments include the following: (a) the fact that a substantial proportion of children with a history of SSD develop normal literacy despite persistent deficits in phonological awareness; (b) the finding that a subgroup of children with SLI and concomitant phonological awareness deficits do not become dyslexic, whereas a similarly affected group who have additional rapid serial naming deficits do become dyslexic; and (c) the effect sizes for cognitive risk factors such as phonological impairment are generally too small to independently account for all cases of the disorder. In a recent individual prediction study using a multiple deficit model approach, Pennington et al. (2011) showed that less than half of the children with dyslexia could be categorized as having a primary deficit in phonological awareness.

Pennington (2006) provided a comprehensive summary of the arguments against single-deficit models for complex disorders. Rather than attempting to identify a single necessary and sufficient cause that is specific to each disorder, Pennington proposed a multiple deficit model for complex disorders like dyslexia, hypothesizing that such complex disorders are heterogeneous conditions that arise from the additive and interactive effects of multiple genetic and environmental risk factors, which then lead to weaknesses in multiple cognitive domains. In keeping with such a multiple deficit model account, several other language and cognitive processing factors have been associated with the expression and/or severity of the dyslexia phenotype. The best studied of these include verbal working memory, semantic and syntactic linguistic skills, and rapid serial naming/processing speed (Peterson, Pennington, Shriberg, & Boada, 2009). However, how these deficits relate to the phonemic awareness deficits often seen in dyslexia can theoretically vary. These cognitive processes and skills are correlated, and the correlation may be due to the fact that they tap the same phonological architecture. However, these skills also appear to have independent components that are not shared with phonology, and these may interact or independently contribute to the dyslexia phenotype.

Specifically, there are various theoretical possibilities in how these deficits may influence the dyslexia phenotype: the additional deficits could be largely independent of a phonemic awareness problem, with several deficits needed to cause the full clinical phenotype (Pennington, 2006); there could be subtypes of dyslexia, each with a different primary deficit (Bosse, Tainturier, & Valdois, 2007; Hadzibeganovic et al., 2010); the phonological representation deficit could arise from a sensory or more general learning problem (Buchholz & Davies, 2007; Nicolson & Fawcett, 2007); or the phonological deficit might be the primary cause of the reading difficulty, but the other deficits are associated for other reasons (Ramus, 2004).

The fact that linguistic deficits precede the onset of formal reading instruction and predict later reading failure is consistent with a causal account. The universality of these findings, including deficits in semantics,

syntax, phonological processing, phonological memory, and rapid serial naming across countries and languages, supports this argument. Whether or not these linguistic deficits can be reduced to lower level speech or auditory perception deficits also has been the focus of intense research. Speech perception studies, in particular, have focused on identifying deficits related to recovery of phonetic information from the speech stream. Various results suggest that children with dyslexia have trouble in this regard. For example, they have difficulties with the use of an amplitude envelope to recover spoken words and with the integration of various cues in word perception (Johnson, Pennington, Lowenstein, & Nittrouer, 2011; Nittrouer & Lowenstein, in press). They also have relative difficulty in voice identification, where allophonic variations have to be used as cues. Whether or not these deficits stem from lower level sensory/temporal deficits, as has been suggested in auditory rise time experiments (e.g., Goswami, 2011), is still being debated.

The issue of rapid serial naming (i.e., rapid automatized naming, RAN) deserves special mention for the purposes of this review, as it has emerged as a potential cognitive candidate in explaining comorbidity. Rapid serial naming has long been hypothesized to be a risk factor for reading failure independent of phonological awareness (Krasowicz-Kupis, Borkowska, & Pietras, 2009; Papadopoulos, Georgiou, & Kendeou, 2009; Wolf & Bowers, 1999). Debate remains about how distinct rapid serial naming is from other aspects of phonological processing (Vaessen, Gerretsen, & Blomert, 2009). Although rapid serial naming tasks certainly require lexical phonology, they also correlate strongly with nonverbal measures of processing speed, which in turn predict reading fluency (McGrath et al., 2011; Shanahan et al., 2006).

One aspect that has made studying the contribution of these various risk factors difficult is that the power of individual predictors likely varies with developmental stage (Pennington & Lefly, 2001; Puolakanaho et al., 2008; Scarborough, 1990; Snowling, Gal-

lagher, & Frith, 2003; Torppa, Lyytinen, Erskine, Eklund, & Lyytinen, 2010). Verbal short-term memory and phonological processing factors seem to act more strongly earlier in development, and may indeed be endophenotypes, as individuals from families at high risk of dyslexia but who do not develop the disorder still manifest relative deficits. Rapid serial naming deficits may be more specific to dyslexia proper; better performance in this domain may act as a protective factor in those with SSD or SLI who do not develop dyslexia. Longitudinal studies with multiple time points are essential to decompose the relative contributions of risk factors mentioned previously, and how these might change across time.

Attention-Deficit/Hyperactivity Disorder

Genetics

Similar to dyslexia, previous studies have demonstrated that ADHD is familial and significantly heritable. Its heritability has been established primarily using twin studies, which take advantage of the fact that monozygotic (MZ) twins share all their genes, while dizygotic (DZ) twins share half of their segregating genes on average. By comparing the similarity of MZ and DZ twin pairs, twin studies provide an estimate of the extent to which a disorder is due to genetic or environmental influences. As mentioned in the previous section, individual differences in reading and extreme scores (e.g., as in dyslexia) are both moderately heritable, with estimates in the 0.5–0.7 range. The two main symptom dimensions of ADHD (i.e., inattention and hyperactivity/impulsivity) are also significantly heritable, with genetic influences accounting for upwards of 75% of the variance in most cases. Most of the rest of the phenotypic variance (20%–30%) in ADHD is accounted for by nonshared environmental influences and measurement error. Figure 2 provides a summary of published twin studies of reading, and the two *DSM-IV-TR* (APA, 2004) ADHD symptom dimensions.

Molecular genetic studies of ADHD have used candidate gene approaches as well as linkage and association analyses to identify

possible genes affecting the disorder. The candidate gene approach initially targeted genes that affected the dopamine pathway, because of the mechanism of action of psychostimulant medication. Hundreds of association studies have been conducted to date, mostly testing polymorphisms in functional genes affecting dopaminergic and seratonergic pathways. Although positive findings have emerged, these have been difficult to replicate. A meta-analysis by Gizer, Ficks, & Wald-man. (2009) identified 7 genes as significant risk factors for ADHD, but each has a small effect size and their cumulative effect only accounts for a small percentage of the genetic variance in the disorder. Because of methodological differences and nonoverlapping selection of single nucleotide polymorphisms (SNPs), the authors acknowledge that some more recent, yet intriguing, findings were not included in the meta-analysis and deserve further study.
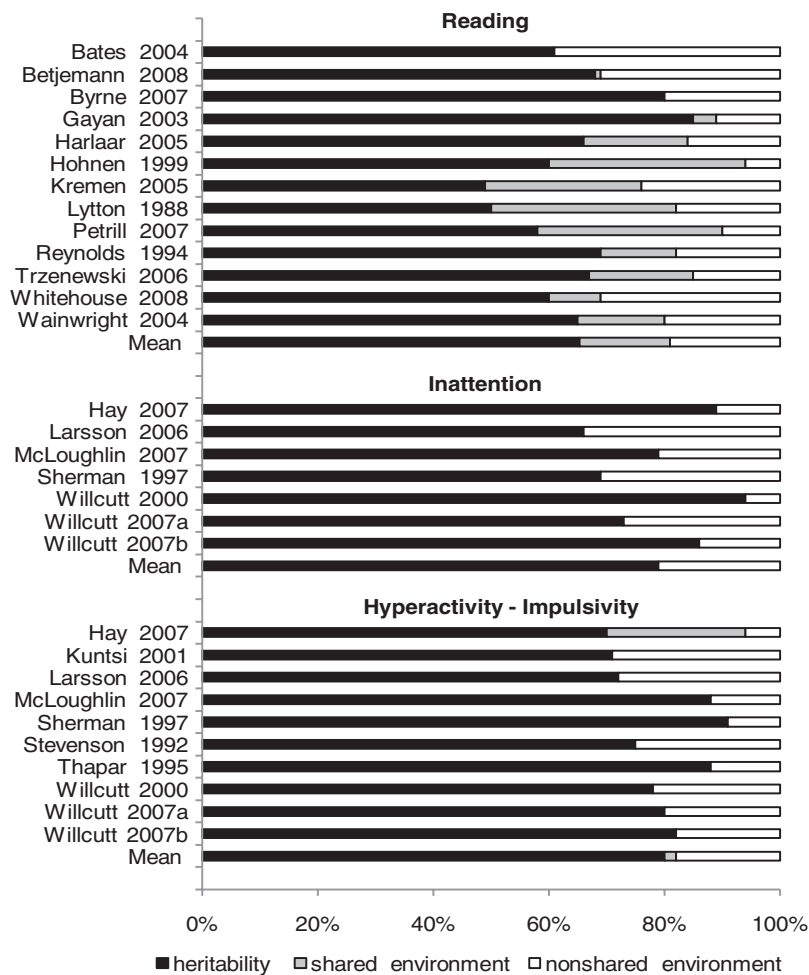

Figure 2. Heritability, shared environment, and non-shared environment estimates for reading, inattention and hyperactivity–Impulsivity symptom dimensions based on twin studies. (From "Etiology and Neuropsychology of Comorbidity Between RD and ADHD: The Case for Multiple-Deficit Models," by E. G. Willcutt, R. S. Betjemann, L. M. McGrath, N. A. Chhabildas, R. K. Olson, J. C. DeFries, et al, 2010, *Cortex, 46*(10), pp. 1345–1361.

Because of the limited amount of variance explained by functionally selected candidate genes, researchers have also conducted genome-wide linkage and association analyses. Some linkage regions with small effect sizes have been identified on chromosomes 5, 6, 10, 12, and 16 (Fisher et al., 2002; Willcutt et al., 2003). Recent genome-wide association studies (GWAS) also have identified susceptibility loci on chromosome 16 and nine other regions, none of which overlapped with the genes identified in the meta-analysis by Gizer et al. (2009). Even when taking all of these findings in aggregate, however, the fact remains that most of the genetic variance in ADHD symptomatology remains unexplained. The conflicting nature of the findings thus far does highlight the complex relationship between genetic factors, brain function, and a heterogeneous ADHD phenotype. It also supports the multifactorial polygenic hypothesis, with multiple genes with small effect sizes, interacting with each other and with environmental risk factors, leading to the manifestation of the disorder.

Neural substrates

As in dyslexia, there have been numerous structural and functional neuroimaging studies in ADHD. Consistency of findings across these studies has not been as robust as in studies of reading, however, likely due to the fact that the reading phenotype is more tightly defined (at least at the single word level) than the ADHD phenotype. The latter's heterogeneity at the behavioral level, in addition to its comorbidity with a number of other learning and psychiatric disorders, can introduce extra sources of variance that affect neuroimaging findings. The attentional network's involvement across multiple sensory modalities, levels of cognitive processing and response selection and execution, likely contributes to the broader set of brain regions identified in functional neuroimaging studies.

Some structural brain abnormalities that have been reported in ADHD include global differences, such as smaller total brain volumes and cerebellar hemispheres, as well as more localized volumetric differences in right frontal lobe, right caudate nucleus, and the cerebellar vermis (Castellanos & Tannock, 2002; Mackie et al., 2007; Valera, Faraone, Murray, & Seidman, 2007). Functional imaging studies using SPECT and PET techniques have revealed differences in the frontal lobe and basal ganglia regions of individuals with ADHD (Ernst, Kimes, & Jazbec, 2003). As documented by Germano, Gagliano, and Curatolo (2010), studies using fMRI have grown exponentially in this population and have shown decreased functioning in dorsolateral prefrontal cortex and dorsal anterior cingulate cortex on tasks requiring inhibitory control (Bush et al., 2008; Rubia et al., 1999; Tamm, Menon, Ringel, & Reiss, 2004; Zang et al., 2005), and activation in the right inferior prefrontal cortex, in the precuneus, and in the posterior cingulated cortex on inhibitory-type tasks (Rubia, Smith, Brammer, Toone, & Taylor, 2005).

Recent studies have partitioned different aspects of attentional control (i.e., sustained attention vs. transient, response-dependent attention) and components that are involved in response selection versus response execution, finding differences in ADHD participants. Results from Banich et al. (2009) suggest that neural dysfunction in ADHD with regard to sustained attentional control occurs across a distributed network, including dorsolateral prefrontal cortex, anterior cingulate, posterior parietal cortex, and right inferior frontal cortex. More transient or response-related attentional processing difficulties were seen in ADHD as well, particularly involving anterior cingulate and right inferior frontal regions.

Conceptualizing ADHD as the manifestation of a disrupted network has been supported by newer studies looking at resting state functional connectivity (i.e., default network). The latter involves coordinated high amplitude/low frequency neural activity (as seen on EEG) across brain regions, which is present in the absence of stimulus-driven cognitive tasks but is suppressed during more purposeful behavior. Sonuga-Barke and

Castellanos (2007) suggest that ADHD could be considered a default network disorder, in which the neural network is not adequately suppressed or regulated by other neural systems. This lack of regulation leads to disruption of ongoing cognition and behavior, much like what is seen in periodic lapses in on-task performance in ADHD. Castellanos and Proal (2012) reports studies where decreased default network coherence and decreased suppression were related to intraindividual variability in children with ADHD.

Neuropsychological factors

A large body of research suggests that the neuropsychology of ADHD is quite complex. Space limitations preclude a comprehensive review of this literature here (see Mueller & Tomblin (2012) for an overview). Briefly, studies have reported that individuals with ADHD perform worse than those without ADHD on a variety of measures, with the most consistent group differences seen on measures of processing speed, response variability, and executive functions such as working memory, response inhibition, and planning (see reviews by Barkley, 1997; Nigg, 2001). Meta-analyses indicate that each of these weaknesses has a small to medium effect size, and none is necessary or sufficient to cause ADHD in isolation. These data suggest that a single core deficit in ADHD is unlikely to be found, and that like dyslexia, ADHD is best described by a multiple-deficit neuropsychological model (Pennington, 2006; Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008).

THE UTILITY OF STUDYING COMORBIDITY

Comorbidity simply means the co-occurrence in a single patient of two or more diagnoses (Feinstein, 1970). As explained in the study by Pennington, Willcutt, and Rhee (2005), the utility of diagnostic constructs depends, in part, on their providing a unifying explanation of the various signs and symptoms presented by a patient. When comorbidity occurs, it poses a special problem for diagnostic constructs. Are the disorders just different manifestations of the same underlying disease process? If so, then one diagnostic construct will suffice. Understanding why comorbidity occurs requires an understanding of the etiological and pathogenetic mechanisms that underlie sets of symptoms. As this occurs, diagnostic boundaries can sometimes be redrawn. Thus, comorbidity provides an opportunity for diagnosticians and theorists alike, as it forces us to move from descriptive to more explanatory diagnostic constructs. This is a particular long-term goal for scientists studying psychiatric and behavioral (including cognitive) syndromes, as these have traditionally been defined in more descriptive terms.

Pennington et al. (2005) outlined various specific reasons why comorbidity is important for both research and clinical practice: (a) the presence of a comorbid disorder may influence the course and treatment of another disorder; (b) if comorbidity is ignored, one may erroneously conclude that some variable is associated with a given disorder when in fact it is associated with the comorbid condition; (c) unexplained comorbidity is a threat to the validity of diagnostic constructs, potentially requiring them to be redefined; and (d) the process of explaining comorbidity can lead to discoveries regarding the underlying mechanisms and developmental trajectories of disorders, which may, in turn, lead to novel diagnostic and treatment approaches.

Comorbidity is clearly the rule rather than the exception for *DSM-IV* disorders in childhood and across the lifespan. For example, 70%–90% of individuals diagnosed with ADHD according to the *DSM-IV-TR* meet criteria for at least one comorbid diagnosis (Faraone, Biederman, Weber, & Russell, 1998; Willcutt, Pennington, Chhabildas, Friedman, & Alexander, 1999). In addition to reading and math learning disabilities, ADHD is also often comorbid with oppositional defiant disorder, conduct disorder, anxiety, depression, Tourette's syndrome, and bipolar disorder. Thus, neuropsychological and genetic models of disorders must account not only for the

emergence of a particular disorder but also for the high rates of comorbidity with other disorders.

Attention-deficit/hyperactivity disorder and dyslexia are comorbid at greater rates than would be predicted by each of their prevalence rates in the general population. Although dyslexia and ADHD each occur in approximately 5% of children in the population, 25%–40% of children with either dyslexia or ADHD also meet criteria for the other disorder (e.g. August & Garfinkel, 1990; Semrud-Clikeman et al., 1992; Willcutt & Pennington, 2000a). Artifactual reasons for comorbidity between these two disorders, such as might occur due to ascertainment or rater bias or shared method variance, generally have not been supported (e.g., Willcutt & Pennington, 2000a; Willcutt et al. 2008). This has led researchers to focus on investigating the etiological and neuropsychological factors that underlie the association between dyslexia and ADHD. In the next section, we describe some of the methods that have been used to do this type of research, and some recent findings.

APPROACHES AND RECENT FINDINGS OF STUDIES INVESTIGATING THE COMORBIDITY BETWEEN DYSLEXIA AND ADHD

A number of methods have proven useful in the study of comorbidity. Following a more traditional medical genetic investigative approach, family studies were initially conducted to show whether common familial risk factors increased risk for both disorders. If this was the case, family members of probands with one disorder (e.g., dyslexia) would be expected to meet criteria for the other disorder (e.g., ADHD) at higher rates than in the general population. In a large sample described in Willcutt et al. (2010), family members of probands with dyslexia or ADHD alone were two to three times more likely to meet criteria for the other disorder compared with probands without either disorder. But just showing that there is common familial risk is not enough to know whether the etiology

of the comorbidity is genetic or environmental because family members share both genes and a common environment.

Etiologically sensitive designs, such as twin studies, have proven invaluable in disambiguating genetic and environmental factors that contribute to the phenotypic correlation between two disorders. By taking advantage of the differential genetic similarity between MZ and DZ twin pairs, quantitative methods have been devised to compute estimates of the degree to which a phenotypic correlation is due to genetic influences (heritability) or environmental factors (e.g., shared or non-shared environment). A thorough explanation of these quantitative behavior genetic methods is beyond the scope of this article, but a thorough account is found in articles by DeFries (1985, 1988) and Neale, Neale, and Sullivan. (2002).

These behavioral genetic methods were first applied using measures of each of the disorders at the symptom level, and results revealed that common genetic influences accounted for most of the phenotypic covariance between reading difficulties and inattention, whereas common genetic influences were lower for reading and hyperactivity/impulsivity (Willcutt et al., 2007a; Willcutt, Pennington, & DeFries, 2000b; Willcutt, Pennington, Olson, & DeFries, 2007b). In addition to these shared genetic influences, individual differences in all three measures were attributable to independent genetic and environmental influences.

As mentioned in the previous section, moving from a descriptive to a more explanatory level requires understanding the underpinnings of a disorder at multiple levels of analysis. The initial twin studies mentioned earlier, although they began to parse genetic and environmental contributions to the comorbidity between dyslexia and ADHD, were doing so using symptom-level variables. The latter are not always the most useful or accurate way of describing a disorder, especially because symptoms are often overdetermined (i.e., they can have multiple causes or components). Thus, the process of investigating

comorbidity also required a parallel advancement in the neuropsychological and brain models of these disorders. As described in the second section (Etiological mechanisms implicated in dyslexia and ADHD), single-deficit cognitive models of dyslexia or ADHD have not held up to scrutiny, partly because they cannot account for the observed level of comorbidity. The transition to multiple deficit models of these disorders at a neuropsychological level, on the contrary, provides a plausible mechanism by which we can get partial overlap of symptoms (i.e., by positing that the disorders have some shared and some unique contributing risk factors).

Building on the studies that had explored the multiple deficit model hypothesis for each disorder, Willcutt et al. (2010) tested children, using a 2x2 design (RD, ADHD, RD+ADHD, controls) to assess the degree of impairment across 6 cognitive phenotypes: response inhibition, processing speed, naming speed, phoneme awareness, verbal reasoning, and working memory. This design allows the researcher to test not only main effects of RD and ADHD but also their interaction, the latter providing information about the relative severity of the comorbid group across the various cognitive domains. Figure 3 summarizes the findings.

Significant deficits were noted for the RD-only and ADHD-only groups, each compared to the control group, across all 6 neuropsychological phenotypes. Both groups with RD were more impaired than the group with ADHD alone on measures of phoneme awareness, verbal reasoning, working memory, and naming speed. Finally, the comorbid group was more impaired than either disorder in isolation on measures of response inhibition and processing speed. Follow-up multiple logistic regression analyses, performed on RD and ADHD separately, showed that RD was independently predicted by lower scores on all cognitive composites except response inhibition. In contrast, overall ADHD status was predicted by response inhibition and processing speed only. Results were similar when the inattentive and combined ADHD subtypes
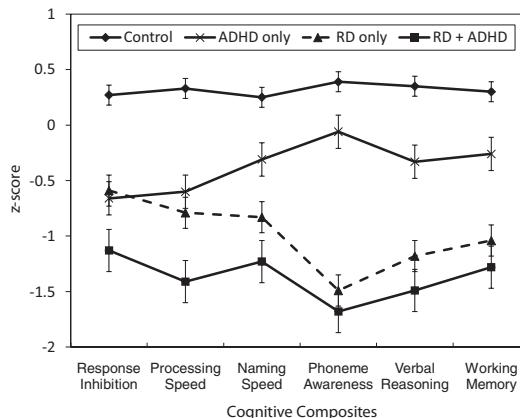

Figure 3. Performance of groups with and without dyslexia and ADHD on six composite cognitive phenotypes. From "Etiology and Neuropsychology of Comorbidity Between RD and ADHD: The Case for Multiple-Deficit Models," by E. G. Willcutt, R. S. Betjemann, L. M. McGrath, N. A. Chhabildas, R. K. Olson, J. C. DeFries, et al, 2010, *Cortex, 46*(10), pp. 1345–1361.

were analyzed separately. Overall, the findings using this approach suggested that processing speed was the most promising candidate for being a shared cognitive weakness in RD and ADHD.

Categorization of a sample into diagnostic subgroups (e.g., dyslexia or not, ADHD or not) is a somewhat arbitrary process, requiring the investigator to select a severity cutoff on an otherwise normal distribution of scores. Dichotomization reduces the available variance significantly, reducing power to detect relationships. Consequently, a structural equation modeling (SEM) approach was used by McGrath et al. (2011), where latent factors of all relevant constructs were used to test which cognitive constructs were shared and which were unique in predicting dyslexia and ADHD symptoms. Figure 4 provides the best fitting SEM model reported by McGrath and colleagues. The results support the multiple deficit model, as each symptom dimension had multiple significant predictors (phoneme awareness, naming speed, and processing speed predicted reading; inhibition and processing speed predicted inattention and
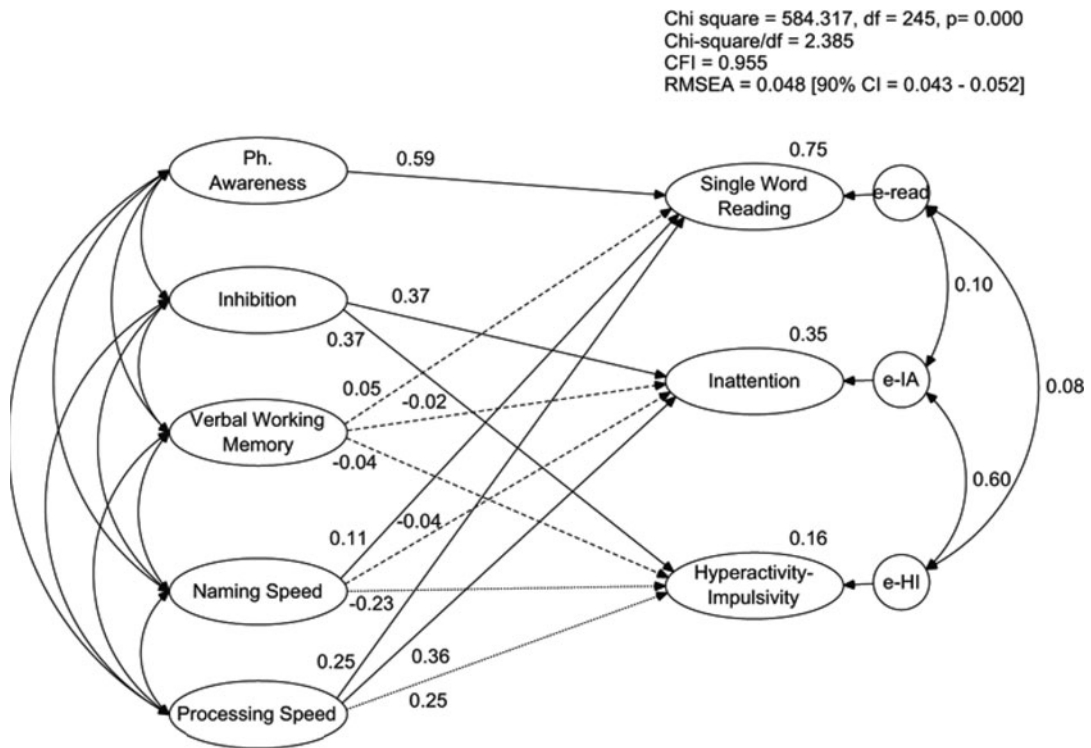
Chi square = 584.317, df = 245, p= 0.000
Chi-square/df = 2.385
CFI = 0.955
RMSEA = 0.048 [90% CI = 0.043 - 0.052]

Figure 4. Structural equation modeling model predicting continuously distributed dyslexia and ADHD symptom dimensions from cognitive dimensions. The measurement components of the model are not depicted for simplification of the figure. Standardized path estimates and correlation coefficients are depicted by single-headed and double-headed arrows, respectively. Numbers above the endogenous latent variables indicate the percent of variance accounted for in each latent variable. Solid lines indicate paths significant at $p < .05$. Dashed lines indicate nonsignificant paths. Dotted lines indicate paths that were significant in this model, but showed inconsistent statistical evidence across different analytic strategies. From "A multiple deficit model of reading disability and attention-deficit/hyperactivity disorder: Searching for shared cognitive deficits" by L. M. McGrath, B. F. Pennington, M. A. Shanahan, L. E. Santerre-Lemmon, H. D. Barnard, E. G. Willcutt, et al, 2011, *Journal of Child Psychology and Psychiatry, 52*(5), pp. 547–557.

hyperactivity/impulsivity). In addition, the path loadings indicated that processing speed was the only shared cognitive risk factor, significantly predicting all three symptom dimensions. Introducing processing speed in the model reduced the correlation between word reading and inattentive symptoms from $r = .41$ ($p < .001$) to $r = .07$ ($p = .28$), and the correlation between word reading and hyperactive/ impulsive symptoms from $r = .22$ ($p < .001$) to $r = .07$ ($p < .30$). Thus, McGrath et al. concluded that processing speed was primarily accounting for the significant correlation (i.e., comorbidity) between the two

disorders. Interestingly, in their final model, verbal working memory did not significantly predict any of the symptom dimensions, even though it has been identified as a risk factor for dyslexia (Brady, 1991) and ADHD independently (Doyle et al., 2005). These results suggest that when other cognitive processes are accounted for, verbal working memory does not make additional unique contributions to word reading or ADHD symptom dimensions. Also of significance in this study is the fact that processing speed significantly predicted unique variance in *untimed* single word reading. The authors interpreted this result as

suggesting that cognitive efficiency also plays a role in the acquisition of word reading skill and does not just contribute to reading fluency.

If processing speed is the shared cognitive deficit that accounts for the comorbidity between dyslexia and ADHD, then one would also predict that it would share common genetic influence with the symptom dimensions of the two disorders. This was investigated using a Cholesky decomposition analysis by Willcutt et al. (2010). This procedure, which was performed in a genetically informed twin sample, estimated the shared and independent genetic influences on reading, inattention, hyperactivity/impulsivity, and the processing speed and naming speed composites. Figure 5 provides a summary of the findings. The significant path loadings on the first genetic factor (A1) indicate that common genetic influences account for significant covari-
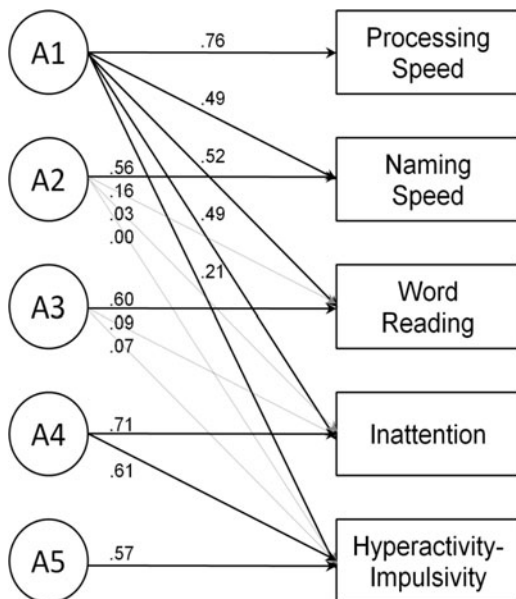

Figure 5. Cholesky decomposition analysis of ADHD, reading, and processing and naming speed. Solid paths are significant ($p < .01$). From "Etiology and Neuropsychology of Comorbidity Between RD and ADHD: The Case for Multiple-Deficit Models," by E. G. Willcutt, R. S. Betjemann, L. M. McGrath, N. A. Chhabildas, R. K. Olson, J. C. DeFries, et al, 2010, *Cortex, 46*(10), pp. 1345–1361.

ance among the five measures. Because the Cholesky model is hierarchical, paths from genetic factors A2–A5 test for additional genetic influences that are independent of those included in A1. A separate genetic factor contributes significantly to covariance between inattention and hyperactivity/impulsivity that is independent of word reading (A4), and there were unique genetic influences on naming speed (A2), word reading (A3), and hyperactivity/impulsivity (A5) that were not significantly associated with any of the other composites.

Notably, the Cholesky decomposition showed that there were no other shared genetic influences on reading and either ADHD symptom dimension after accounting for the genetic influences that are shared with processing speed. These results suggest that comorbidity between reading difficulties and ADHD is primarily attributable to common genetic influences that lead to slow processing speed. Willcutt and colleagues tested the specificity of this result by performing additional analyses with working memory or inhibition entering first into the Cholesky decomposition; in each of these subsequent models, there still were significant shared genetic influences between reading and inattention that were independent of the genetic influences that were shared with inhibition or working memory.

In sum, the series of studies presented here illustrate a set of approaches that have been used to identify possible factors that could account for the comorbidity between dyslexia and ADHD. It is noteworthy that these approaches were used in concert to help us move from a descriptive level to one of explanation. On the basis of the conceptual shift to a multiple deficit model for complex disorders, cognitive risk factors were identified for each disorder. These in turn were tested using a design that captured the interactive effects of dyslexia and ADHD on cognitive phenotypes. A more comprehensive SEM model, wherein multiple influences could be tested simultaneously, led to identification of processing speed as the most likely shared

cognitive risk factor. Finally, genetic influences on processing speed, dyslexia, and ADHD symptom dimensions were tested in a genetically informed sample, confirming that what was shared at a cognitive level was also shared at a genetic level. These studies have moved the field forward to a more in-depth understanding of the factors involved in comorbidity between dyslexia and ADHD but have left a number of unanswered questions as well. In the next section, we briefly discuss some of these issues and provide some potential next steps in the analysis of comorbidity among the four neurodevelopmental disorders of interest in this special issue of *Topics in Language Disorders*.

FUTURE DIRECTIONS

Processing speed has been a part of the theoretical conceptualization of both dyslexia and ADHD, but the exact role that it plays in the development of symptoms of each disorder is not well understood. Furthermore, the fact that processing speed is now a primary candidate for understanding the comorbidity between dyslexia and ADHD makes it even more important that researchers focus on this particular construct in future research. There are certainly a number of unanswered questions, some of which are highlighted in the following paragraphs.

In dyslexia, the Double Deficit Hypothesis posits that two distinct sources of difficulty combine to create single word decoding difficulties: phonological deficits and naming speed (Wolf & Bowers, 1999). In the SEM analyses from McGrath and colleagues, processing speed and naming speed were highly correlated ($r = .77$), but it was processing speed that emerged as a unique predictor. This result may be driven primarily by the relation between naming speed and the other verbal constructs in the model (verbal working memory and phonological awareness), such that there was not enough unique explanatory variance left for naming speed for it to be a significant predictor. The Cholesky decomposition showed that there is common genetic influence that affects both processing speed and naming speed, suggesting the possibility that either one could potentially be a shared risk factor if the other is not in the model. It is also noteworthy that processing speed predicted untimed single word reading; this is in contrast to the more typical finding, wherein naming speed and processing speed are more closely related to reading fluency in dyslexia (Caravolas, 2005; Compton, Davis, DeFries, Gayan, & Olson, 2001). Overall, it would be beneficial to clarify the relationship between naming speed and processing speed. Understanding the subcomponents of these two constructs (e.g., lexical retrieval, visual attention, decision making, visuomotor execution) will likely yield even more proximal endophenotypes that can be used to explore genetic and brain mechanisms in these disorders.

In ADHD, there are several theories that implicate processing speed in the cognitive account of the disorder, such as the Cognitive-Energetic Model (Swanson et al., 2000) and the notion of "sluggish cognitive tempo"(Hartman, Willcutt, Rhee, & Pennington, 2004). But again, the exact nature of how processing speed influences the manifestation of ADHD symptoms remains unclear. Given recent discussion about the transient manifestations of attentional disturbance (see Banich et al., 2009), one also could question whether the types of processing speed tasks traditionally used are just more nuanced measures of inattention. Attempting to partial out, or decompose, the various components inherent in processing speed measures (e.g., sustained attention, response selection, motor execution) may improve understanding of the relationship between this shared cognitive risk factor and the disorders of interest.

Another puzzle that arises from the studies of cognitive endophenotypes in dyslexia and ADHD is the relation between working memory and processing speed. Both cognitive processes are related to each disorder when dyslexia and ADHD are studied individually; yet, working memory is not a shared risk factor when entered simultaneously with

processing speed into models. Slower processing speed typically taxes working memory processes, but the exact relationship between these two constructs needs to be elucidated further.

As is the case with most, if not all, complex disorders, refinement of the phenotypic constructs, whether at a theoretical level or in terms of measurement, will benefit imaging neuroscientists and geneticists. It is likely going to be the case that no large effect genes or polymorphisms will be found for these disorders; nevertheless, results of a whole GWAS for reading have yet to be reported using a sufficiently large sample to identify genes with small to medium effects. Use of more refined cognitive phenotypes that are less heterogeneous will eventually reduce error variance in such GWAS models and may potentially facilitate identification of subtypes that can be validated at a genetic and clinical level.

When a sufficiently powered GWAS study of dyslexia is concluded, it could potentially yield new genes or genetic regions of interest that have not been previously identified. These regions would then need to be tested to see if they are pleiotropic (i.e., one gene influencing multiple phenotypic traits) for ADHD, as well as for SSD and SLI, which would then add to the explanation of comorbidity at the genetic level. Ideally, a large population sample of children would be used for such a GWAS, with careful measurement of symptoms of each disorder as well as all potential cognitive and linguistic endophenotypes previously described. This sample would likely need to be followed longitudinally, as the disorders of interest manifest maximally at different ages. In addition, there is the possibility that phenotype–genotype relations may vary depending on when along the developmental trajectory they are measured. Although the literature thus far has not supported the distinction at a cognitive level between IQ-discrepant and non–IQ-discrepant dyslexia, it will be important to investigate whether this distinction is valid at the genetic level. Recent research has found that the her-

itability of reading increases as a function of IQ. Lastly, it will be important to continue to explore gene by environment interactions across all four disorders, as these may likely add an additional layer of explanatory variance to their relationship.

In ADHD, researchers are looking for ways of leveraging SNP findings within genes and their immediate noncoding regions to improve detection in follow-up association studies. As the advances in identification of candidate genes continue, we may get to the point where genetically informed imaging studies can be performed. The latter may eventually integrate resting state connectivity, structural connectivity, and functional imaging approaches, to capture better the dynamic differences among subgroups of individuals at risk for both dyslexia and ADHD.

One of the largest challenges that we face is how to expand the approaches mentioned in this article to the study of four comorbid disorders. The multidimensional space created by the risk factors for four disorders will be quite daunting. The problem may have to be approached from both directions: systematically analyzing pairings (or triplets) of risk factors, to see what symptom level profiles emerge, while at the same time, analyzing large population samples that can be subdivided into groups of children with different disorder combinations (pairs, triplets, or all four) to see what risk factors they comprise. As these types of studies will require very large samples, efforts will need to be coordinated at a national or international level, so that genetically informed samples can be ascertained using common measures for all four disorders and their respective risk factors. Some consortiums already exist, but usually they have focused on one disorder. Collaborations will need to be reinvigorated across disciplines, laboratories, and countries, to achieve the consensus and cooperation required to examine the causes of comorbidity across the wider set of disorders.

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